The study of prediction through unexpected stimulus omission in adults and children

Thesis

for the degree of

doctor rerum naturalium (Dr. rer. nat.)

approved by the Faculty of Natural Sciences of Otto von Guericke University Magdeburg

by M.Sc. Tjerk T. Dercksen

born on the 31st of January, 1992 in Assen (Netherlands)

Examiner: Prof. Dr. Tömme Noesselt

Prof. Dr. Alexandra Bendixen

submitted on: 3rd of May, 2023

defended on: 29th of November, 2023

Acknowledgements

Due to data protection concerns, the Otto von Guericke University Magdeburg has prohibited me from publishing my words of gratitude in the online version of this thesis.

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Abbreviations

A1	Primary auditory cortex
A2	Secondary auditory cortex
ADHD	Attention deficit hyperactive disorder
ANOVA	Analysis of variance
BF_{10}	Bayes Factor
$BF_{inclusion}$	Inclusion Bayes Factor
BF_{r0}	Replication Bayes Factor
CI	Confidence interval
d	Cohens *d*
dB	Decibel
EEG	Electroencephalography
EES BF_{01}	Effect Size Bayes Factor
EFA	Exploratory factor analysis
EOG	Electrooculogram
ERP	Event related potential
FIR	Finite impulse response
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
Hz	Hertz
IC	Independent component
ICA	Independent component analysis
IPI	Inter-press-interval
IR	Incongruency response
ISI	Inter-stimulus-interval
LC	Locus coeruleus
MEG	Magnetoencephalography
mm	Millimeter
MMN	Mismatch negativity
ms	Millisecond(s)
NE	Norepinephrine
oN1	Omission N1
oN2	Omission N2
oN3	Omission N3
oP3	Omission P3
PCA	Principal component analysis
PDR	Pupil dilation response
PPC	Posterior parietal cortex
rANOVA	Repeated measures ANOVA
RMS	Root mean square
ROI	Region of interest
RS	Repetition suppression
s	Second
SD	Standard deviation
SEP	Stimulus evoked potential
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
sinc	Sine cardinal
sMMN	Somatosensory mismatch negativity

SNR	Signal to noise ratio
SSA	Stimulus-specific adaptation
η^2	Eta Squared
η_G^2	Generalized eta squared
µV	Microvolt

Summary

THE STUDY OF PREDICTION THROUGH UNEXPECTED STIMULUS OMISSION IN ADULTS AND CHILDREN

Doctoral thesis submitted by M.Sc. Tjerk T. Dercksen

Rather than passively receiving sensory input, the brain seems to actively predict the world around us, utilizing errors in these predictions to learn. Such top-down predictions have a substantial impact on the brain's processing of sensory input and have been suggested to play a crucial role in cognitive development. However, studying prediction in the brain is challenging due to the influence of confounding factors associated with bottom-up stimulus processing. To avoid such confounds, this thesis takes a relatively underexplored approach, examining the brain's response to the unexpected omission of a stimulus. This approach minimizes the influence of bottom-up input and enables analysis of brain activity that can only reasonably be explained by prediction.

This thesis includes four studies, three in adults and one in both 6–8 year old children and adults, which used either electroencephalography or pupillometry as a measure of cognitive processing. Omission responses were elicited using action-effect couplings, where button presses were paired with the presentation of a stimulus that was occasionally omitted. The responses to these occasional omissions were compared to a physically identical motor control setting, where any differences in activity were considered prediction-related activity.

Several key findings emerged from this research. First, omission responses are not only triggered by specific but also by unspecific sound predictions, suggesting a more flexible system than previously assumed. Second, the consistent pattern of omission responses seen in auditory studies results in analogous responses in the somatosensory modality, in line with current models of prediction in the brain. Third, pupillometry can be used to observe an omission response resulting from action-effect couplings, with similar elicitation across the auditory and somatosensory modality. Fourth, despite immature sound processing, children exhibit auditory omission responses that are remarkably similar to those of adults, consistent with the assumed central role of prediction in development.

Overall, this thesis systematically demonstrates that the omission response is an appropriate, reliable, and sensitive tool to study prediction in the brain. Additionally, an omission approach may be especially suitable for investigating prediction in the developing brain. Findings contribute to the general understanding of neural mechanisms that underlie prediction and are discussed within the broader framework of deviance detection.

Zusammenfassung

DIE UNTERSUCHUNG DER VORHERSAGE DURCH UNERWARTETE REIZAUSLASSUNGEN BEI ERWACHSENEN UND KINDERN.

Doktorarbeit eingereicht von M.Sc. Tjerk T. Dercksen

Anstatt nur passiv auf sensorische Reize zu reagieren, scheint das Gehirn aktiv Vorhersagen über unsere Umgebung zu treffen und Fehler in diesen Vorhersagen für Lernprozesse zu nutzen. Solche Top-Down-Vorhersagen haben einen erheblichen Einfluss auf die Verarbeitung des sensorischen Inputs im Gehirn und spielen eine entscheidende Rolle in der kognitiven Entwicklung. Die Auswirkung konfundierender Faktoren, die mit der Bottom-Up-Stimulusverarbeitung verbunden sind, stellt jedoch eine Herausforderung für die Untersuchung von Vorhersagen des Gehirns dar. Um solche Konfundierungen zu vermeiden, verfolgt diese Arbeit einen relativ neuen bzw. bisher vernachlässigten Ansatz und untersucht Reaktionen des Gehirns auf das unerwartete Ausbleiben eines Stimulus. Dieser Ansatz minimiert die Einwirkung von Bottom-Up-Einflüssen und ermöglicht die Analyse von Hirnaktivitäten, die auf Vorhersageprozesse zurückgeführt werden können.

Diese Arbeit umfasst drei Studien mit Erwachsenen sowie eine Studie mit sowohl 6-8-jährigen Kindern als auch Erwachsenen, die Elektroenzephalographie oder Pupillometrie als Maß für kognitive Verarbeitung verwenden. Auslassungsreaktionen wurden durch unerwartete Handlungskonsequenzen ausgelöst, indem ein an einen Tastendruck gekoppelter Stimulus überraschend ausblieb. Die Reaktionen auf dieses gelegentliche Ausbleiben des Reizes wurden mit einer Motorkontrollbedingung verglichen, wobei Unterschiede in der Hirnaktivität als vorhersagebezogene Aktivität betrachtet wurden.

Aus dieser Forschung ergaben sich mehrere wichtige Erkenntnisse. Erstens werden Auslassungsreaktionen nicht nur durch spezifische, sondern auch durch unspezifische Vorhersagen einer auditiven Handlungskonsequenz ausgelöst. Dies weist auf ein flexibleres System hin als bisher in der Literatur angenommen. Zweitens wurde das konsistente Muster von Auslassungsreaktionen in der auditiven Modalität auch in der somatosensorischen Modalität beobachtet, was im Einklang mit aktuellen Modellen zu Vorhersagemechanismen im Gehirn steht. Drittens kann die Pupillometrie genutzt werden, um eine Auslassungsreaktion aufgrund von Handlungskonsequenzen zu beobachten, wobei eine ähnliche Auslösung in der auditiven und somatosensorischen Modalität erkennbar wird. Viertens zeigen Kinder trotz sich noch entwickelnder auditiver Verarbeitungsmechanismen Auslassungsreaktionen, die bemerkenswert ähnlich zu denen von Erwachsenen sind, was mit der Annahme einer zentralen Rolle von Vorhersagemechanismen in der Entwicklung übereinstimmt.

Die Ergebnisse dieser Arbeit zeigen konsistent, dass die Auslassungsreaktion ein geeignetes, zuverlässiges und sensibles Instrument zur Untersuchung von Vorhersagemechanismen im Gehirn ist. Darüber hinaus ist dieser Ansatz geeignet, um Vorhersagen im sich entwickelnden Gehirn zu untersuchen. Die Ergebnisse tragen zum besseren Verständnis der neuronalen Mechanismen bei, die Vorhersagen zugrunde liegen, und werden im Rahmen eines breiteren Konzepts der Detektion von Veränderungen in der Umgebung diskutiert.

Chapter 1: Introduction

From the moment we enter the world, our minds possess the ability to predict. Initially, this ability is mainly limited to simple associations, but as our knowledge increases, so does our predictive capacity. Researchers have long used this capacity as a means to study cognitive development, for example in the realm of object knowledge: if an infant shows a predictive look to the mouth when an experimenter picks up a spoon to eat, it indicates the presence of early knowledge about the function of spoons (Kochukhova & Gredebäck, 2010). However, over the past years, the focus has shifted towards a deeper exploration of the prediction process itself. Prediction might not be a consequence of our knowledge of the world, but rather the driving mechanism that acquires it (Emberson, 2017; Köster et al., 2020). This compelling idea is the main motivation behind the research presented in this thesis.

Over the past decades, developmental research has firmly established the central role of prediction in cognitive development, but predominantly using behavioral measures (for reviews, see Köster et al., 2020; Saffran & Kirkham, 2018; Stahl & Feigenson, 2019). My objective was therefore to explore prediction closer to the source, on the level of the functioning brain. However, existing methods used to study prediction in the brain are, in my estimation, suboptimal. The majority of experiments does not isolate prediction from other factors related to stimulus processing, leaving room for alternative explanations that do not involve prediction (Heilbron & Chait, 2017; Schröger et al., 2015). My aim was to address this issue by developing an underexplored paradigm, the omission paradigm, which leverages unexpected stimulus omissions to isolate prediction-related brain activity while minimizing the influence of stimulus-related factors. However, as I will explain in this chapter, much is still unknown about how the brain responds to unexpected omissions. That is why this thesis is largely devoted to expanding the knowledge about omission responses in adults, providing a solid foundation for future research on prediction during development. Additionally, this thesis presents a study where omission responses are used to study prediction in children, demonstrating the potential for future research. Therefore, on the basis of the findings presented in this thesis, I will defend two main positions:

1. *The omission response is an appropriate, reliable, and sensitive tool to study prediction;*

2. *An omission approach is especially suitable for studying prediction processes in the developing brain.*

The increasing emphasis on prediction in developmental literature is heavily influenced by modern theories of brain function. These theories reject the traditional view of the brain as a passive processor of sensory information, and propose that the brain actively generates predictions and uses feedback from the senses to refine them, a concept known as predictive coding (Mumford, 1992; Rao & Ballard, 1999). This framework accounts for a wide range of brain functions such as perception, attention, and learning under a single mechanism driven by prediction (Clark, 2013; Feldman & Friston, 2010; Friston, 2005, 2009). In addition to the two main positions, this thesis presents convincing evidence supporting core ideas of how predictive coding is implemented in the brain and proposes some necessary adjustments to existing ideas.

In this opening chapter, I will lay out the most important theoretical concepts and principles that form the foundation of my studies. I will begin by presenting the concept of predictive coding, followed by

how predictive coding explains a number of well-documented brain phenomena. Subsequently, I will address the methodological challenges associated with investigating prediction via these phenomena and propose the use of an omission approach to circumvent them. Finally, I will briefly touch upon the role of prediction in the developing brain, before concluding the chapter by outlining the scope and research questions of this thesis.

1.1 Predictive coding

The formal origins of predictive coding models can be traced back to vision research, with early contributions from Mumford (1992), Rao and Ballard (1999), and Lee and Mumford (2003). These models were inspired by the seminal work of Helmholtz (1867), who posited that perception arises from unconscious inferences drawn from past experience and a priori knowledge of the world. Perception from this perspective is thus not considered a bottom-up reconstruction process where representations are constructed from sensory input, but rather an inference process that draws on pre-existing knowledge to deduce the underlying causes of sensory input.

The definition of predictive coding in this thesis is broadly defined as encompassing the work proposed by Friston and colleagues (Feldman & Friston, 2010; Friston, 2005, 2009, 2010, 2018; Friston & Kiebel, 2009a, b; Garrido et al., 2009a, b, c; Kilner et al., 2007) as well as the similar work referred to as "predictive processing" (Clark, 2013, 2015, 2016; Hohwy, 2013, 2020; Köster et al., 2020). At the heart of predictive coding lies the cortical hierarchy, where lower brain areas are defined as being closer to sensory input (or motor areas) and higher brain areas as more distant. Predictive coding proposes that these hierarchical levels in the brain serve as generative models, modelling low-dimensional stimulus features at lower levels and more complex, abstract concepts at higher levels. The key mechanism that enables successful perception is the reciprocal exchange of information between these levels. Higher levels generate predictions about neural activity in the lower levels and send these downward, where in lower levels they are compared to actual activity. Where predictions are incorrect, this causes the elicitation of prediction errors that are sent back to higher levels. Higher levels in turn use the information from prediction errors to correct perception and adapt their generative models in order to make better predictions in the future (see Figure 1). By continuously striving for the minimization of prediction error, this model converges to a best guess of the underlying causes of sensory input based on prior knowledge of the world, providing a concrete implementation of unconscious inference as described long ago by Helmholtz (1867).

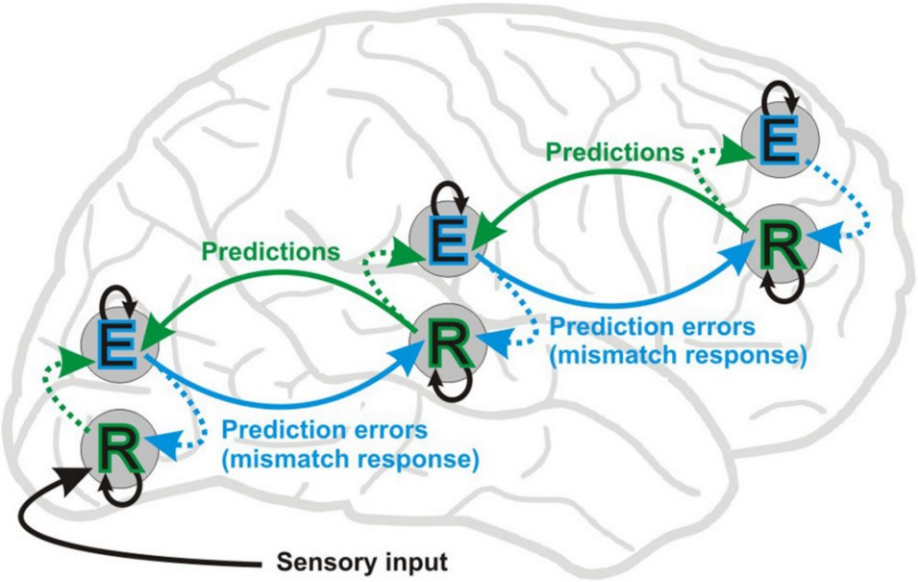

Figure 1: Schematic overview of predictive coding as presented in Stefanics et al. (2014, p. 4). Perception is realized through a cortical hierarchy, where predictions regarding expected input flow from higher, representational units (R) down to lower error units (E). In sensory areas, predictions are compared to actual input, resulting in prediction error where predictions are incorrect. In turn, prediction error serves to adapt representations on equal and higher levels, adapting the model to make better predictions in the future.

The model architecture of predictive coding closely resembles the hierarchical organization of the brain. Although there are many open question regarding the precise anatomical and neuronal implementation of predictive coding, a number of influential proposals have been put forward. The central claim of these proposals is that prediction and prediction error are represented by distinct neural populations that reside in separate cortical layers. Predictions are thought to be propagated through pyramidal neurons in deep layers (V/VI), while prediction errors are thought to originate from pyramidal neurons in superficial layers (II/III) and propagate to middle layers in higher cortical areas (Adams et al., 2013; Bastos et al., 2012; Lee & Mumford, 2003; Mumford, 1992; Shipp, 2016). Despite the remarkable congruence between anatomically observed neural circuits and predictive coding, functional brain evidence that supports these claims is still scarce and inconsistent (Heilbron & Chait, 2018). This thesis therefore maintains an agnostic attitude towards these proposals, embedding them in the discussions but acknowledging the need for further research and evidence to support their validity.

Prediction error is higher in some environments than in others. For example, in a busy restaurant the randomness of sounds in the background (other people talking, chairs moving, music playing) is harder to predict than the silence in a library. However, not all prediction errors are equally relevant. For example, when trying to understand what a friend is saying in a busy restaurant, prediction errors regarding the speech sounds of that friend are highly relevant, whereas prediction errors regarding background sounds are not. The solution to this problem is commonly known as attention, and is implemented under the term precision weighting in the predictive coding framework (Feldman & Friston, 2010). Precision weighting entails that the weight that is appointed to prediction error units can be selectively adapted based on their expected precision. Background sounds are highly fluctuating and irrelevant, resulting in down-weighted prediction errors, diminishing their influence on higher-level models. On the other hand, relevant or reliable signals are assumed to be up-weighted, increasing the influence of prediction error signals that are thought to be most beneficial in updating the model of the world. The attention- or precision-related effects that play a role in the studies presented in this thesis are predominantly considered from this precision weighting perspective.

The research presented in this thesis draws heavily on predictive coding as a means of interpreting and understanding results. Although predictive coding is not without its critics (see e.g. the commentaries included in Clark et al., 2013), the decision to take this approach was a deliberate one. Predictive coding offers a comprehensive model of brain function that, importantly, provides testable hypotheses. In my opinion, the verification, falsification, and subsequent refinement of a common model is what allows modern science to progress. In this respect, I consider predictive coding to be a valuable tool that allows the embedding of findings within the larger body of research and facilitates communication across different subfields of neuroscience. Naturally, the use of any tool comes with its own limitations and biases, to paraphrase Maslow (1966): if all you have is a hammer, everything looks like a nail. I acknowledge this risk, and have aimed to additionally maintain a diverse perspective of relevant literature when interpreting my findings.

1.2 How prediction explains ERP phenomena: mismatch negativity, repetition suppression, incongruency response, and self-generation

The main strength of predictive coding lies in its explanatory power of a variety of psychophysiological phenomena. Although these phenomena extend to a broad range of measurement methods (e.g. Carbajal & Malmierca, 2018; Hohwy et al., 2008), I will focus the introduction of this topic primarily on electroencephalography (EEG), as it is the primary method used in this thesis. More specifically, this thesis uses the averaged EEG over events of interest, known as the event related potential (ERP), to study brain activity. Enhanced activity in the ERP is often explained as prediction error in the predictive coding framework and forms the basis from which to explain a number of well-documented phenomena, from which I will describe four of the most prominent ones.

The first phenomenon is the mismatch negativity (MMN), which is typically elicited using an “oddball” paradigm. This paradigm involves repeated presentation of the same standard sounds, with occasional and unexpected interruption by deviant or oddball sounds. By subtracting the ERP of the standard sound from that of the deviant sound, a negativity is observed around 100-250 ms after sound onset, with the strongest activations typically occurring over fronto-central channels (Butler, 1968; Näätänen et al., 1978; Squires et al., 1975). In-depth study of the MMN has demonstrated that it is not only elicited in response to simple pitch changes but also to deviance from more abstract rules in the sensory pattern (Näätänen et al., 2001; Saarinen et al., 1992; Tervaniemi et al., 1994a). Furthermore, the MMN has been observed across various modalities, including visual MMN (Pazo-Alvarez et al., 2003) and somatosensory MMN (Näätänen, 2009), supporting its role as a general mismatch signal. Predictive coding explains the MMN as a prediction error signal resulting from prediction violation. Initially, a prediction is generated in response to the standard stimulus to minimize prediction error. This prediction is propagated down the cortical hierarchy, where it is compared to actual input in lower sensory areas. When a deviant stimulus is presented, the difference between the prediction and the input leads to prediction error, which is then propagated up the hierarchy to adjust models and correct perception. This explanation is consistent with several characteristics of the MMN, including its dependence on the magnitude of the discrepancy between standards and deviants (Schröger, 1996), its dependence on probabilistic structure (Baldeweg, 2007), and its localization to sensory areas (Liebenthal et al., 2003).

The phenomenon of repetition suppression (RS) could be considered a counterpart of the MMN and has been studied in great depth, particularly with regard to stimulus-specific adaptation (SSA) in animal studies (Carbajal & Malmierca, 2018; Escera & Malmierca, 2014). RS is characterized by a decrease in neural activity following the initial presentation of a stimulus. Early explanations for RS focused on simple bottom-up processes, such as neural fatigue (Grill-Spector et al., 2006), but empirical evidence seems to point increasingly to an explanation that involves prediction (Baldeweg, 2006, 2007). Indeed, studies have shown that when repetition of a stimulus is unexpected, suppression is impaired, indicating that top-down prediction is crucial (Summerfield et al., 2008; Todorovic et al., 2011, 2012). In EEG research, RS can be systematically demonstrated using a roving paradigm, a variation of the oddball paradigm. These studies typically analyze the fixed pattern of responses to sounds in the ERP, consisting of a sequential elicitation of P1, N1, P2, and N2 components. With regard to RS, the auditory N1, a frontocentral negativity elicited around 100 ms, is of particular interest. In the roving paradigm, a standard sound is presented repeatedly and occasionally replaced by a deviant sound, which then becomes the next standard sound. These studies show that the large amplitude auditory N1 elicited by the first, unpredictable deviant sound of the sequence is followed by an increasingly attenuated (more positive) N1 on subsequent identical sounds (Costa-Faidella et al., 2011; Garrido et al., 2008, 2009a, b; Haenschel et al., 2005; sometimes also interpreted as a repetition positivity). From a predictive coding perspective, various detailed models have been proposed to account for this attenuated response, which is thought to result from increasingly accurate prediction of the stimulus (Auksztulewicz & Friston, 2016; Carbajal & Malmierca, 2018; Grotheer & Kovács, 2016).

Another variant of a mismatch signal is the incongruency response (IR). The IR has been interpreted as a prediction error resulting from cross-modal predictions, and has mainly been investigated in visual-auditory settings. For example, Widmann et al. (2004) visually presented a score-like sequence of four to six high and low bars that were followed by the same number of high- or low-pitched sounds. Most of the time (probability of 90%), the sound was congruent with the visual score, but occasionally the sound was incongruent with what would be expected based on the visual information (e.g. high bar but low sound). The difference between congruent and incongruent trials reveals a bilateral negativity around 100 ms that is similar to the MMN in the same latency (Pieszek et al., 2013). The IR has been replicated in a number of settings, for example using trial-by-trial designs (Dercksen et al., 2021; Stuckenberg et al., 2019, 2021), and is considered a key indicator of how visual and auditory information are integrated in the brain.

As a brief aside, it is worth noting that the MMN and IR are typically succeeded by a P3 or P300 response. This broad positivity in the ERP around 300 ms is assumed to be involved in reorienting of attention and updating of knowledge following the initial mismatch (Nieuwenhuis, 2011a; Polich, 2007). The P300 is thought to reflect the activity of the locus coeruleus norepinephrine (LC-NE) system, where a phasic response to salient stimuli from the subcortical LC causes an enhancement of neural responsivity in the cortex induced by NE (Nieuwenhuis et al., 2005; Vazey et al., 2018). Another way of measuring such subcortical LC activity is through the use of pupillometry. Human and animal studies suggest a causal link between phasic LC activity and pupil dilation (see Joshi & Gold, 2020 for a review). Salient or surprising stimuli that would typically elicit a P300 response in the ERP therefore also result in an enhanced response of the pupil compared to standard stimuli (Bonmassar et al., 2020; Murphy et al., 2014; Wetzel et al., 2016). In this thesis, one study measures omission responses through the use of pupillometry. When interpreting results and comparing them to ERP studies, it is important to keep this link between LC activity and the P300 in mind.

Finally, the fourth EEG finding often explained in terms of prediction is the sensory attenuation effect observed in self-generation studies, also referred to as contingent paradigm studies. Typically, these studies employ three experimental conditions: motor-stimulus, stimulus, and motor, and aim to compare sensory responses between self-generated and externally generated stimuli (Horváth, 2015). In the motor-stimulus condition, participants trigger stimuli by performing an action (e.g. pressing a button), whereas in the stimulus condition the stimuli are passively presented with similar timing, and in the motor condition, only the action is performed without presentation of the stimulus. To control for motor activity, the motor condition is subtracted from the motor-stimulus condition, enabling a comparison of sensory responses between the motor-stimulus and stimulus conditions. Results have shown attenuated sensory responses when stimuli are self-generated compared to when they are externally generated, and this has been shown using auditory (Aliu et al., 2009; Knolle et al., 2012; Martikainen et al, 2005; Timm et al., 2013; for reviews, see Horváth, 2015; Hughes et al., 2013), visual (Csifcsák et al., 2019; Hughes & Waszak, 2011; Ody et al., 2022) and somatosensory (Blakemore et al., 1998, 1999, 2000; Kilteni & Ehrsson, 2020) stimuli. Traditional perspectives attributed these findings to an efference copy that reflects the sensory feedback of a movement (Sperry, 1950; von Holst & Mittelstaedt, 1950), resulting in attenuated responses when the copy and sensory input correspond (Blakemore et al., 2000; Crapse & Sommer, 2008; Miall & Wolpert., 1996). However, attenuated responses are not only seen when coupled to movement, but also when stimuli can be predicted based on sensory information (Ghio et al., 2017; Poonian et al., 2015; Vroomen & Stekelenburg, 2010). These new perspectives, congruent with predictive coding, suggest that both motor and sensory information is used to predict sensory input, resulting in diminished neural responses that supposedly reflect diminished prediction error (Korka et al., 2022).

1.3 Confounds when studying prediction

The four phenomena introduced above are often referred to in seminal papers as key evidence in support of predictive coding (Clark, 2013; Friston, 2005). While these phenomena are probably best explained from a predictive coding perspective, alternative perspectives expose some critical shortcomings that demonstrate the limitations of these established paradigms as appropriate methods to study prediction. One alternative perspective that is particularly relevant to the MMN and RS is the neural adaptation hypothesis (Jääskeläinen et al., 2004; May, 1999, 2021; May et al. 1999; May & Tiitinen, 2001, 2004, 2010). This model attributes the MMN to low-level neural adaptation or RS to the standard sound. With each repetition of the standard sound, RS builds up as neurons in the auditory cortex exhibit attenuated responses due to synaptic depression or lateral inhibition. Importantly, only neural populations specific to the standard sound are suppressed, leaving other neural populations unaffected. When a deviant sound is subsequently presented, neurons associated with the deviant sound (fresh afferents) are less adapted, and thus, exhibit an increased response to the sound. This heightened response may be seen as a consequence of different adaptation levels, which manifests as an increased negativity known as the MMN when subtracting the standard from the deviant sound response. More precisely, according to the adaptation hypothesis, instead of a separate component the MMN is an amplified and delayed auditory N1 compared to the adapted N1 response to standard sounds (May & Tiitinen, 2010; Ulanovsky et al., 2003).

The neural adaptation hypothesis offers an innovative and critical view of the literature, and has sparked a fruitful debate around the MMN and RS. For example, the many-standards paradigm uses a standard sound from a separate condition where always different sounds are presented, arguably

bypassing adaptation effects. Analysis of the resulting difference wave, where the supposed proper control sound is used, reveals that the original MMN is a mixture of both adaptation and "genuine" MMN effects (Campbell et al., 2007; Horváth et al., 2008; Jacobsen & Schröger, 2003; Maess et al., 2007; Schröger, 1997; Schröger & Wolff, 1996). However, May and Tiitinen (2010) reject the validity of this control condition, claiming that lateral inhibition could be stronger in the deviant than in the control sound. Similarly, several studies have attempted to refute the adaptation hypothesis by demonstrating that the MMN is not only evoked by sound frequency changes but also by alterations to more abstract patterns. For example, the MMN is elicited when a sound is repeated in a series of ascending or descending sounds (Tervaniemi et al., 1994a) or tone pairs (Saarinen et al., 1992), seemingly at odds with results that would be expected from adaptation. In response, May and Tiitinen (2010) argue that the auditory cortex does not merely encode simple tonotopic features but also complex spectral and temporal features such as sound direction, which are sensitive to adaptation as well.

Although the validity of the above-described counterarguments from May and Tiitinen (2010) can be debated (see e.g. Wacongne et al., 2012), it cannot be denied that the neural adaptation hypothesis reveals some fundamental shortcomings when employing the MMN to study prediction. First, it underscores the true complexity of the brain and how little is yet known about even basic functions such as stimulus processing. Any sensory stimulation cannot be viewed as an independent event, but should be viewed in the context of preceding events that influence the cortex in largely unknown ways (Hajizadeh et al., 2022). Given the incomplete knowledge regarding how SSA/RS affects stimulus processing, the mechanisms behind these effects should, in my opinion, be considered a black box. Second, the notion of the neural adaptation hypothesis that latency differences play a substantial role when comparing stimulus responses is supported by compelling empirical evidence. For example, the latency of auditory-evoked components is dependent on stimulus features such as sound frequency (Mäkelä et al., 2002; Roberts, & Poeppel, 1996), intensity (Picton et al., 1976; Rapin et al., 1966), and identity (Obleser et al., 2003; Tiitinen et al., 2005). This implies that any comparison of stimuli is inevitably influenced by feature-specific activity, potentially contaminating conclusions regarding prediction-related activity. In short, the adaptation hypothesis highlights the unknown influence of bottom-up effects that play a role in MMN generation, hindering a proper analysis of prediction processes.

For the IR, an explanation involving low-level adaptation seems less convincing, given the influence of the visual modality on auditory processing. Nevertheless, there is an ongoing discussion about what the IR may actually reflect (Dercksen et al., 2021; Stuckenberg et al., 2019, 2021). On the one hand, the IR may reflect an increased response to incongruent sounds, signaling prediction error. On the other hand, as the IR results from a difference wave between stimuli, it could reflect suppressed processing of the congruent sound. The problem of disentangling suppression from prediction error is therefore still unresolved. Moreover, both the MMN and IR are hampered by the issue that they likely reflect two distinct signal types: one related to input that was encountered but not predicted, and one related to input that was predicted but was absent (Schröger et al., 2015; see Figure 2).

As the above examples illustrate, difficulties in interpretation tend to arise in paradigms where stimulus responses are compared, and this is likewise the case in self-generation studies. The attenuated response when a motor act predicts the sensory input could be ascribed to decreased prediction error, but might also be ascribed to other processes such as attention (Bendixen et al., 2012;

Saupe et al., 2013; Timm et al., 2013), sensory gating (Chapman & Beauchamp, 2006), or a reduced orienting response (SanMiguel et al., 2013b).

In other words, MMN, RS, IR, and self-generation effects are either contaminated by other neural activity or are, at best, indirect indicators of predictive coding. Moreover, any detailed analysis of the underlying neural sources of prediction error is complex and questionable in the presence of simultaneous bottom-up activity. Hence, to evade these problems, the influence of bottom-up input should be minimized. This is the fundamental idea behind omission studies, which minimize bottom-up influence by replacing unexpected deviant stimuli with unexpected omissions. Following the predictive coding arguments, a somewhat paradoxical effect would be expected. That is, if a prediction is present but input is absent, the comparison between prediction and input should result in a prediction error (see Figure 2), and thus a measurable response in the ERP to the absence of a stimulus. Although this is a promising approach, there are some important practical as well as theoretical details to consider.

1.4 The omission approach

Most omission studies to date have simply replaced the deviant stimulus in an oddball paradigm with a stimulus omission. That is, standard stimuli are presented in a fixed rhythm that is occasionally interrupted by an unexpected stimulus omission. The recorded brain response to this stimulus absence is typically referred to as the omission MMN (Yabe et al., 1997). Despite its predominant use, findings related to the omission MMN have shown to be both unreliable and unspecific, and its theoretical interpretation could be considered ambiguous. These problems may have caused researchers to be cautious towards employing omission studies in general, possibly explaining their relative scarcity in the field.

The primary factor making the omission MMN unreliable is its tendency to vanish as the latency between presented stimuli increases. Only when stimuli are presented with an inter-stimulus-interval (ISI) that has a maximum of around 200 ms the omission MMN is consistently observed (Andreou et al., 2015; Chennu et al., 2016; Horvath et al., 2010; Lehmann et al., 2016; Oceak et al., 2006; Recasens & Uhlhaas, 2017; Tervaniemi et al., 1994b; Wacongne et al., 2011; Yabe et al., 1997, 1998). While some studies have extended this interval slightly, doing so often leads to more ambiguous omission responses (Chouiter et al., 2015; Janata, 2001; Jongsma et al., 2004; Joutsiniemi & Hari, 1989; Karamürsel & Bullock, 2000; Motz et al., 2013; Raij et al., 1997; Salisbury, 2012; Todorovic et al., 2011). According to Yabe et al. (1997, 1998), the apparent time limitations observed in the omission MMN can be attributed to the stimuli being presented outside the temporal window of sound integration, preventing the formation of a compound memory trace. However, there may be a more straightforward explanation. Hughes et al. (2001) suggest that the response to omissions with increased ISIs could be difficult to measure due to temporal dispersion. Indeed, it is reasonable to assume that humans do not possess a sense of rhythm with precision to the millisecond, particularly when gaps between stimuli widen. Slight deviations in the timing of the expected stimulus could lead to temporal deviations in the omission MMN, causing them to disappear in average-based measurements like the ERP. These temporal deviations could also explain why the omission MMN is regularly recorded as a broad, unspecific response (e.g. Joutsiniemi & Hari, 1989; Raij et al., 1997; Rogers et al., 1992) compared to the sharp and specific morphology of the stimulus-evoked MMN. Additionally, differences in temporal consistency between individuals may explain why only a subset of participants sometimes demonstrate an omission MMN (Recasens & Uhlhaas, 2017).

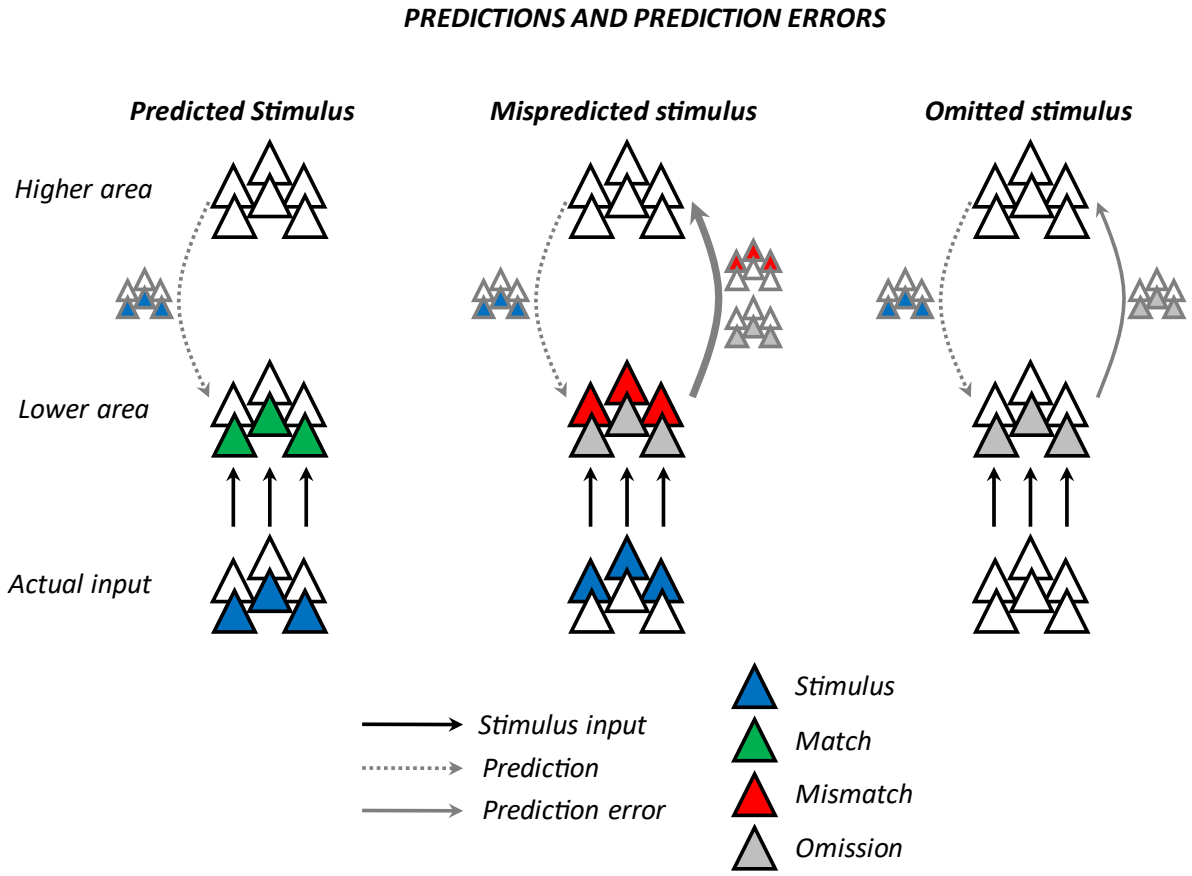

Figure 2: Schematic representation of prediction and prediction error in the brain. Higher-level predictions of sensory input are sent to lower, sensory levels. When a stimulus is correctly predicted (left), sensory input matching the prediction template does not result in prediction error. When a stimulus is mispredicted (middle), i.e. a deviant in an oddball paradigm, prediction error comprises two signal types: one related to input that was encountered but not predicted, and one related to input that was predicted but was absent. Finally, when a stimulus is predicted but omitted (right), the comparison of sensory input with the prediction template results in prediction error signaling stimulus absence. Figure adapted from Schröger et al. (2015, p. 647) and Korka et al. (2022, p. 331).

Apart from this practical, likely measurement-related problem, there are also some theoretical objections to the omission MMN as an objective indicator of prediction error. First, the use of short and fixed interstimulus intervals in omission MMN paradigms raises the possibility that the observed activity in the omission time window is merely a reflection of time-locked activity related to the preceding sound. Second, May and Tiitinen (2001) suggest that the omission MMN may be attributed to low-level oscillatory adaptation mechanisms of neuronal populations. This view regards the omission response as a rebound response of the auditory cortex that does not involve higher-level prediction. Given the specific setup of the omission MMN paradigm, this possibility cannot be disregarded.

Compelling evidence supporting the role of prediction in the omission response is derived from experimental designs where manipulations of the predictability of a tone result in changes to the omission response. For example, Janata (2001) demonstrated that omission responses were only elicited when participants had actively formed expectations about the continuation of a melody. Similarly, Kraemer et al. (2005) used functional magnetic resonance imaging (fMRI) to reveal increased activation of the auditory cortex when omitting a portion of a well-known song compared to an unknown song. However, in both these studies it is difficult to determine the impact of active imagery.

Therefore, Bendixen et al. (2009) presented participants with a sequence of tones in which every second tone was predictable, as it was a repetition of the preceding tone. Omission of the predictable tone resulted in an omission response in the ERP while omission of the unpredictable tone did not. This indicates that the predictability of the tone is crucial to the omission response independent from active imagery. Still, the high presentation rate in this study (150 ms ISI) only permitted a temporally limited analysis (but see Bendixen et al., 2014 for a relevant alternative).

Ideally, one would therefore design an experiment where the omission response does not suffer from temporal shifts, can only be explained in the context of prediction, and allows for analysis over a broader time window. A small number of relatively recent studies meet these criteria, with the pioneering work of SanMiguel et al. (2013c) being a prime example. In this study, action-effect couplings were used to induce predictions. Participants were asked to repeatedly press a button every 600 – 1200 ms, where button presses resulted in either the direct presentation of a sound or the omission of a sound. In one condition, sounds were presented with 88% of the button presses, while in 12% of the button presses, the sound was unexpectedly omitted. In this condition, the presentation of a sound with the majority of button presses theoretically builds a sound prediction, which should lead to prediction error when the sound is unexpectedly absent (see Figure 2). Conversely, in an alternative condition, the chance of a sound being presented with a button press was only 50%, while in the other 50% of button presses, the sound was omitted. In this condition, there is no reliable coupling between button press and sound, resulting in no sound prediction and therefore theoretically no prediction error when the sound is omitted. Finally, a motor control condition was conducted where only the button was pressed without any accompanying sounds (100% omission). This condition reflects the neural activity associated with the motor act of pressing the button (or, perhaps better, the prediction of silence with the button press). Using this setup, SanMiguel et al. (2013c) elegantly validated the hypothesis that the omission response is closely tied to prediction: compared to the motor control condition, the 88%-condition showed an omission response in the ERP, while the 50%-condition was indistinguishable from motor activity. This paradigm fulfills the criteria stated above. First, it effectively eliminates any temporal dispersion of the response by time-locking the omissions to participant-initiated actions. Second, as events that are compared across conditions are identical (a button press that does not result in a sound), any additional neural activity can be confidently attributed to alterations in prediction accompanying the button press. Third, the substantial time between stimuli allows for the analysis of a broad time window around the omission event. Fourth, the use of self-paced button presses introduces temporal variability, ruling out explanations that rely on low-level neural oscillators (May & Tiitinen, 2001) and eliminating the possibility of time-locked neural activity from previous trials systematically affecting the omission period.

In a follow-up study, SanMiguel et al. (2013a) tested whether distinct types of prediction – either specific or unspecific – could elicit different omission responses. Similar to SanMiguel et al. (2013c), sounds were presented with 88% of button presses during experimental conditions, while 12% of presses resulted in an unexpected omission of a sound. Two experimental conditions were employed: in the specific condition, the sound presented with the button press was always the same, resulting in an identity-specific prediction of a sound. In the unspecific condition, the sound changed on every button press, resulting in an unspecific prediction of a sound. Again, a motor control condition was implemented to determine if an omission response was elicited. SanMiguel et al. (2013a) observed an omission response in the specific condition, but not in the unspecific condition, suggesting that a specific prediction is necessary for an omission response to be elicited. This seems remarkable, as self-

generation studies have shown attenuation with both predictable and unpredictable sounds (Bäß et al., 2008), implying that the brain can employ both specific and unspecific predictions. The null result in SanMiguel et al. (2013a) for the unspecific condition would suggests that the omission response may not be sensitive to more subtle types of prediction. However, another possibility is that this study may have lacked sufficient statistical power to detect more subtle omission effects. To investigate this possibility further, this thesis includes a replication study of SanMiguel et al. (2013a).

Stekelenburg and Vroomen (2015) adopted a comparable approach to SanMiguel et al. (2013c), but expanded their investigation to include not only motor-auditory couplings, but also visual-auditory couplings. In order to facilitate the latter, participants were presented a video of two hands coming together for a hand clap, enabling them to accurately anticipate the sound based on visual cues. Interestingly, the omission responses for both motor-auditory and visual-auditory couplings were strikingly similar, which is congruent with recent frameworks that state that both motor and sensory information feed into a common prediction system (Korka et al., 2022). Given the important role of action over the course of development (see section 1.5), I chose to focus my research on motor-based couplings in this thesis. The findings of Stekelenburg and Vroomen (2015) nevertheless suggest that conclusions can likely be carried over to visual-auditory couplings. This is further supported by Van Laarhoven et al. (2017), who used visual-auditory couplings to test whether specific and unspecific predictions produce different omission responses, analogous to SanMiguel et al. (2013a). Their results seem to confirm the conclusions of SanMiguel et al. (2013a), showing that omission responses are only triggered when the identity of the upcoming sound is known. In addition to this, Van Laarhoven et al. (2017) demonstrated that the omission response disappears when the timing of the sound relative to the visual stimulus is randomized. This finding further strengthens the idea that a reliable time-locking cue, either provided by motor activity or visual information, is essential for detecting omission responses.

Predictive coding hypothesizes that predictions flow down a cortical hierarchy, where they are compared to actual input at lower, sensory levels. Prediction error in response to omission should thus elicit a cascade of responses, with initial activity in sensory areas followed by higher-level error processing. Both motor- and visual-auditory paradigms show a multistage elicitation of omission components that could be interpreted accordingly. Across studies, omissions are followed by three components, termed the omission N1 (oN1), omission N2 (oN2), and omission P3 (oP3). The oN1, emerging 80 – 100 ms after omission, is thought to reflect the low-level, sensory prediction error that results from the comparison between sensory prediction and sensory input. This component shows a distinct temporal topography and possible generators in auditory areas (SanMiguel et al., 2013a, c; Van Laarhoven et al., 2017). Next, around 150-200 ms the oN2 is elicited, showing a frontocentral topography and thought to reflect higher-level error processing (SanMiguel et al., 2013a; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). Finally, the broad centrally elicited oP3 around 240-500 ms is thought to reflect similar high-level processes as the P300 such as attention orienting and model updating (SanMiguel et al., 2013a; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). This complex sequence of omission responses, whose detection is likely facilitated by reliable time-locking of the brain activity, provides a unique opportunity to investigate prediction-related activity at multiple stages. The omission paradigm using action-effect couplings thus offers a method with a lot of potential and therefore serves as a starting point from which to further explore whether omission responses are a suitable tool to study prediction.

In summary, the omission response holds the promise of studying prediction without the interference of bottom-up input. Nevertheless, the employment of oddball paradigms in evoking these responses poses a series of practical and theoretical problems. These can be resolved using motor-auditory or visual-auditory couplings in combination with a (motor or visual) control condition, resulting in the observation of a complex omission response that is thought to reflect different stages of prediction error processing. Going forward, this approach will be further explored to gauge its suitability as a tool to study prediction.

1.5 The role of prediction during development

The study of prediction in the developing brain is increasingly relevant in the context of behavioral studies, where prediction is thought to be a driving influence of cognitive development (Emberson, 2017; Köster et al., 2020). For example, as young as 6 months, infants exhibit predictive behavior, such as looking towards the mouth when an experimenter picks up a spoon (Kochukhova & Gredebäck, 2010) or towards the ear when a phone is picked up (Hunnius & Bekkering, 2010). Additionally, numerous studies have revealed the presence of surprise in infants, indicating prediction error (see Berger & Posner, 2022 and Köster et al., 2020 for reviews). A surprise response can be detected in various ways, such as through prolonged gaze towards an unexpected outcome. For example, Spelke et al. (1992) conducted a study in which they showed infants a ball rolling over a hole in a table. In the unsurprising situation, the ball would fall through the hole, but in the surprising situation the ball would defy gravity and float over it. The infants' gaze was found to be significantly longer towards the surprising situation, indicating surprise in response to their knowledge and assumptions about gravity being challenged. Similar studies have also indicated surprise in relation to infants' numerical knowledge (e.g., Coubart et al., 2014), probabilistic intuitions (e.g., Fiser & Aslin, 2002), and theory of mind (e.g., Gergely et al., 1995).

The interplay between prediction and surprise is not only present from a young age, but also seems to play a crucial role in shaping the learning process. For example, Stahl and Feigenson (2015) presented infants with toys that either conformed to their predictions or violated them, and found that infants demonstrated a preference for the surprising toys when deciding which to continue playing with. Moreover, the way in which the toy violated the infants' predictions had a significant impact on their subsequent playing behavior, as they tested the specific beliefs that the toy had challenged, and learning regarding these toys was enhanced. The findings of Stahl and Feigenson (2015) are supported by several lines of research, showing that surprise guides behavior and shapes how knowledge is gathered from the world (Perez & Feigenson, 2022; Stahl & Feigenson, 2017; see Sim & Xu, 2019 and Stahl & Feigenson, 2019 for reviews).

The studies described above indicate a perpetual cycle that infants and children seem to engage in during development. Through a process of ongoing prediction and testing, they are continuously assessing their understanding of the world around them. When these predictions are contradicted, surprise is evoked, triggering further investigation and exploration to update and refine knowledge. This is notably similar to how predictive coding is described in adults, and suggests that understanding the maturation of the brain mechanisms involved in prediction would substantially further our understanding of how cognitive functions are shaped by experience over development.

Although there is a wealth of behavioral evidence demonstrating the central role of prediction in development, information about how these processes develop in the brain is relatively scarce. Most

studies have focused on the MMN in children and infants, showing both similarities and differences. For example, infants show a different MMN topography (Martin et al., 2003), sometimes even showing a positive mismatch response (Liu et al., 2014; Maurer et al., 2003), that is delayed compared to adults (Morr et al., 2002). Moreover, compared to adults, a larger discrepancy between sounds is needed to elicit a MMN in children (Morr et al., 2002), where in children frontal generators of the MMN seem to mature earlier than the sensory-specific system (Gomot et al., 2000). Interestingly, the emergence of the MMN can serve as a marker of certain developmental stages such as language acquisition (Cheour et al., 1998; Tremblay et al., 1998). Still, as discussed in section 1.3, the MMN is a suboptimal tool to study prediction considering the role of bottom-up input. Importantly, bottom-up input might disproportionately influence developmental populations, as auditory processing undergoes major changes from infancy until adulthood (Wunderlich & Cone-Wesson, 2006). Furthermore, bottom-up input is likely influenced by other developing functions such as attention (Wetzel et al., 2006) or memory (Sprondel et al., 2011). Of course, given the connections between top-down and bottom-up processing hypothesized by predictive coding, these immature functions might still play a role in the omission response as well. However, as the omission response can be considered purely prediction-related activity, this means that any of these influences would be relevant in the context of prediction. The omission response might therefore be especially suitable to study prediction in developmental populations.

A few recent studies have successfully employed stimulus omissions to study prediction during development. For example, Emberson et al. (2015) and Boldin et al. (2018) used functional near-infrared spectroscopy (fNIRS) in infants to show that if the visual component of an audiovisual stimulus is omitted, activity is elicited in occipital areas. Similarly, Zhang et al. (2019) showed an increased pupil dilation response, a marker of surprise, in infants when a visual stimulus was unexpectedly omitted. These studies show the potential of omission responses to study prediction-related processes in more detail, revealing the brain processes that underlie behavioral studies. However, the use of omission in developmental studies is still extremely uncommon. This thesis in fact presents the first electrophysiological omission study performed in children.

As discussed in section 1.4, an omission paradigm using a time-locking cue is likely most suited to study omission responses. This is possible by either coupling a stimulus to a motor act (e.g., button press to a sound) or to another stimulus (e.g., visual stimulus to a sound). For this thesis, I chose to study omission responses using motor couplings. This choice was mainly influenced by ongoing research that regards motor activity as central to learning and developmental processes (Berger & Posner, 2022; Copete et al., 2016; Hunnius & Bekkering, 2014; Koziol et al., 2012; Koziol & Lutz, 2013). The use of motor couplings was therefore an opportunity to contribute to this literature, showing if and how predictions are related to action in childhood. In other situations, the more passive coupling to another stimulus may be more suitable, for example when studying infants. The choice of using a motor-auditory paradigm also influenced the measured age group, where in this thesis children aged 6–8 years were measured. This age range ensured that children on the one hand were able to perform the task, and on the other hand still demonstrated an immature brain response to sounds.

1.6 Scope and research questions

Before elaborating on the scope and research questions of this thesis, I will first provide a brief overview of the topics discussed so far. I introduced the concept of predictive coding, highlighting the importance of studying prediction to understand brain function. After that, I discussed key

electrophysiological phenomena and considered them from the perspective of predictive coding. I argued that the bottom-up confounds and exogenous nature of the MMN, RS, IR, and sensory attenuation make these phenomena suboptimal to study prediction. Next, I introduced the omission response as an appropriate alternative, bypassing bottom-up input and presumably reflecting solely prediction-related activity. A review of the omission literature showed that omission responses are somewhat of an unreliable phenomenon, vanishing with increasing latencies and showing broad, unspecific effects. The use of action-effect couplings seems to solve this problem, as the time-locking effect of the action may allow for the observation of a more distinct pattern of omission responses. However, the scarce studies using such couplings seem to only show omission responses in the context of highly specific predictions, implying an insensitivity to more subtle predictions. Finally, I discussed the role of prediction during development, stressing the need to better understand these processes and the potential of an omission approach in this context.

Overall, despite the promising theoretical interpretation of the omission response, empirical evidence is lacking in some important aspects. Specifically, issues regarding the reliability and sensitivity of the omission response require further understanding to draw well-founded conclusions regarding prediction. A better understanding of such responses may be especially beneficial to understand how prediction shapes cognitive development. This brings us back to the two main positions that I will defend in this thesis, as presented at the start of this chapter:

1. *The omission response is an appropriate, reliable, and sensitive tool to study prediction;*

2. *An omission approach is especially suitable for studying prediction processes in the developing brain.*

To effectively argue in favor of these positions, some definitions have to be laid out, after which a number of research questions will be derived. Regarding the first position, the concepts of appropriateness, reliability, and sensitivity require further elaboration.

The appropriateness of the omission response to study prediction has already been discussed to some extent. That is, in contrast to other markers of prediction in the brain, the omission response is an endogenous response to prediction error that is minimally influenced by bottom-up input. Appropriateness is thus considered from the perspective of the fit between the observed phenomenon (the omission response) and the variable of interest (prediction).

The definition of reliability in this thesis is a multifaceted concept. Reliability in science has become increasingly relevant in light of the replication crisis in scientific research (Ioannidis, 2005), which has affected neuroscientific research as well. The high dimensionality of EEG and other brain imaging data, combined with relatively small sample sizes, drastically increases the probability of false reports (Szucs & Ioannidis, 2017). Replication is one of the most effective ways to confirm the robustness of an effect (Pavlov et al., 2021), and this is especially relevant for studies measuring ERPs as sample and effect sizes tend to be poor (Clayson et al., 2019). Reliability in this thesis therefore involves the ability to replicate former omission studies. However, while successful replication can confirm the reliability of an effect within a particular context, additional investigation is required to establish the reliability of the underlying phenomenon. That is, does the effect persist when modifying the context or measuring method? This can be considered a variation on simple replication of a study, and is also known as the principle of consilience (Wilson, 1998). Moreover, this approach is a strong test of the theoretical

interpretation of the omission response, enabling new insights into prediction processing in the brain. In sum, the reliability of the omission response in this thesis is defined in terms of replication, not only in the context of previous studies, but also in different contexts and using different measuring methods.

The sensitivity of the omission response in this thesis is defined as its ability to detect subtle prediction effects, as well as to indicate the magnitude of these effects. This has been introduced in section 1.4, as neither SanMiguel et al. (2013a) nor Van Laarhoven et al. (2017) found omission responses for unspecific predictions, whereas unspecific predictions do seem to be reflected in self-generation studies (Bäss et al., 2008). This would disqualify the omission response as a sensitive tool to study prediction, as it appears unresponsive to unspecific predictions. However, in both SanMiguel et al. (2013a) and Van Laarhoven et al. (2017), trends towards an omission response in the unspecific conditions seemed to be present. Increased power may thus help determine whether the omission response is also sensitive to more subtle types of prediction.

The second position states that an omission approach is especially suitable for studying prediction processes in the developing brain. Here, the word *especially* signals a particular benefit for developmental populations. This was already touched upon in section 1.5, referring to the fact that the omission response minimizes bottom-up effects of immature cognitive functions such as stimulus processing, attention, or memory.

Now that the necessary definitions have been outlined, these can be used in the further introduction of the four main research questions of this thesis. These research questions will be introduced in chronological order of occurrence in the thesis, each corresponding to one study (Chapters 3 to 6). Main research questions are divided into several sub-questions to answer different aspects of the main question. The first three studies/questions relate to the first position, demonstrating empirical evidence mainly regarding the reliability and sensitivity of the omission response as defined above. The fourth study/question relates to the second position, demonstrating the application of an omission approach to study prediction in children, and comparing responses to adults.

1.6.1 Study 1 (Chapter 3)

In **Study 1**, the omission study of SanMiguel et al. (2013a) was replicated. In the original study, button presses were coupled to either specific or unspecific predictions of a sound, where an omission response was only observed when the prediction was specific. **Study 1** was therefore particularly suitable to answer questions regarding the reliability (replication of previous omission results) and sensitivity (responsiveness to unspecific predictions) of the omission response. The main research question **Q1** was:

Q1 To what extent can specific and unspecific omission findings in the motor-auditory paradigm be replicated?

With a specific sound prediction, several omission studies (SanMiguel et al., 2013a, c; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017) observed an initial temporal oN1, followed by a frontal oN2 and central oP3 response. Therefore, sub-question **Q1a** regarding the specific condition of **Study 1** was:

Q1a Can the different components of the omission response in the specific condition be replicated?

To objectively determine the components in the omission response, principal component analysis (PCA) was used to analyze the ERP. PCA estimates the underlying components in a data-driven manner, eliminating the subjectivity involved with visual inspection of ERPs (see section 2.6 for a more detailed explanation). The hypothesis regarding **Q1a** was therefore that PCA would be able to reveal the different omission components identified by earlier omission studies in the specific condition.

To determine the sensitivity of the omission response to unspecific predictions, **Study 1** increased power by increasing the amount of participants and applying sophisticated preprocessing (see section 2.5.2). By increasing power, it could be determined whether the trends visible in SanMiguel et al. (2013a) and Van Laarhoven et al. (2017) in the unspecific condition merely reflected noise or instead reflected a true omission response. Sub-question **Q1b** regarding the unspecific condition of **Study 1** was therefore:

Q1b Are unspecific sound predictions reflected in the omission response?

An omission response in the unspecific condition would suggest that the brain can flexibly implement both specific and unspecific predictions. This would be in line with the self-generation study of Bäss et al. (2008), who show attenuation also in response to unspecific sound predictions. Together with the trends observed in earlier studies, the hypothesis regarding **Q1b** was therefore that an attenuated omission response would also be observed in the unspecific condition.

1.6.2 Study 2 (Chapter 4)

In **Study 2**, the omission response was studied in the somatosensory modality, using a similar motor-sensory paradigm as used in SanMiguel et al. (2013c). Studying the omission response in a different modality allowed for a better judgement of the reliability of the omission response, as well as a test of its theoretical assumptions. As this paradigm was not applied before in the somatosensory modality (or any other modality outside the auditory), the main research question **Q2** was:

Q2 How do motor-sensory omission responses transfer to the somatosensory modality?

Predictive coding hypothesizes that predictions flow down to sensory levels, where they are compared to actual input (see Figure 2). As the prediction of a stimulus is compared to the absence of input in sensory areas, first prediction error responses should be elicited from sensory areas. For this reason, it is assumed that the oN1 reflects sensory prediction error. If this is indeed the case, the oN1 using somatosensory stimuli should indicate somatosensory sources. Sub-question **Q2a** was therefore:

Q2a Is initial prediction error in the omission response elicited from sensory areas?

In **Study 2**, the left hand is stimulated. Considering that sensory stimulation of the left hand is processed in the right hemisphere, the hypothesis was that the oN1 topography should resemble unilateral activation of the right hemisphere. Moreover, if prediction error is elicited in the same areas responsible for stimulus processing (Bastos et al., 2012), the oN1 topography would be expected to resemble part of the stimulus-evoked response.

The oN1 is typically followed by the oN2 and oP3 responses. In auditory omission studies, these have been interpreted as higher-level responses (SanMiguel et al., 2013a; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). However, it was unknown if and how these responses would manifest in a somatosensory setting. Different elicitation compared to previous auditory studies would indicate

that these components reflect modality-specific processing, while similar elicitation would indicate modality-unspecific processing. Sub-question **Q2b** was therefore:

Q2b Is later prediction error processing modality-specific or modality-unspecific?

The processes ascribed to the oN2 and oP3 have been higher-level error detection for the oN2 (SanMiguel et al., 2013a) and attention-orienting and updating processes for the oP3 (Van Laarhoven et al., 2017). As these processes are presumably modality-unspecific, the hypothesis was that these components would be similarly elicited across auditory and somatosensory omission responses.

1.6.3 Study 3 (Chapter 5)

In **Study 3**, both motor-auditory and motor-somatosensory omission responses were measured using pupillometry. Demonstrating the omission response using a different measuring method and in different modalities is a strong indication of its reliability, especially considering the inconsistent omission findings using pupillometry in the past (Cooper et al., 1978; Damsma & Van Rijn, 2017; Stemmerding et al., 2022). Moreover, pupil dynamics are closely connected to subcortical activity (Joshi et al., 2016, 2020), to which EEG is largely insensitive, and pupillometry is a convenient method to use in future developmental studies (see e.g. Wetzel et al., 2016). The main research question **Q3** was:

Q3 How are omission responses using motor-auditory and motor-somatosensory couplings reflected in pupillary activity?

Theoretically, if the oP3 as observed in **Study 1** and **Study 2** in the ERP reflects processes similar to the P300, this implies subcortical activity that would result in pupil dilation (Nieuwenhuis et al., 2005). This would be in line with previous studies demonstrating the connection between pupil dilation and surprise (Mathôt, 2018). However, as both motor activity (Hupé et al., 2009) and surprise activity influence the pupil, it was not straightforward that the action-effect couplings as used in EEG studies could isolate surprise associated with omission in the pupil. Sub-question **Q3a** was therefore:

Q3a Can action-effect couplings be used to measure omission responses in the pupil?

The scarce number of studies that have recorded omission responses using pupillometry have shown inconsistent results, often suffering from similar problems as the omission MMN (as described in section 1.4). As action-effect couplings seem to solve these issues, the hypothesis was that this approach would result in reliable omission responses measurable using pupillometry.

Both auditory and somatosensory modalities were tested in **Study 3**. Apart from being a good test of the reliability of the omission response, this also allows for a direct comparison between modalities. Sub-question **Q3b** was therefore:

Q3b Do auditory and somatosensory omission responses in the pupil elicit similar or different responses?

As **Study 1** and **Study 2** showed similar oP3 responses between modalities, and these responses are associated with subcortical activity that influence pupil dilation, the hypothesis was that omission responses in the pupil would be similar between modalities rather than different.

1.6.4 Study 4 (Chapter 6)

To demonstrate the potential of an omission approach to study prediction in developmental populations, **Study 4** compared motor-auditory omission responses between children (6–8 years old) and adults in a paradigm comparable to **Study 1**. Including both children and adult groups enabled a direct comparison of sound and omission responses, allowing a demonstration of the specific benefits of an omission approach to study prediction in developmental populations. The main research question **Q4** was:

Q4 Are omission responses elicited in children, and how do these responses compare between children and adults?

The stimulus-evoked auditory ERP is very different in children compared to adults. As the oN1 is thought to be elicited by areas responsible for sound processing, an interesting question was how this sensory prediction error is reflected in the omission response. Therefore, sub-question **Q4a** was:

Q4a How do sensory prediction errors manifest in children compared to adults?

Given the scarcity of omission studies in children, no straightforward a priori hypotheses could be formed. On the one hand, sound processing is clearly immature in 6–8 year old children (Wunderlich & Cone-Wesson, 2006), possibly resulting in a completely different elicitation of the oN1. On the other hand, temporal components of sound processing (N1a, N1c) are relatively mature in children (Bruneau et al., 1997), and these possibly generate the oN1 (see Chapter 3). From this perspective, the oN1 could also already be relatively mature in children.

Study 4 presents the same conditions as **Study 1**, testing both specific and unspecific sound predictions. Findings from **Study 1** indicated that the omission response is also sensitive to unspecific predictions, but that these responses are attenuated compared to the specific condition. Therefore, an interesting question was whether the same pattern could be observed in children, resulting in sub-question **Q4b**:

Q4b Do specific and unspecific sound predictions have similar effects on omission responses in children compared to adults?

If prediction error is indeed a major source of learning for children, distinguishing between specific and unspecific predictions seems an important prerequisite. That is, the violation of a high confidence, specific prediction should adapt the model of the world more than the violation of a low confidence, unspecific prediction. Consequently, the hypothesis regarding **Q4b** was that a similar pattern should be observed in children compared to adults.

From the four studies in this thesis, three studies have been published (**Study 1**, **Study 3**, and **Study 4**), while one has been submitted for publication (**Study 2**). When published, the reference to the publication is included at the start of the chapter that presents the study (Chapters 3 to 6). To facilitate integration of the publications in this thesis, minor adaptations have been applied that include numbering of tables and figures and changing conceptual phrasing for congruency throughout the thesis.

Chapter 2: General methodology

This second chapter provides an overview and some necessary background of the methods used in the four studies. Some information in this chapter may be redundant in light of the chapters that follow, which offer detailed methodological information regarding their respective studies. This redundancy is deliberate, intended to offer a general, holistic impression of the methodology employed throughout the thesis.

2.1 Participants and general procedure

All data presented in this thesis were collected at the Neurocognitive Development Group laboratory, located at the Leibniz Institute for Neurobiology in Magdeburg. Written consent was obtained from all participants prior to experimentation, while in the case of child participants, parents additionally provided written consent. Furthermore, in the case of children, before giving written consent it was vocally explained that (translated from German): "I participate voluntarily and if I am tired or would like to stop doing the experiment, it is perfectly ok and we can stop." If the child consented, they would write their name at the bottom of the form that had the vocally mentioned statement written on it. Adult participants ranged from 18 to 39 years of age and child participants ranged from 6 to 8 years of age. None of the participants had a known history of neurological of psychological disorders, and none reported taking medication that affected the central nervous system. Adults were compensated through monetary payment or course credits, while children received a voucher that could be used in a children's shop. All studies were approved by the ethics committee of the medical faculty of the Otto von Guericke University Magdeburg.

2.2 Stimuli

For sound stimuli, 48 different commonly occurring environmental sounds (e.g., dog, car-horn, trumpet) rated as identifiable by an independent sample of participants were used (in 200 ms form, see Wetzel et al., 2011). Sounds were presented binaurally for 200 ms and were tapered-cosine windowed (10 ms rise- and 10 ms fall-time) and root mean square matched. For visual stimuli, in **Study 1**, **Study 2**, and **Study 3**, participants looked at a white fixation cross (0.67° × 0.67° visual angle) in the middle of either a black (**Study 1**) or grey (**Study 2**, **Study 3**) screen. In **Study 4**, participants watched a silent movie in the middle of a grey screen (10.3° × 18.9° visual angle). For somatosensory stimuli, inflatable membranes were placed on the left middle and index fingers at the volar aspect of the distal phalanx. The air pulses that inflated the membrane had a duration of approximately 40 ms.

2.3 Apparatus

All experimental sessions were performed in a dimly lit, electrically shielded and acoustically attenuated chamber, while seating in an office chair with arm rests and back support. Auditory stimuli were presented using Sennheiser HD-25 headphones. Visual stimuli were presented using a VIEWPixx-EEG display (resolution 1920 horizontal x 1080 vertical – 23.6 inch diagonal display size) that was placed at a comfortable distance of about 60 cm from the participant. Somatosensory stimuli were presented using pulses of pressurized air (3 bar) that inflated a membrane, which was controlled using a somatosensory stimulus generator (University of Münster, Germany) that was placed outside the chamber. To trigger stimuli or omissions, a custom-built button was used in order to ensure a

completely silent button press. The button used an infrared photoelectric mechanism and was additionally padded with sound absorbing material. When button presses resulted in sounds, these were presented immediately after the button press with a negligible delay. However, somatosensory stimuli had a small delay of approximately 40 ms because of the travel time of the air pulse. All experiments were programmed using Psychtoolbox (Brainard, 1997) and ran on a Linux-based system using GNU Octave.

2.4 Experimental design

Experimental designs were adapted from either SanMiguel et al. (2013a) or SanMiguel et al. (2013c). In all studies and conditions, participants were assigned a simple task of pressing a button at regular intervals, where they aimed to keep the interval between 600 to 1200 ms. The primary purpose of the button press was to mark the precise time of stimulus presentation, time-locking the prediction and therefore also the possible prediction error. The act of pressing the button results in neural responses related to motor activity. As this activity was not of interest, all experimental designs included a motor control condition that was later subtracted from the experimental conditions. In the motor control condition, the participant only pressed the button at regular intervals, never resulting in the presentation of a stimulus. Apart from the motor control condition, every study presented two experimental conditions, either a specific and unspecific condition (**Study 1**, **Study 4**), or an 88%- and 50%-condition (**Study 2**, **Study 3**).

The former design was based on SanMiguel et al. (2013a), where in both the specific and unspecific conditions 88% of button presses resulted in a stimulus, while 12% resulted in an unexpected omission. In the specific condition, an experimental block always presented the same sound with the button press, leading to an identity-specific prediction. Conversely, in the unspecific condition the sound presented with the button press was never the same. Because a sound still appeared in the majority of button presses, there should still be a sound prediction, however, this prediction was identity-unspecific.

The latter design was based on SanMiguel et al. (2013c). In the 88%-condition, 88% of button presses resulted in the presentation of a stimulus. The reliable coupling between the button press and stimulus in this condition established the prediction that a button press would trigger a stimulus, theoretically resulting in a prediction error when the stimulus was absent. In contrast, in the 50%-condition, only 50% of button presses resulted in a stimulus presentation. Since there was no reliable association between the button press and stimulus in this condition, omission of the stimulus should not elicit a prediction error. Theoretically, any significant activity in the ERP other than the motor activity can be considered prediction-related activity, which would seemingly make the 50%-condition redundant. However, potentially the mere presence of an occasional stimulus together with the button press could elicit an omission response, allowing for an explanation that excludes prediction. Hence, the comparison with the 50%-condition provided strong support that it was the prediction that caused the omission response.

2.5 Measuring EEG and pupillometry

2.5.1 EEG and its neurophysiological basis

EEG is one of the most used brain imaging techniques in neuroscience and offers a non-invasive method to study brain activity with high temporal resolution. The measurement of EEG is performed

by placing electrodes on the scalp that pick up electrical fields, where resulting signals are amplified, digitized, and recorded as EEG data. The resulting data comprises a mixture of diverse sources, such as cardiac activity, ocular activity, or external electromagnetic fields, where typically brain activity only makes up for a small portion of the signal. Nonetheless, the brain signal can in some cases be observed directly, as first demonstrated by Hans Berger who detected the alpha rhythm over occipital areas (Berger, 1929). To be able to detect more subtle brain activity, for example related to stimulus processing, the ERP method was developed (Dawson, 1951). ERPs operate on the notion that similar events elicit similar, repeatable brain activity, which is combined with randomly distributed noise to form the raw signal. To compute the ERP, similar events are repeatedly presented, and event-related activity is averaged over the multiple trials. This operation cancels out the randomly distributed noise, while preserving the brain signal associated with the event of interest. In other words, ERPs increase the signal to noise ratio (SNR) of the recorded EEG. The ERP reveals brain activity with millisecond precision, but due to volume conduction effects spatial resolution for source localizing the activity is limited (Oostenveld & Oostendorp, 2002). From a practical perspective, however, the vast majority of conclusions drawn in this field do not require high spatial precision (Cohen, 2017). EEG-detected brain activity is believed to reflect summed dendritic postsynaptic potentials of thousands to millions of geometrically aligned pyramidal cells (Lopes da Silva, 2013; Mitzdorf, 1985; Nunez & Srinivasan, 2006). The electrical signal at the scalp drops off very rapidly as the neural source is placed deeper in the brain, making EEG especially sensitive to cortical but not subcortical sources (Jackson & Bolger, 2014).

2.5.2 EEG recording and preprocessing

EEG in **Study 1**, **Study 2**, and **Study 4** was continuously recorded during the experiment at a sampling rate of 500 Hz (using Vision Recorder software, version 1.21), with an ActiChamp amplifier, and 31 (**Study 1, Study 4**) or 63 (**Study 2**) active electrodes mounted on an EEG cap (Brain Products GmbH, Gilching, Germany). Electrodes were placed according to the extended 10-20 system, where the first letters of the channel label describe the electrode locations (Fp = prefrontal; F = frontal; C = central; P = parietal; T = temporal; O = occipital) and the hemisphere is indicated by odd (left) or even (right) numbers, where z indicates midline electrodes (Chatrian et al., 1985). Additional electrodes were placed at the left and right mastoids (M1, M2) and the electrooculogram (EOG) was recorded from three electrodes placed left and right of the outer canthi of the eyes and below the left eye. The reference electrode was placed at the tip of the nose.

Data preprocessing was performed with MATLAB software, using custom-made scripts that largely consisted of functions from or related to the EEGlab toolbox (Delorme & Makeig, 2004) as well as some custom functions. EEG preprocessing always included filtering, data segmentation (i.e., epoching), artifact removal, baseline correction, and computing grand-averages. As mentioned in section 2.5.1, the ERP method is aimed at enhancing the brain signal of interest while reducing unrelated noise, where more trials result in better signal. In this thesis, the SNR of the data was further improved by filtering and independent component analysis (ICA). Choices and procedures regarding these methods differ substantially in the field, which is why some background information will be provided here.

The signal and noise in EEG data is typically disproportionately distributed among the frequencies in the data. Very high frequencies primarily contain artifactual activity such as muscle contractions or electrical noise and relatively little neural activity, whereas the proportion of neural activity in middle and lower frequencies might be substantially higher. Similarly, very low frequencies might mainly represent drifts of non-neural origin, for example caused by head movements or sweating, while

containing little or irrelevant (in the context of the studied phenomenon) neural activity. Filters benefit the SNR by exploiting this disproportionate distribution, attenuating frequencies with high noise while retaining frequencies with high signal. Theoretically this seems like a straightforward procedure, but filters inevitably impact the signal in various ways. For example, low-pass filters attenuate higher frequencies but also tend to artificially increase signal onset, decrease signal offset, reduce peak amplitude, and introduce artificial oscillations (VanRullen, 2011; Widmann et al., 2015; Widmann & Schröger, 2012). Likewise, high-pass filters that attenuate lower frequencies reduce peak amplitudes as well, and are especially prone to "leak" activity of larger later components to earlier timepoints in opposite polarity, possibly creating artificial components (see Figure 5 in Widmann et al., 2015). An example of such a filter artifact can be observed in **Study 1**, where two preprocessing pipelines were compared that use different high-pass filters. Here, the 1 Hz high-pass filter likely caused activity from the large oP3 component to artificially inflate the earlier oN2 and oN1 components. The other pipeline instead used a 0.1 Hz high-pass filter, which effectively mitigated this effect and still filtered out noise-related drifts. This 0.1 Hz high-pass filter (-6 dB, Kaiser windowed sinc FIR filter, order=8024, beta=5, transition band width=0.2 Hz) was subsequently used in **Study 2** and **Study 4**. For the low-pass filter, given that power transmission in Germany produces a 50 Hz signal, a 48 Hz filter was used that has full attenuation at 50 Hz (-6 dB, Kaiser windowed sinc FIR filter, order=402, beta=5, transition band width=4 Hz).

Filters are a powerful method to attenuate noise that is clearly separable from signal in the frequency domain. However, a proportion of the noise overlaps with typical neural frequencies and can thus not be attenuated using filters. To attenuate such noise, independent component analysis (ICA) can be applied to identify patterns in the data that are likely to be artifacts, which can then be removed from the data. The mathematical operation that ICA performs decomposes the multi-channel EEG data into a weighted linear mixture of maximally independent (assumed) sources. It is important to note that as a consequence of this operation, independent components tend to represent repeating patterns in the data. This makes ICA particularly useful to remove recurring stereotypical artifacts like eye-blinks or heart beats from the data, but incidental or highly variable sources of noise are harder to catch. ICA can greatly improve the SNR and has seen increasing adoption over the years (Chaumon et al., 2015; Jung et al., 2000; Makeig et al., 2002). One of the main challenges of ICA is determining which components should be classified as noise and thus removed from the data. Although fully automated approaches have been proposed, in order to avoid removing important neural components it has been advised that humans still make the final decision (Chaumon et al., 2015). This unavoidably leads to some subjectivity, which I tried to mitigate in two ways. First, ICA component rejection was always performed independently by two experts, who then discussed their judgements to reach a final consensus on which components to reject. Second, the experts were supported by the IClabel plugin (Pion-Tonachini et al., 2019). This crowdsourcing project uses thousands of independent component judgements from humans to train an artificial neural network to classify independent components in one of seven categories: brain, muscle, eye, heart, line noise, channel noise, or other. The IClabel plugin facilitated objectivity and helped to not miss clear noise or neural contributions.

2.5.3 Pupillometry and its neurophysiological basis

The size of the pupil changes in various situations, for example in response to light exposure or when looking at a nearby object. More relevant to cognitive researchers is that the pupil dilates in response to increased cognitive activity. Such effects have been described as early as the 18th century (Loewenfeld, 1958), but neuroscientific research has only recently been able to identify the responsible

brain circuits that give rise to this phenomenon. Starting at the eyes, pupil dilation is controlled by two main muscles in the iris: the ring-shaped iris sphincter muscle and the radial iris dilator muscle. The iris sphincter muscle serves to constrict the pupil and is innervated by the parasympathetic nervous system, while the iris dilator muscle dilates the pupil and is innervated by the sympathetic nervous system (Mathôt, 2018). Pupil dilation therefore reflects mainly subcortical activity, making it an interesting method to complement EEG, which is largely blind to subcortical activity. More specifically, pupil size has been associated with activity of the LC-NE system and the superior colliculus. For example, Murphy et al. (2014) employed simultaneous fMRI and pupillometry to show a correlation between phasic LC activity and pupil size. This phasic activity was elicited using an oddball paradigm, in which activation of the LC-NE system is thought to influence the cortical P300 as recorded using EEG (Nieuwenhuis et al., 2005). Indeed, optogenetic phasic activation of the LC in rats results in a P300-like ERP response measured from the cortex (Vazey et al., 2018). The causal influence of the LC on pupil dilation has been demonstrated in animal studies, where electric microstimulation of the LC reliably evokes pupil dilations in both monkeys and rats (Joshi et al., 2016; Liu et al., 2017). A similar influence has been reported for the superior colliculus, where microstimulation reliably evokes pupil dilation (Joshi et al., 2016; Wang et al., 2012). Because of these seemingly causal relationships, the LC and superior colliculus are thought to be key structures underlying pupil dilation, although a host of other subcortical structures could be involved as well (Joshi & Gold, 2020).

Similar to EEG, the pupil response in this thesis is averaged over multiple events to increase SNR, resulting in an event-related average called the pupil dilation response (PDR). The advantage of pupillometry over EEG is that the SNR of the raw data is substantially better for pupil data. This results in a decrease of the required number of trials and consequently a decrease of experiment duration (Wetzel et al., 2016). Additionally, pupillometry offers a number of other advantages, such as ease of preparation, absence of head-attached equipment, increased freedom of movement, and costs. On the other hand, there are some limitations as well. Most notably, the pupil responds to a great variety of factors, which all converge into a single measurement. This makes it hard to isolate specific cognitive effects in the brain. Additionally, as pupil dilation is a measure of muscle activity, it is only an indirect measure of neural activity and offers limited temporal resolution for decoding underlying brain signals (Joshi & Gold, 2020).

2.5.4 Pupillometry recording and preprocessing

In **Study 3**, pupillometry was used to study omission responses. This was done using an infrared EyeLink Portable Duo eye-tracker (SR Research Ltd., Mississauga, Ontario, Canada), set up in remote mode at a sampling rate of 500 Hz. Compared to EEG preprocessing, pupil data preprocessing consists of considerably fewer steps. The main artifacts that are corrected for are blinks and eye saccades, both using a combination of software provided by the eye-tracker as well as custom functions. Details regarding this process can be found in section 5.2.4.

2.6 Principal component analysis to analyze ERPs

The data matrix resulting from an EEG experiment is inherently complex, typically consisting of sampling points × participants × electrodes × conditions. The traditional analysis strategy for such a matrix consists of plotting subsets of the data, for example subsets of electrodes and conditions, and visually inspecting whether differences are present. If a difference appears present, sampling points

are chosen based on subsequent visual inspection for further statistical testing, resulting in the conclusion of either a statistically significant difference or not.

There are two major problems with this approach (described in more detail in Scharf et al., 2022). The first problem is that this approach does not meet the standards of good scientific practice, and therefore demonstrably leads to results that in reality often do not exist. The visual inspection of differences between ERP waves can be considered equivalent to performing uncorrected *t*-tests on each sampling point. Combined with repeated visual inspection of other subsets of the data matrix, the probability of Type I error compounds rapidly. Luck and Gaspelin (2017) therefore estimate that using this approach, the probability of obtaining at least one non-existing effect exceeds 50% in many ERP experiments. Using visual inspection to analyze ERPs therefore contributes heavily to unjustified inferences, exacerbating the problems concerning the replication crisis as discussed in Chapter 1.

The second problem with this approach derives from the fact that the observed ERP signal is a mixture of underlying signals in the brain. Consequently, any voltage measurement from the scalp is likely to be influenced by multiple sources with distinct spatial and temporal activations, rendering the signal peaks a poor indicator of the underlying components. This is aptly illustrated below in Figure 3 that is taken from Scharf et al. (2022). These simulated ERPs show the average reaction to two events (i.e., conditions) under three distinct scenarios, with the ERP resulting from two underlying components (red lines). In all scenarios, Event 1 is characterized by a more negative response of the first component and a more positive response of the second component, while Event 2 exhibits the opposite pattern, with a more positive response of the first component and a more negative response of the second component. In scenario A, this pattern can easily be observed by looking at the peaks of the resulting ERP wave (top row of Figure 3), as there is only mild overlap between the two components. However, issues arise when overlap between components is increased, as is the case in scenarios B and C. In scenario B, the negative and positive peak suggest that two distinct components are present, but relying solely on peaks in the signal would result in a severe bias regarding component latencies and amplitudes. In scenario C, the ERP consists of a single broad peak instead of two, where relying solely on peaks in the signal would result in inaccurate conclusions regarding the number of underlying components as well as the differences between events. Visual inspection of the ERP signal thus not only contains the risk of identifying effects that do not exist, but also of misinterpreting genuine effects.

To address these issues, data-driven methods are required that explicitly acknowledge the ERP as a mixture of underlying signals. In this thesis, temporal PCA is used for this purpose. PCA is a factor-analytic method that aims to decompose the observed signal into a set of underlying factors, summarizing sampling points with a similar activity pattern across participants, electrodes, and conditions (Scharf et al., 2022). The factors resulting from a PCA are, in the best case, estimates of the true underlying components. As an example, see in Figure 3 the comparison between the true underlying components in the middle row and the factors resulting from a PCA in the bottom row. It must be noted that the decomposition is not always successful in disentangling all underlying components, and the degree of success is partly dependent on certain parameters and methods choices in the PCA. Given the rapidly evolving knowledge in this field, it is hard to determine optimal choices, and optimal choices might only be possible in the context of the data (Scharf et al., 2022). For this reason, slight variations exist among the studies in this thesis regarding the determination of the number of factors and the selection of the rotation method to optimize the rotation criterion. Although

such modifications may slightly influence the results, they are unlikely to significantly impact the primary conclusions (see, e.g. Scharf & Nestler, 2019 for a systematic analysis of rotation methods, and Braeken & Van Assen, 2017 for a systematic analysis of dimensionality assessment).

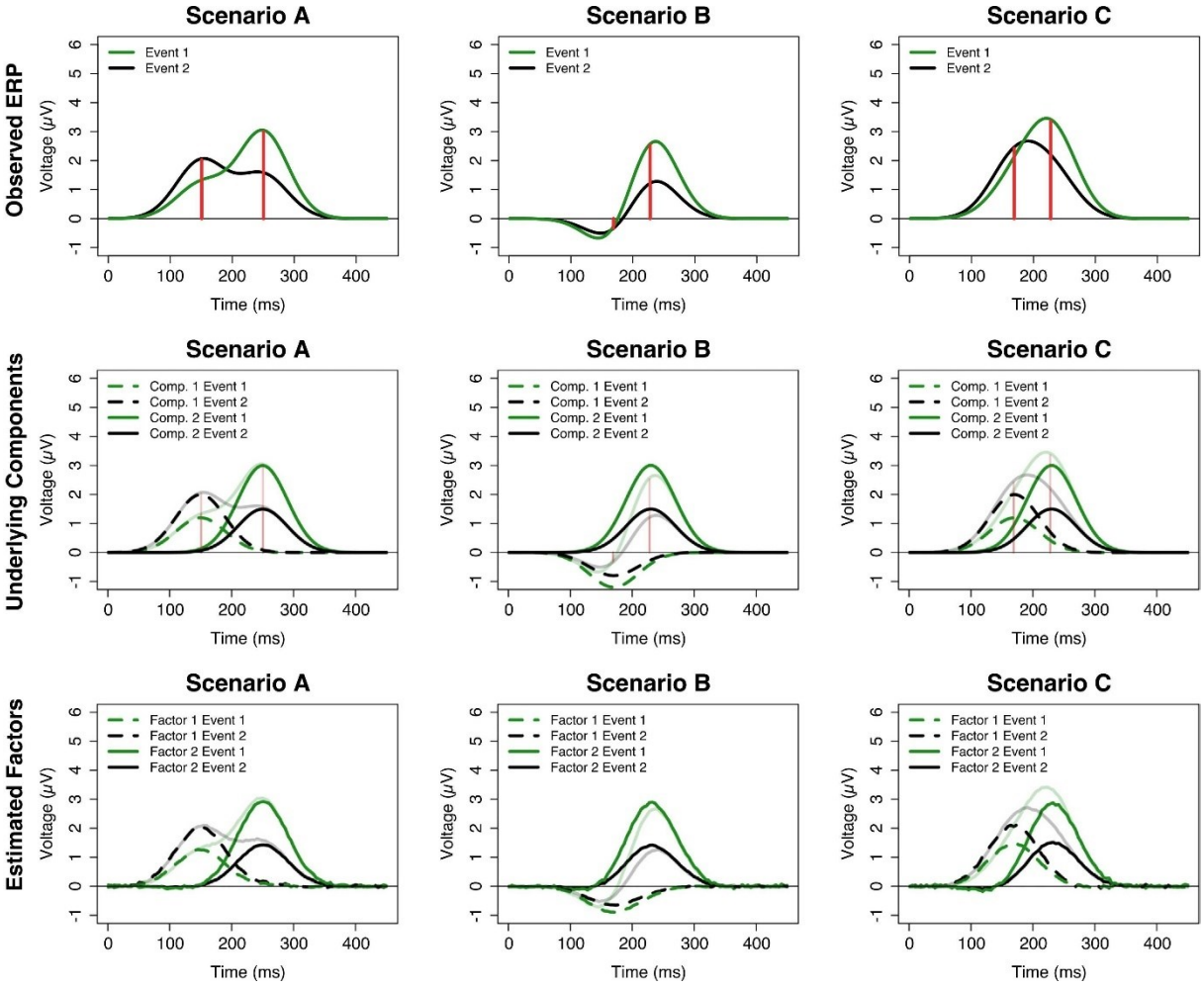

Figure 3: The problem with interpreting peaks in the ERP and the solution offered by temporal PCA, from Scharf et al. (2022, p. 3). Simplistic, simulated ERPs show three scenarios with mild (A) and severe (B & C) temporal overlap of the underlying components. The upper row depicts the ERPs "elicited" by two events (black and green lines). Vertical red lines mark the true peak of the underlying components shown in the middle row. The lower row depicts the factors estimated by the temporal PCA approach. The estimated factors (lower row) resemble the underlying components (middle row) well.

As a final remark, it should be mentioned that although in this thesis the label "PCA" is used, technically the algorithm estimates an exploratory factor analysis (EFA). Because differences between PCA and EFA estimates are negligible (see Scharf et al., 2022, footnote 11) and the term PCA is dominant in the field, I have opted to keep referring to PCA while keeping this technicality in mind.

2.7 Statistical analyses

This thesis adopts a primarily Bayesian approach to statistics. Within the Bayesian framework, no special status is assigned to either the null or alternative hypothesis, but rather the performance of the competing models is evaluated, and preference is given to the model capable of generating the most precise sequence of sequential forecasts (Wagenmakers et al., 2006). A useful consequence of this approach is that Bayesian statistics can indicate evidence in favor of the null hypothesis. This thesis uses Bayesian counterparts to the frequentist *t*-test and ANOVA, resulting in a Bayes Factor (BF_{10}) to indicate which model is best supported. If the BF_{10} is larger than 1, it suggests evidence in favor of the

alternative hypothesis, and if smaller than 1, in favor of the null hypothesis. The BF_{10} is easy to interpret, for example a BF_{10} of 10 indicates that the observed data is 10 times more likely to occur under the alternative hypothesis compared to the null hypothesis.

Apart from its straightforward interpretation and ability to indicate evidence in favor of the null hypothesis, the BF_{10} can also reveal that neither of the hypotheses is particularly convincing (typically defined as a BF_{10} between 0.33 and 3; Lee & Wagenmakers, 2013). This can be problematic using frequentist statistics, where data unlikely under the null hypothesis may lead to its rejection, even though these data are just as unlikely under the alternative hypothesis (Wagenmakers et al., 2018). Generally, an inconclusive BF_{10} indicates the need for more data. A concrete example of this can be found in **Study 1**, where the Bayesian analysis of the effects in the original study showed that there was no convincing evidence in favor or against an effect in the unspecific condition. In the original study (SanMiguel et al., 2013a), frequentist statistics were used that indicated that the null hypothesis should not be rejected, leading to the conclusion that there was no omission effect in this condition. However, **Study 1** shows that if Bayesian statistics had been used instead, it would have been clear that further data was needed to draw convincing conclusions.

Finally, Bayesian statistics are especially suitable for updating beliefs based on prior observations. **Study 1** leveraged this characteristic by utilizing two specialized statistics: the Replication Bayes Factor (BF_{r0}) and Effect Size Bayes Factor ($EES\ BF_{10}$). These statistics are specifically designed to determine the presence or absence of effects in replication studies, taking into account both the original and replication data (Verhagen & Wagenmakers, 2014).

Although main conclusions were drawn on the basis of Bayesian statistics, frequentist statistics were reported as well in all studies. This was done to keep the statistics accessible and convincing to readers unfamiliar with or sceptic towards Bayesian statistics. Statistical analyses were performed using R (R Core Team, 2014) and JASP (JASP Team, 2021).

Chapter 3: Study 1

OMISSION RELATED BRAIN RESPONSES REFLECT SPECIFIC AND UNSPECIFIC ACTION-EFFECT COUPLINGS

The present chapter is based on the following publication:
Dercksen, T. T., Widmann, A., Schröger, E., & Wetzel, N. (2020). Omission related brain responses reflect specific and unspecific action-effect couplings. *NeuroImage*, *215*, 116840.

Abstract

When an auditory stimulus is predicted but unexpectedly omitted, an omission response can be observed in the EEG. This endogenous response to the absence of a stimulus demonstrates the important role of prediction in perception. SanMiguel et al. (2013a) showed that in order to observe an omission response, a specific prediction concerning the identity of an upcoming stimulus is necessary. They used button presses coupled to either a single sound (predictable identity), or a random sound (unpredictable identity). In the event-related potentials, a sequence of omission responses consisting of oN1, oN2, and oP3 was observed in the single condition but not in the random condition. Given the importance of omission studies to understand the role of prediction in perception, we replicated this study. We enhanced statistical power by doubling the sample size and adjusting data pre-processing, and applied temporal principal component analysis and replication Bayes statistics. Results in the single sound condition were successfully replicated. Principal component analysis additionally revealed attenuated oN1 and oP3 omission responses in the random sound condition. These results suggest the existence of both specific and unspecific predictions along the sound processing hierarchy, where precision weighting possibly influences the strength of prediction error. Results are discussed in the framework of predictive coding and are congruent with everyday life, where uncertainty often requires broader or more general predictions.

3.1 Introduction

Our actions often result in predictable sensory consequences. For instance, when ringing a doorbell, the press of the doorbell bears the predictable sensory consequence of a ringing sound. This kind of sensorial predictability plays a central role in perception. Predictive coding and related theories suggest that the brain generates predictions of expected sensory input, which are sent down a cortical hierarchy (Clark, 2013; Feldman & Friston, 2010; Rao & Ballard, 1999). At the expected moment – for example when a doorbell is pressed – predicted sensory input is compared to actually encountered sensory input. Where prediction does not match actual input, a prediction error is generated that flows up the cortical hierarchy, adjusting models on cortical levels in order to make better predictions in the future (Friston, 2005). Central in the current study is the case of stimulus omission, i.e. when a prediction does not meet any sensory input, which in our example is best illustrated by pressing a broken doorbell. In this case, the unexpected lack of auditory input, where a prediction of a sound was present, should elicit a prediction error response. The observed electrophysiological omission response is thought to reflect this prediction error (Schröger et al., 2015; Wacongne et al., 2011).

Auditory prediction error is traditionally studied by presenting a rare deviant ("oddball") sound that cannot be predicted upon the regularity established within a sequence of frequent sounds; deviants elicit the Mismatch Negativity (MMN) component of the event-related potential (ERP; Näätänen et al., 2007). In auditory omission studies, the deviant is an unpredicted absence of a sound. Several studies have demonstrated neural responses to sound omission, consisting of early and later ERP components (SanMiguel et al., 2013a, c; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017; Wacongne et al., 2011; Yabe et al., 1997, 1998). This response is only observed when a prediction about the upcoming stimulus is present (SanMiguel et al., 2013c) and has been interpreted as a cascade of prediction error propagating from lower to higher levels through the cortical hierarchy (Wacongne et al., 2011). The absence of bottom-up input makes omission paradigms powerful evidence in support of prediction-based theories of brain function (Heilbron & Chait, 2018; Schröger et al., 2015), as only theories that include prediction can straightforwardly explain these responses. Although omission responses have shown to be rather variable across studies (Heilbron & Chait, 2018), several studies demonstrate that timing cues and the specificity of predictions are important factors influencing its occurrence.

SanMiguel et al. (2013a, c), Stekelenburg and Vroomen (2015), and Van Laarhoven et al. (2017), reliably show omission responses in paradigms where precise temporal information is available about the supposed onset of a stimulus. In the two studies of SanMiguel et al., 2013a, SanMiguel et al., 2013c, and in Stekelenburg and Vroomen (2015), this was achieved by coupling auditory stimuli to the press of a button. Subsequently, Stekelenburg and Vroomen (2015) and Van Laarhoven et al. (2017) show that the visual display of a handclap can also function as a timing cue in order to observe an omission response. Van Laarhoven et al. (2017), by manipulating the timing onset, confirm that a precise prediction regarding the timing of stimulus onset is crucial in order to detect an omission response in the ERP.

Apart from being able to predict "when" a stimulus is presented, Bendixen et al. (2009) show that being able to predict "what" is presented is also a crucial factor influencing whether an omission response is observed. Presenting series of sounds where every other sound was a repetition of its predecessor, omission of the repeating sound yielded ERP responses similar to the sound ERP. In contrast, omission in an unpredictable series of sounds did not show such a response. A modelling

study of Friston and Kiebel (2009a) showed that such responses are to be expected, as a prediction of the specific sound – possibly propagated through deeper layers into primary sensory areas - elicits a prediction error response generated in superficial layers of these areas. While the study by Bendixen et al. (2009) focused on early omission responses, SanMiguel et al. (2013a) and Van Laarhoven et al. (2017) also considered later responses. These studies reveal a complex omission response consisting of an oN1, oN2 and oP3 component only when the identity of the upcoming sound was predictable (single sound condition). Here, oN1 has been discussed to reflect the difference between sensory prediction and sensory input (Van Laarhoven et al., 2017), where the subsequent oN2 and oP3 have been interpreted to represent higher-order processes or prediction errors (SanMiguel et al., 2013a, c; Van Laarhoven et al., 2017; Wacongne et al., 2011). In contrast to this condition, no omission components were observed when the sound changed on every trial (random sound condition), leading to the conclusion that an identity specific prediction is necessary in order to elicit a prediction error. Recent fMRI and MEG decoding studies support this finding, showing activation of a sensory template in omissions where an identity specific prediction was present (Berlot et al., 2018; Demarchi et al., 2019; Kok et al., 2017).

Contrary to these studies, research on N1-attenuation reveals a system that is flexible in terms of both timing and identity. Studies show that when a sound is self-generated by a button press, the N1 of the evoked potential is attenuated compared to externally generated stimuli also when timing and identity cannot be exactly predicted (Bäß et al., 2008; Bednark et al., 2015). Similar to omission studies, sensory prediction is thought to give rise to this effect. The flexibility regarding timing and identity in N1 attenuation studies strongly contrasts the rigid prediction model described by omission studies. Furthermore, a flexible model seems to better fit situations encountered in everyday life, where sensory consequences of actions are often only broadly predictable. For example, when putting a cup on a table, a prediction can be formed that some sound will occur, but characteristics of the cup, the table, or to what degree the cup is filled (among many others) inevitably lead to significant variations of the resulting sound. In terms of predictive coding, one could question the importance of prediction if its role is limited to cases with exact foreknowledge of “what” and “when”. SanMiguel et al. (2013a), in discussing their findings, also hypothesized that – based on previous literature – at least the N2–P3 complex would be expected in the random condition, as the surprising absence of a stimulus would trigger higher-order evaluation and cognitive control processes.

Apart from N1-attenuation studies, based on the predictive coding concept of precision weighting an oN1 effect would also be expected when sound identity is unpredictable. Precision weighting entails that uncertainty in predictions is reflected in the weight that is attributed to the corresponding error units (Feldman & Friston, 2010). Because of this weighting, highly precise predictions elicit large prediction errors when violated, whereas lower precision attenuates prediction error. The conditions in the study of SanMiguel et al. (2013a) can be interpreted as a manipulation of precision, as the single condition enables a highly precise prediction (predictable sound identity), and the random condition only allows an imprecise prediction (unpredictable sound identity). This would result in a strong oN1 in the single condition, as observed in earlier studies (SanMiguel et al., 2013a; Van Laarhoven et al., 2017), but should also result in an attenuated oN1 in the random condition.

Because of the discrepancy between N1-attenuation studies and the oN1 in omission studies with respect to the importance of the predictability of “what” information, and because of the important role of omission effects for predictive coding theories, a rigorous replication of an omission study is

warranted. The current study aimed to replicate the experiment done by SanMiguel et al. (2013a), as it combines omission and identity specific and unspecific effects, and has shown to be a robust paradigm (Van Laarhoven et al., 2017), making it highly interesting for predictive coding. Collecting data from double the amount of participants, and adapting several preprocessing and analysis steps, we expected the current study to have higher statistical power than the original study. This is especially important in analyzing omissions in the random condition, where based on N1-attenuation studies and precision weighting mechanisms an effect would be expected. With these changes, we expected that in the current study we would be able to determine whether omission responses in the random condition were either absent (including Bayesian statistics allowing to evaluate the support of the data for the null hypothesis not reported in the original study) or perhaps only diminished compared to the single condition. This would imply a system of prediction that is more flexible than previous omission studies indicate. Finally, we expected to replicate the observed omission components in the single condition, as well as the higher amplitude omission responses in the single compared to the random condition.

It is often unclear to what extent a replication attempt results in a success or failure. In order to quantify the replication success of the effects in this study compared to the original study, we use the Replication Bayes Factor developed by Verhagen and Wagenmakers (2014). This test indicates support either for the hypothesis that effects in the replication study are similar (or larger) to the original study, or for the hypothesis that no effect was observed. In order to do this, the original study's posterior is used as an informed prior from which to update beliefs about the effect.

3.2 Material and methods

3.2.1 Participants

EEG and behavioral data was acquired from 31 participants. One participant was excluded because of repeatedly falling asleep during the experiment. The remaining participants (10 female; age range: 18–39; mean age: 25, SD = 5 years; all right handed as measured by an adapted German version of the Oldfield Scale; Oldfield, 1971) reported normal hearing, and gave written consent prior to the experiment. Compensation for participation was either financial or in the form of credit points. The project was approved by the local ethical committee.

3.2.2 Stimuli

Sound stimuli consisted of 48 different common environmental sounds (e.g. dog, car-horn, trumpet) rated as identifiable by an independent sample of participants (Wetzel et al., 2011). Identical to SanMiguel et al. (2013a), sounds were tapered-cosine windowed (10 ms rise- and 10 ms fall-time), root mean square (RMS) matched and presented binaurally. Loudness was set at 80.5 dB SPL for all participants (in SanMiguel et al. (2013a), loudness was set individually to a comfortable level before the experiment and thus not controlled). During the experiment, participants focused on a white fixation cross (0.67° × 0.67° visual angle) in the middle of a black screen, at a distance of approximately 60 cm from their eyes.

3.2.3 Apparatus

Participants were seated in a dimly lit, electrically shielded and acoustically attenuated chamber, while EEG was continuously recorded. The experiment was programmed using Psychtoolbox (version 3.0.15; Brainard, 1997) and ran on a Linux-based system using GNU Octave (version 4.0.0). Auditory stimuli

were presented using Sennheiser HD-25 headphones. Visual stimuli were presented using a VIEWPixx-EEG display (resolution 1920 horizontal x 1080 vertical – 23.6 inch diagonal display size). In SanMiguel et al. (2013a), participants wore soft-foam earplugs to silence sounds generated by the button presses. To ensure that our button did not make any sound when pressed, a custom-built infrared photoelectric button was used that was additionally padded with sound absorbing material. The button was connected to the stimulus computer using an RTbox (Li et al., 2010).

3.2.4 Task and procedure

The methods section of SanMiguel et al. (2013a) was leading in the design of the experiment. Participants sat in front of a screen, having their right index finger on a button. In every condition, a button was pressed every 600–1200 ms. Two distinct sound conditions (single sound, random sound) and a motor control condition were presented. In the sound conditions, a button press resulted in a sound 88% of the time, where the remaining 12% of trials were unexpectedly omitted. Sound blocks had 198 sound trials and 29 omission trials, and motor control blocks had 200 trials. Omissions were randomly placed, under the restricting conditions that the first five trials of every block were always sound trials, and every two trials following an omission were always sound trials. In the single sound condition, the same sound was presented in all sound trials of the block. Different sounds were used as the single sound in separate blocks, where all 48 sounds were balanced across participants. In the random sound condition, sounds changed on every trial. To be able to subtract the neural activity related to the pressing of the button, a no-sound motor control condition was included in which no sound was presented with the button press. Starting the experiment, a short training block was completed where participants attempted to press the button every 600–1200 ms. Feedback was presented visually after every button press, displaying the number of milliseconds that was in between the last button presses. No sounds were presented in the training block. The experiment included 17 experimental blocks (3 motor condition, 7 single sound condition, 7 random sound condition). The order of blocks was pseudorandomized in three parts. In the first part one no-sound motor control block, three single and three random sound condition blocks were randomly presented. In the following two parts, one no-sound motor control block, two single and two random sound condition blocks were randomly presented in each part. Blocks were approximately 3 min long. A total of 1386 sound trials and 203 omission trials were performed for each sound condition, and 600 trials were performed as no-sound motor control. Total experiment time was about 80 min including breaks. These procedures are the same as in SanMiguel et al. (2013a), with two exceptions: in the original study, participants sat 100 cm away from the screen (60 cm in the current study), and used their thumb (instead of index finger in this study) to press the button.

3.2.5 Data recording

EEG was recorded from a total of 31 active electrodes, placed according to the extended international 10–20 system at the following positions: FP1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, Oz, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, FP2, and the left (M1) and right (M2) mastoids. Furthermore, EOG was recorded from three electrodes placed left and right of the outer canthi of the eyes and below the left eye. The reference electrode was placed on the tip of the nose. A BrainAmp MR amplifier was used, recording at 500 Hz using Vision Recorder software (version 1.21).

3.2.6 EEG data preprocessing

EEG data analysis was performed with MATLAB software using the EEGLAB toolbox (Delorme & Makeig, 2004). Two preprocessing methods were used to analyze the data. One method that replicates

the preprocessing used in SanMiguel et al. (2013a), and one method using recently developed techniques (in particular independent component analysis (ICA) based removal of eye artifacts) and parameters to optimize data quality. Especially the 1 Hz high-pass part of the bandpass filter that was used in the original study may have distorting effects on the results. Because of this filter, large later effects can non-causally influence earlier effects (Acunzo et al., 2012; Widmann et al., 2015).

Replicating SanMiguel et al. (2013a), first the EEG was bandpass filtered offline from 1 to 100 Hz (windowed sinc FIR filter, Kaiser window, Kaiser beta 5.653, filter order 908). Then, regression-based eye-movement correction was done following Schlögl et al. (2007), and a 25 Hz low-pass filter was applied (25 Hz lowpass, windowed sinc FIR filter, Kaiser window, Kaiser beta 5.653, filter order 908). Data was segmented into epochs starting 200 ms before, and ending 500 ms after button press. All trials outside the 600–1200 ms button-press time limit were excluded. Remaining artifacts were rejected by applying a 75 µV maximal signal-change per epoch threshold. Also, the first five trials of each block, and the two trials following an omission were excluded from analysis. The average number of trials per subject used for each condition was: 484 trials (SD = 102, range = 173–574) for motor condition, 163 omission trials (SD = 42, range = 37–200) for single sound condition, and 166 omission trials (SD = 42, range = 47–199) for random sound condition. As in SanMiguel et al. (2013a), no baseline correction was applied.

For the second analysis, data was filtered offline with a 0.1 Hz high-pass filter (Kaiser windowed sinc FIR filter, order = 8024, beta = 5, transition bandwidth = 0.2 Hz) and a 48 Hz low-pass filter (Kaiser windowed sinc FIR filter, order = 402, beta = 5, transition bandwidth = 4 Hz). Data was segmented into epochs starting 200 ms before, and ending 500 ms after button press. All trials outside the 600–1200 ms button-press time limit were excluded. Noisy channels were removed from the data, which were defined as having a robust z-score of the robust standard deviation larger than 3 (Bigdely-Shamlo et al., 2015). These channels were removed from analysis and interpolated after ICA. Epochs exceeding a 600 µV signal-change threshold were removed (in order to remove large non-stereotypical artifacts but to keep stereotypical artifacts as blinks and eye-movements to be later removed using ICA). ICA was performed to correct for artifacts. In order to improve decomposition, this was done on raw data that was 1 Hz high-pass filtered (Kaiser, order = 1604, beta = 5, transition bandwidth = 1 Hz) and 48 Hz low-pass filtered (same as above), after which the data was segmented −200 to 500 ms around the button press. The same channels and trials were removed as was done in the previous step. The obtained demixing matrix was subsequently applied to the 0.1–48 Hz filtered data. Artifact ICs were detected with support of the IClabel plugin (Pion-Tonachini et al., 2019). Two independent raters judged components, aiming to remove all heart and eye-related components (blinks, horizontal and vertical movements of the corneo-retinal dipoles and pre-saccadic spike potentials). Selected components were then discussed to come to a final judgement of components to be removed. Each epoch was baseline corrected by subtracting the mean amplitude of the −200 to −100 ms window preceding stimulus onset. This interval was chosen in order not to introduce pre-stimulus motor activity into the analysis. Finally, the first five trials of each block, the two trials following an omission, and trials that exceeded 125 µV signal-change per epoch were excluded from analysis. The average number of trials per subject used for each condition was: 547 trials (SD = 43, range = 404–585) for motor condition, 186 omission trials (SD = 17, range = 131–203) for single sound condition, and 189 omission trials (SD = 18, range = 125–202) for random sound condition. Individual ERPs were computed for each condition and every participant.

3.2.7 ERP replication analysis

In order to determine prediction related activity, omission ERPs in the two sound conditions (single, random) were compared with the no-sound motor control condition. If time-locked neural activity is present in addition to the neural activity related to pressing the button, this activity is considered to be prediction related. Subsequently, omission ERPs of the two sound conditions were compared to determine if prediction related activity differs between the two conditions. The study of SanMiguel et al. (2013a) and other omission studies (SanMiguel et al., 2013c; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017) show an oN1, oN2, and oP3 response to auditory omission of sound with predictable timing and identity.

In this analysis replicating the original experiment (replication analysis), ERPs were computed from the data that was preprocessed following the original study. Time-windows were identical to the original study for oN1 (42–92 ms), oN2 (144–164 ms), and oP3 (278–356 ms). The original study defines three regions of interest (ROIs): left temporal (FT7, FC5, T7, C5), frontocentral midline (Fz, FCz, Cz) and right temporal (FC6, FT8, C6, T8). As 31 electrodes were used in the current study (opposed to 64 in the original), missing electrodes were interpolated. These were: FT7, FT8, C5, C6, FCz. Statistical analyses of all components were carried out on the mean amplitude of the component time windows, averaged over ROI.

3.2.8 PCA

The second analysis used temporal PCA to analyze ERPs. These analyses were performed on data from an adapted preprocessing pipeline compared to the original study, which is described in the second part of section 3.2.6. In order to analyze distinct aspects of the data, two PCAs were performed using the MATLAB-based ERP PCA toolkit (Dien, 2010). Both PCAs used Promax rotation ($\kappa = 3$) with a covariance relationship matrix and Kaiser weighting. The number of components to be retained was determined using Horn's parallel test (as implemented in the toolkit). First, the omission-PCA focused on the analysis of the omission components (oN1, oN2, oP3), and was computed on the individual averages of the motor control, single sound omissions, and random sound omissions. Second, a sound-PCA was done to compare sound elicited N1 topographies to oN1 topographies from the omission-PCA. This analysis was computed on the individual averages of the motor control, the single sounds, and the random sounds. No subsequent statistical analysis was performed on the results of the sound-PCA. Based on the topographies of the separate components, distinct ROIs were defined for statistical testing. For oN1 using temporal electrodes: T7, CP5, T8, CP6. For oN2 and oP3-3 using frontal electrodes: F3, F4, Fz, FC1, FC2. For oP3-1 using fronto-central electrodes: Fz, FC1, FC2, Cz. For oP3-2 using centro-parietal electrodes: Cz, CP1, CP2, Pz.

3.2.9 Statistical analyses

Because in the original study no significant conclusions were drawn regarding ROI, regions were pooled together for simplicity. For oN1 temporal ROIs were pooled together, after which paired, two-tailed *t*-tests were performed testing for prediction effects (single omission (SO) vs. motor control (M)/random omission (RO) vs. motor control (M)) and effects between sound conditions (SO vs. RO). Equivalent Bayesian *t*-tests were performed. For oN2 paired, two-tailed *t*-tests were performed on fronto-central electrodes, testing for prediction effects (SO vs. M/RO vs. M) and effects between sound conditions (SO vs. RO). Equivalent Bayesian *t*-tests were performed. For oP3 temporal and fronto-central ROIs were pooled together, after which paired, two-tailed *t*-tests were performed testing for prediction

effects (SO vs. M/RO vs. M) and effects between sound conditions (SO vs. RO). Equivalent Bayesian *t*-tests were performed.

Statistical testing of PCA components was done using both frequentist and Bayesian statistics. For the omission-PCA, selected components were tested using paired, two-tailed *t*-tests separately testing for differences between conditions (SO vs. M, RO vs. M, SO vs. RO) in the ROIs defined in section 3.2.8. Equivalent Bayesian *t*-tests were performed (SO vs. M, RO vs. M, SO vs. RO) in R using the BayesFactor package (Morey & Rouder, 2018). The null hypothesis corresponded to a standardized effect size $\delta = 0$, while the alternative hypothesis was defined as a Cauchy prior distribution centered around 0 with a scaling factor of $r = 0.707$ (the default "medium" effect size prior scaling). To mitigate the problem of subjectivity of the selection of an appropriate prior a sensitivity analysis of the effect size prior scaling parameter *r* was performed for all Bayesian tests and included in the supplementary data (section 3.8). The analysis shows no different conclusions as a result of the effect size prior being $r = 0.707$, $r = 1$, or $r = 1.414$ ("medium", "wide", and "ultrawide" effect size priors in the BayesFactor R package). Bayes Factors were interpreted following Lee and Wagenmakers (2013), who give the labels anecdotal (0.33–3), moderate (3–10 or 0.33–0.1), strong (10–30 or 0.1–0.033), and very strong (>30 or <0.033) for specific ranges of the Bayes Factor. We replaced the label "anecdotal" with "weak", and "very strong" with "decisive" to aid interpretation. Analyses were conducted using R 3.6.1 for frequentist statistics and Bayesian statistics. Statistical tests were not corrected for multiple comparisons.

SanMiguel et al. (2013a) did not report Bayesian statistics. In order to compare (Bayesian) results between studies, *F*-values from the original study were converted to *t*-values, after which the Bayes factor was computed using the *t*-value, sample size and *r* scale = 0.707 (as demonstrated in Rouder et al. (2009), using the BayesFactor package in R (Morey & Rouder, 2018)).

3.2.10 Replication Bayes Factor

To properly judge to which extent replication of the effects in the current study was successful, Verhagen and Wagenmakers (2014) developed a method using Bayesian statistics. This method can answer whether the observed effect in the current study is similar to the effect that was found before, or that it is absent. It achieves this by using the posterior distribution of the original study as a prior from which to update beliefs. Subsequently, the resulting Bayes Factor reflects the idealized belief about the existence of the effect after observing results of the original and current study. This result is the Replication Bayes Factor (BF_{r0}), where a number below one indicates support for the skeptic's hypothesis (there is no effect) and a number above one indicates support for the effect found in the original study. The results of the original study and the current replication analysis pipeline are used to compute the BF_{r0}. The code of Verhagen and Wagenmakers (2014) additionally computes the Effect Size Bayes Factor (*EES* BF_{01}) to test for equality of effect sizes across the two studies. Here, a number below one indicates support for unequal effect sizes, while a number above one indicates support for equal effect sizes. Note that for consistency purposes with the Replication Bayes Factor, in which a number above one represents replication success, Verhagen and Wagenmakers (2014) choose to report the equal effect sizes Bayes Factor as *EES* BF_{01} instead of *EES* BF_{10}. As the code of Verhagen and Wagenmakers (2014) requires *t*-values as input, *F*-values of the ANOVA main effects were transformed into *t*-values to be able to run the code. Only main effects were tested, as no significant conclusions were drawn from interaction effects.

3.3 Results

In this paradigm, physically identical stimuli (a silent button press) are compared in conditions that manipulate the prediction that is paired with the button press. As the motor control condition should be free of auditory prediction, any activity additional to the no-sound motor response is considered prediction related activity. Subsequently, to determine whether prediction-related activity is stronger in the single compared to the random condition, omission responses from single/random conditions are compared directly. ERP waves and topographies of the replicated preprocessing pipeline are shown in Figure 4. ERP waves of the adapted preprocessing pipeline, as well as PCA components and topographies, are displayed in Figure 5.

Participants had no significant problems maintaining a stable pace between button presses throughout the experiment. Where participants aimed to press the button every 600–1200 ms, group averages show time between button presses to be 922 ± 103 ms (SD) in single sound, 903 ± 100 ms in random sound, and 929 ± 92 ms in motor condition. A repeated measures ANOVA showed no significant differences between conditions ($F_{(2,58)}$=1.971, p=0.15). A Bayesian repeated measures ANOVA showed moderate evidence against a difference between conditions (BF_{10}=0.32).

Table 1: Summary of the statistical results based on the replicated data preprocessing pipeline. Conditions where we did not (gray) or not fully (light gray) replicate the results of the original are highlighted. SO = single condition omission; RO = random condition omission; M = motor control. BF_{r0} (Replication Bayes Factor) indicates evidence for a similar or larger effect in replication (BF_{r0} > 1) vs. no effect (BF_{r0} < 1). BF_{r0} in brackets are not interpreted as there was no effect in the original study. *EES* BF_{01} (Equality-of-Effect-Sizes Bayes Factor) indicates evidence for equal (BF_{01} > 1) vs. unequal (BF_{01} < 1) effect sizes between studies.

Component	Contrast	Original study				Replication study				Replication tests	
		d	***BF*$_{10}$**	***t*(14)**	***p***	***d***	***BF*$_{10}$**	***t*(29)**	***p***	***BF*$_{r0}$**	***EES BF*$_{01}$**
oN1	SO vs. M	−0.86	10.27	−3.35	.005	−1.11	13146	−6.05	<.001	80466	3.65
	RO vs. M	−0.5	1.14	−1.93	.074	−0.88	576	−4.82	<.001	1933	2.58
	SO vs. RO	−0.66	2.9	−2.57	.022	−0.74	79.3	−4.02	<.001	388	4.87
oN2	SO vs. M	−1.06	35.3	−4.09	.001	−0.92	972	−5.03	<.001	5316	4.55
	RO vs. M	0.07	0.27	0.26	.802	−0.68	40	−3.74	<.001	(14.4)	0.39
	SO vs. RO	−1.24	118	−4.81	<.001	−0.78	151	−4.29	<.001	382	2.43
oP3	SO vs. M	1.39	302	5.40	<.001	1.27	121965	6.94	<.001	961420	4.32
	RO vs. M	0.11	0.29	0.44	.670	0.9	760	4.93	<.001	(311)	0.30
	SO vs. RO	1.08	41.2	4.18	<.001	0.89	645	4.87	<.001	3278	4.29

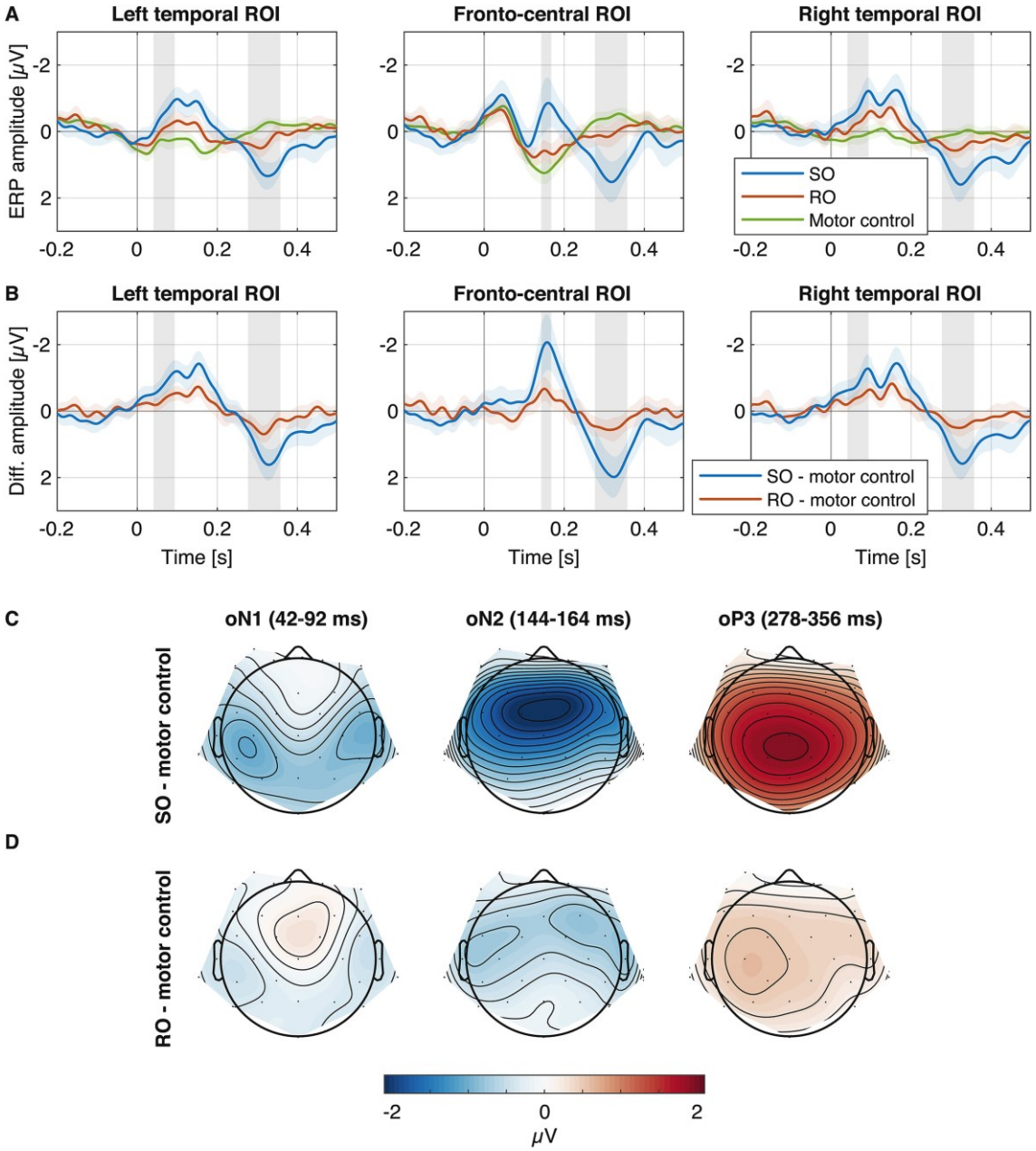

Figure 4: Grand-average omission responses, difference waves, and topographies resulting from the replicated preprocessing pipeline. Panel A: Grand-average omission responses in the single (SO; blue) and random sound (RO; red) and motor control conditions (green) ERPs incl. 95%-confidence intervals. Gray bars illustrate the time windows used for statistical analysis and topographies (as shown in panels C and D). Panel B: Grand-average omission minus motor control difference waves in the single and random sound conditions incl. 95%-confidence intervals. Panels C and D: Grand-average omission minus motor-control difference topographies waves in the single and random sound conditions for the oN1 (42–92 ms), oN2 (144–164 ms), and oP3 (278–356 ms) time windows as reported in the original study.

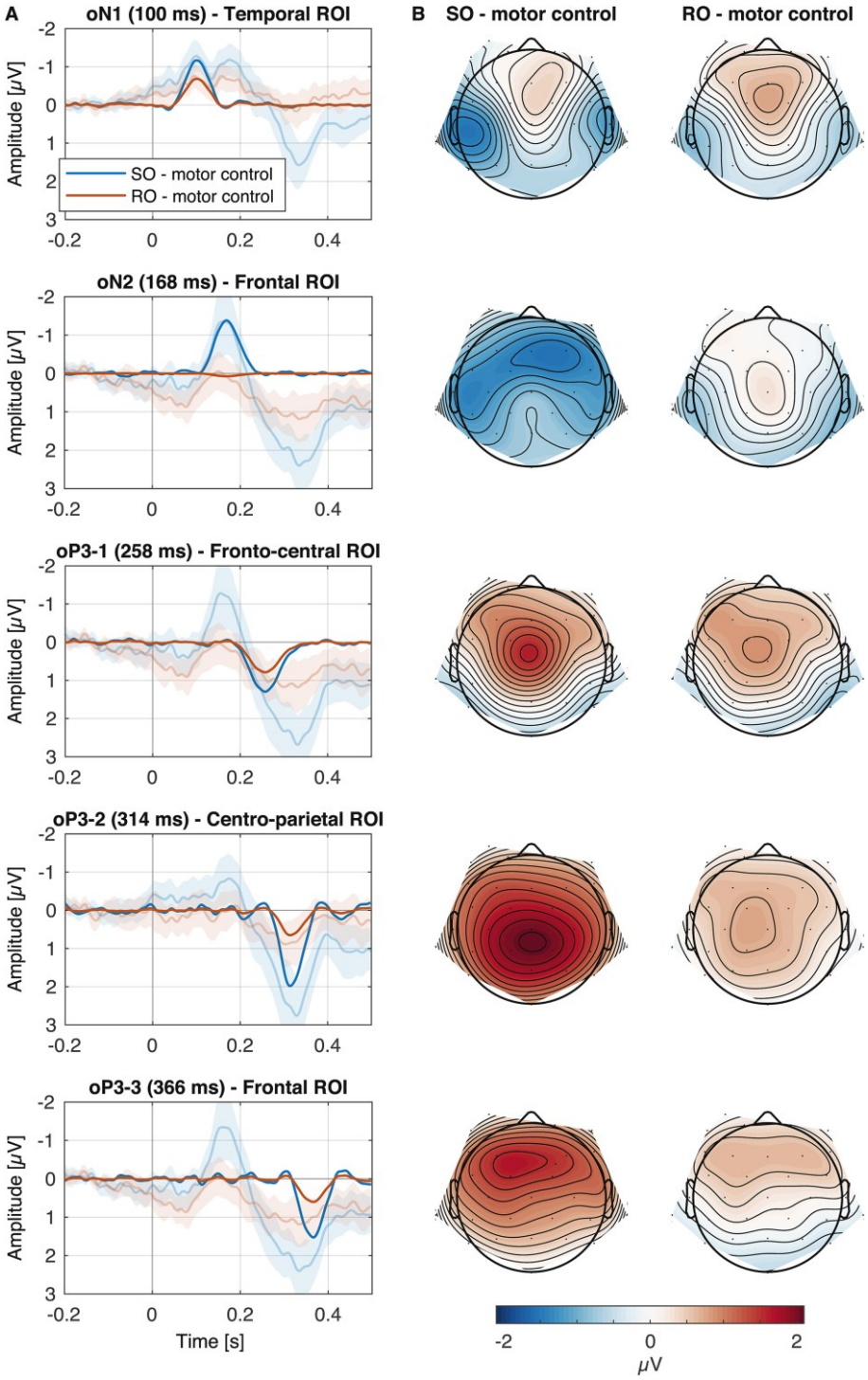

Figure 5: Reconstructed PCA component difference waveform (oN1, oN2, and the three oP3-subcomponents), grand-average difference waves, and topographies resulting from the adjusted preprocessing pipeline and principal component analysis (PCA). Panel A: PCA component waveforms were scaled to µV-units by multiplying the component loadings times SD times component score per component (of interest), condition, participant, and electrode location. The result reflects the relative contribution of the component to the observed ERP responses (see Appendix of Dien, 1998 for a proof of this procedure). Omission minus motor control in the single (SO; blue) and random sound conditions (RO; red) difference component waveforms are shown in opaque colors. Grand-average ERPs incl. 95%-confidence intervals are shown in transparent colors for comparison purposes. Panel B: Omission minus motor control difference component topographies at component peak latencies (as reported in panel A) in the single (left column) and random sound conditions (right column). Difference amplitudes were significantly larger in the single than in the random sound condition for all components of interest.

oN1. The data reported by SanMiguel et al. (2013a, Table 1) provided strong evidence for an oN1 component in response to sound omissions in the single sound condition (d=−0.86, BF_{10}=10.27) and inconclusive evidence for an oN1 component in the random sound condition (d=−0.5, BF_{10}=1.14). Their data provided weak evidence for more negative oN1 amplitudes in the single sound condition compared to the random sound condition (d=−0.66, BF_{10}=2.9).

The data observed in our replication study (Table 1) analyzed with the replicated data preprocessing pipeline provided decisive evidence for an oN1 in response to sound omissions in the single sound condition (d=−1.11, BF_{10}=13146) and also in the random sound condition (d=−0.88, BF_{10}=576). The data provided decisive evidence for more negative oN1 amplitudes in the single sound condition compared to the random sound condition (d=−0.74, BF_{10}=79.3). Frequentist results are shown in Table 1.

The replication Bayes Factors indicate replication success, that is, in the replication study effects similar (or larger) to the original study rather than no effects were observed, for all comparisons (SO vs. M: BF_{r0}=80466; RO vs. M: BF_{r0}=1933; SO vs. RO: BF_{10}=388). This might sound counterintuitive as an oN1 component in response to omissions of random sounds was not reported in the original study but observed in our replication study. However, in the original study there was a trend and the evidence provided by the data for or against an effect was inconclusive (*BF* range between 0.33–3) but interpreted as absence of an effect on the basis of the frequentist statistics. The data of the replication study with the higher sample size now provided conclusive evidence.

The equality-of-effect-sizes Bayes Factor indicated moderate evidence for similar rather than different effect sizes in the original and the replication study for oN1 amplitudes in the single sound condition (*EES* BF_{01}=3.65) and the direct comparison of oN1 amplitudes between single and random sound conditions (*EES* BF_{01}=4.87). Also in the random sound condition the data provide support rather for similar than different effect sizes for oN1 but the provided evidence is weaker than in the single sound condition (*EES* BF_{01}=2.58).

PCA component 4 explaining 10.4% of variance presumably reflected the oN1 component. The oN1 had a peak latency of 100 ms (that is, considerably later than the 42–92 ms analysis time window used in the original study and the replicated preprocessing) and was maximal over temporal leads only slightly more posterior than reported by SanMiguel et al. (2013a; see Figure 5). The data provided decisive evidence for an oN1 component in response to sound omissions in the single (d=−1.07, BF_{10}=8104) and the random sound condition (d=−0.74, BF_{10}=87.3). There was moderate evidence for a more negative oN1 amplitude in the single sound condition compared to the random sound condition (d=−0.56, BF_{10}=8.46). Frequentist results are shown in Table 2.

In sum, the replicated data preprocessing pipeline as well as the PCA analysis provided evidence for an oN1 component in the single and the random sound conditions with larger oN1 amplitudes in the single sound condition.

oN2. The data reported by SanMiguel et al. (2013a) provided decisive evidence for an oN2 component in response to sound omissions in the single sound condition (d=−1.06, BF_{10}=35.3) but moderate evidence against an oN2 component in the random sound condition (d=0.07, BF_{10}=0.27). Their data provided decisive evidence for more negative oN2 amplitudes in the single sound condition compared to the random sound condition (d=−1.24, BF_{10}=118).

The data observed in our replication study analyzed with the replicated data preprocessing pipeline provided decisive evidence for an oN2 in response to sound omissions in the single sound condition (d=−0.92, BF_{10}=972) and decisive evidence for an oN2 in the random sound condition (d=−0.68, BF_{10}=40). The data provided decisive evidence for more negative oN2 amplitudes in the single sound condition compared to the random sound condition (d=−0.78, BF_{10}=151). Frequentist results are shown in Table 1.

The replication Bayes Factors indicate replication success for oN2 in the single condition and for a more negative oN2 amplitude in the single condition compared to the random condition (SO vs. M: BF_{r0}=5316; SO vs. RO: BF_{r0}=382). BF_{r0} for oN2 in the random condition was not interpreted, as there was no effect in the original study. The replication Bayes factor compares the null hypothesis of a zero effect size to the alternative hypothesis of an effect size similar as in the original study. In case of a zero or very small effect size in the original study (as seen for oN2 and oP3 in the random condition) these hypotheses cannot easily be distinguished and the replication Bayes factor interpreted (the replication Bayes factor may even give paradoxical results in case the null hypothesis fails to account for the data; see Ly et al., 2019, Appendix C for detailed discussion).

The equality-of-effect-sizes Bayes Factor indicated moderate evidence for similar rather than different effect sizes in the original and the replication study for oN2 amplitudes in the single sound condition (*EES* BF_{01}=4.55). There was weak evidence for different effect sizes in the random sound condition (RO vs. M: *EES* BF_{01}=0.39) and similar effect sizes in the direct comparison of oN2 amplitudes between single and random sound conditions (SO vs. RO: *EES* BF_{01}=2.43).

PCA component 2 explaining 12.4% of variance presumably reflected the oN2 component. The oN2 had a peak latency of 168 ms (later than the 144–164 ms analysis time window used in the original study and the replicated preprocessing) and was maximal over frontal leads, significantly more frontal than reported by SanMiguel et al. (2013a; see Figure 4). The data provided strong evidence for an oN2 component in response to sound omissions in the single sound condition (d=−0.59, BF_{10}=13.1). Data provided moderate evidence against an oN2 in the random sound condition (d=0.06, BF_{10}=0.2). There was decisive evidence for a more negative oN2 amplitude in the single sound condition compared to the random sound condition (d=−0.8, BF_{10}=180). Frequentist results are shown in Table 2.

In sum, the replicated data preprocessing pipeline provided evidence for an oN2 component in both the single and random sound condition, whereas PCA analysis provided evidence for an oN2 component in the single condition, but evidence against an oN2 component in the random condition. Both analyses indicate a more negative oN2 amplitude in the single sound condition compared to the random sound condition.

oP3. The data reported by SanMiguel et al. (2013a) provided decisive evidence for an oP3 component in response to sound omissions in the single sound condition (d=1.39, BF_{10}=302) but moderate evidence against an oP3 component in the random sound condition (d=0.11, BF_{10}=0.29). Their data provided decisive evidence for more positive oP3 amplitudes in the single sound condition compared to the random sound condition (d=1.08, BF_{10}=41.2).

The data observed in our replication study analyzed with the replicated data preprocessing pipeline provided decisive evidence for an oP3 in response to sound omissions in the single sound condition (d=1.27, BF_{10}=121965) and decisive evidence for an oP3 in the random sound condition (d=0.9, BF_{10}=760). The data provided decisive evidence for more positive oP3 amplitudes in the single

sound condition compared to the random sound condition (d=0.89, BF_{10}=645). Frequentist results are shown in Table 1.

The replication Bayes Factors indicate replication success for oP3 in the single condition and for a more positive oP3 amplitude in the single condition compared to the random condition (SO vs. M: BF_{r0}=961420; SO vs. RO: BF_{r0}=3278). BF_{r0} for oP3 in the random condition was not interpreted, as there was no effect in the original study.

The equality-of-effect-sizes Bayes Factor indicated moderate evidence for similar rather than different effect sizes in the original and the replication study for oP3 amplitudes in the single sound condition (*EES* BF_{01}=4.32) and the direct comparison of oP3 amplitudes between single and random sound conditions (*EES* BF_{01}=4.29). Data provide moderate evidence for different effect sizes for oP3 in the random sound condition (*EES* BF_{01}=0.3).

PCA extracted three oP3 components, presumably reflecting separate parts of the oP3 response. PCA component 3 explaining 12.3% of variance was identified as the first subcomponent of the oP3 (oP3-1). The oP3-1 had a peak latency of 258 ms (falling outside the analysis time-window used in the original study and the replicated preprocessing), and was maximal over anterior leads. The data provided strong evidence for an oP3-1 component in response to sound omissions in the single sound condition (d=0.67, BF_{10}=34.3) and the random sound condition (d=0.64, BF_{10}=21.9). Data provided weak evidence against a difference between single and random sound conditions (d=0.32, BF_{10}=0.76). PCA component 6 explaining 8.1% of variance was identified as the second subcomponent of the oP3 (oP3-2). The oP3-2 had a peak latency of 314 ms, and was maximal over posterior leads. The data provided decisive evidence for an oP3-2 component in response to sound omissions in the single sound condition (d=0.95, BF_{10}=1460) and strong evidence in the random sound condition (d=0.59, BF_{10}=12.8). Data provided decisive evidence for a difference between single and random sound conditions (d=0.79, BF_{10}=174). PCA component 7 explaining 6% of variance was identified as the third subcomponent of the oP3 (oP3-3). The oP3-3 had a peak latency of 366 ms (falling outside the analysis time-window used in the original study and the replicated preprocessing), and was maximal over frontal leads. The data provided decisive evidence for an oP3-3 component in response to sound omissions in the single sound condition (d=1.19, BF_{10}=43399) and in the random sound condition (d=0.77, BF_{10}=120). Data provided decisive evidence for a difference between single and random sound conditions (d=0.76, BF_{10}=115). Frequentist results are shown in Table 2.

In sum, the replicated data preprocessing pipeline provided evidence for an oP3 component in both the single and random sound condition, where the single sound condition showed a more positive amplitude compared to the random sound condition. PCA analysis extracted three oP3 components in both the single and random sound condition. More positive amplitudes in the single than in the random sound condition were observed for oP3-2 and oP3-3, but not for oP3-1.

A second PCA was done to compare sound elicited N1 topographies to the oN1 topographies from the omission PCA. This analysis included motor control trials, single sounds, and random sounds. The sound elicited N1 component was identified as component 3, explaining ~12% of variance and peaking at 96 ms. Although topographies show that both the sound and omission elicited N1 component are temporally oriented, the sound elicited N1 topography seems to be slightly more oriented towards the vertex (see Figure 6).

Table 2: Summary of the statistical results based on the PCA analysis. SO = single condition omission; RO = random condition omission; M = motor control.

Component	Contrast	*d*	BF_{10}	*t*(29)	*p*
oN1	SO vs. M	−1.07	8104	−5.86	<.001
	RO vs. M	−0.74	87.3	−4.06	<.001
	SO vs. RO	−0.56	8.46	−3.06	.005
oN2	SO vs. M	−0.59	13.1	−3.26	.003
	RO vs. M	0.06	0.20	0.31	.762
	SO vs. RO	−0.8	180	−4.36	<.001
oP3-1	SO vs. M	0.67	34.3	3.67	<.001
	RO vs. M	0.64	21.9	3.48	.002
	SO vs. RO	0.32	0.76	1.76	.089
oP3-2	SO vs. M	0.95	1460	5.19	<.001
	RO vs. M	0.59	12.8	3.24	.003
	SO vs. RO	0.79	174	4.34	<.001
oP3-3	SO vs. M	1.19	43399	6.53	<.001
	RO vs. M	0.77	120	4.19	<.001
	SO vs. RO	0.76	115	4.18	<.001

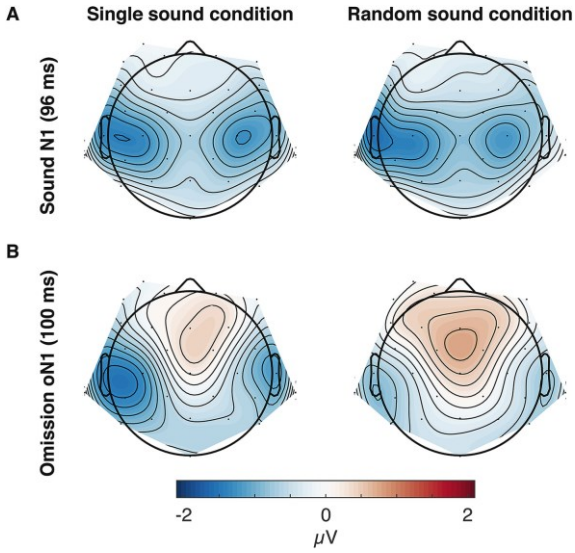

Figure 6: N1 and oN1 (PCA) component sound and omission minus motor control difference topographies. Panel A: N1 difference component topographies in response to sounds in the single (left column) and random sound conditions (right column) resulting from the second PCA computed on the sound and motor control individual ERP averages. Panel B: oN1 difference component topographies in response to omissions in the single and random sound conditions. Note that these are identical to the corresponding topographies in Figure 5 and are displayed here for comparison purposes only. N1 in response to sounds is distributed more centrally than oN1 in response to omissions.

3.4 Discussion

The current study aimed to replicate the omission ERP responses observed in SanMiguel et al. (2013a). We collected data from more participants compared to the original study and applied additional analysis techniques. Omission components in the single sound condition (predictable identity) were convincingly replicated, as were the larger amplitude responses in the single sound compared to random sound condition (unpredictable identity). However, notable differences were observed in the random sound condition, where temporal PCA revealed significant oN1 and oP3 components.

Predictive coding and N1-suppression studies consider the N1 to reflect the unconscious comparison of sensory prediction and sensory input, i.e. prediction error (Arnal & Giraud, 2012; Friston, 2005; Knolle et al., 2012; Schröger et al., 2015). A higher amplitude oN1 in the single sound condition implies stronger prediction error compared to the random sound condition, suggesting that an identity specific prediction was present that was not present in the random sound condition. This is in accordance with the conclusions of SanMiguel et al. (2013a), and is in line with studies showing identity specific activation in omission responses (Berlot et al., 2018; Demarchi et al., 2019; Kok et al., 2017). However, the elicitation of an oN1 in the random sound condition implies that some form of prediction is also present when the upcoming sound identity is unpredictable. This contradicts the conclusions of SanMiguel et al. (2013a) and Van Laarhoven et al. (2017), who observed no omission components in the random sound condition and therefore stated that an identity specific prediction was crucial in order to elicit an omission response. In the study of SanMiguel et al. (2013a), replication Bayes analysis indicates that the null effect presumably was due to a lack of power. Van Laarhoven et al. (2017) included an only marginally smaller number of participants in their study compared to our study (n = 27). An explanation of the reported null effect in their study therefore rather might result from different experimental parameters. Particularly, they focused on visual-auditory predictions and presented short movies of hands clapping followed by auditory stimuli as opposed to the motor timing cue (button press) used in the current paradigm. Apart from the observed differences to previous

omission studies, our results are more in line with aforementioned N1-suppression studies that show suppression also without (or even false) knowledge of sound identity (Bäß et al., 2008; Bednark et al., 2015; Knolle et al., 2013b, 2019). Some of these studies observe increased N1-suppression when specific foreknowledge of the upcoming sound is present (Bäß et al., 2008; Knolle et al., 2013b), which is in line with the increased oN1 amplitude in the current study when an identity specific prediction is violated. Furthermore, oN1 results are congruent with the concept of precision weighting. In the single sound condition, the highly weighted prediction of expected sound features might have played a role in the strongly elicited omission response. In contrast, the random sound condition only allowed broad, imprecise predictions, possibly leading to a lower weighted and thus diminished prediction error response. Increased omission responses as a consequence of precision weighting have been interpreted as such by Chennu et al. (2016). Southwell and Chait (2018) also interpret their increased sustained response amplitude to regular sound patterns as a consequence of precision weighting.

The present data suggest the activation of an auditory prediction template not only in the single sound condition (SanMiguel et al., 2013a) but also in the random sound condition. Similar oN1 topographies in both conditions support this notion. Possibly, a diffuse prediction template was mapped on the tonotopically organized auditory cortex in the random condition, as the wide range of sounds primed areas of the auditory cortex that are responsive to a broad range of frequencies. Functional MRI research has shown that certain clusters of the auditory cortex respond to a frequency range spanning over multiple octaves (Moerel et al., 2013). These clusters might become part of the prediction template despite the changing sound in the random condition, and might therefore be responsible for the oN1 response in the random condition. The additional activity of narrowly defined tonotopic clusters to the prediction template could in turn explain the stronger oN1 response in the single sound condition.

Although the activation of a prediction template is supported by a number of studies (Berlot et al., 2018; Demarchi et al., 2019; Kok et al., 2014, 2017; Leonard et al., 2016), a recent intracranial study shows omission activation only in a subset of auditory responsive sites (Fonken et al., 2019). Also in the current study, the topographies of the sound-related N1 and the oN1 are quite distinct (Figure 6). These results suggest that the omission response may not be generated by exactly the same areas that are activated when sound is perceived. This is incongruent with current predictive coding models, that hypothesize the sensory processing hierarchy to be the key pathway where prediction error is generated and propagated (e.g. Bastos et al., 2012). An explanation of the different topographies possibly lies in the distinction between lemniscal and nonlemniscal pathways in the auditory cortex. The lemniscal pathway is thought to feed “raw” auditory information to the generative model, without being an active part of it (Carbajal & Malmierca, 2018; Parras et al., 2017). On the other hand, the nonlemniscal pathway is thought to be the prime host of top-down prediction and bottom-up prediction error (Carbajal & Malmierca, 2018). Therefore, the absence of lemniscal activity in omissions might be responsible for the observed differences in the topography of the ERP. However, these studies should be interpreted with caution, as paradigms differ significantly and conclusions are partly based on results in other species.

Components succeeding the oN1 are often described in the context of cognitive processing following the initial perception of prediction error. The studies of SanMiguel et al. (2013a) and Van Laarhoven et al. (2017) interpret the oN2 broadly as a component related to deviance detection and error monitoring, being part of the N2–P3 complex. However, our results show an oP3 but no oN2 effect in

the random condition. Additionally, participants in the current study were not asked to consciously attend to omissions – normally crucial for N2b elicitation (Patel & Azzam, 2005) – and the N2b component tends to peak later in time (200–350 ms) than the currently observed oN2 (Folstein & Van Petten, 2008). Alternatively, the oN2 could be interpreted as an omission MMN. Both the MMN and N2b respond to deviant events, and can be confounded due to similar anterior topographies (Wei et al., 2002). However, a distinguishing characteristic of the mismatch negativity is a polarity reversal at mastoid electrodes, which is not observed for N2b (Sussman et al., 2014). In the current study, such a polarity reversal is observed at mastoid electrodes, supporting the idea that the oN2 could be an omission MMN (Figure 5). This would be a notable finding, as the elicitation of an omission MMN has been described to typically disappear with ISIs larger than 150 ms (Yabe et al., 1997, 1998). The precise information regarding timing provided by the button press may possibly have enabled the detection of an omission MMN. Stekelenburg and Vroomen (2015) argue against the interpretation of the oN2 as an omission MMN, as they do not observe an oN2 in an auditory-only condition with comparably long ISIs, where participants could predict stimulus onset through the rhythm regularity of the sound. However, the lack of a timing cue (button press) in this condition could have caused jittered elicitation of components, resulting in the absence of an ERP effect (Ouyang et al., 2016). Predictive coding explains the MMN as a prediction error that is the result of higher cortical levels attempting to fit their abstractions of the world to data received from lower areas (Garrido et al., 2009c). According to Horváth et al. (2008), the MMN reflects higher order deviance detection than the simple, first-order change detection reflected by the N1. In this context, observed results in the current study can be explained straightforwardly: where in the single condition a clear higher-order representation of the sound is present and a strong MMN is elicited, in the random condition no higher-order representation can be formed. In the random condition, this might explain why an oN1 is elicited, possibly based on common auditory features, but no oN2, based on higher order sound identity. However, despite similarities, caution must be taken in considering omission components as equal to sound elicited components, as many specifics regarding omission components are still unclear. Additionally, in this study the replicated data preprocessing pipeline showed an oN2 effect also in the random condition. We consider this likely to be an artifact of the 1 Hz high-pass filter used in the preprocessing pipeline due to the subsequent oP3 observed in our replication study. Increased later effects have shown to potentially introduce artifactual earlier effects of opposite polarity with comparable high-pass filters (Tanner et al., 2015; Widmann et al., 2015). In the original study no subsequent oP3 was observed, therefore also no filter artifacts may have been introduced in this condition (but note that oN2 in the single sound condition might have been artifactually enhanced by the high-pass filter in the original study; indeed we observed considerably lower oN2 amplitudes in the PCA analysis compared to the replicated data preprocessing pipeline and the original study). Moreover, the topography of oN2 in the random sound condition in the PCA analysis does not show any indication of an oN2 component as in the single sound condition. We would therefore consider the alternative explanation that a true present oN2 effect is hidden by some overlapping slow potential as unlikely.

The omission related P3 has been attributed to attention orienting and updating of the forward model in response to prediction error (SanMiguel et al., 2013a; Van Laarhoven et al., 2017). Contrary to SanMiguel et al. (2013a) and Van Laarhoven et al. (2017), oP3 was elicited in both single and random conditions. PCA separated the observed oP3 component into three distinct subcomponents. All of them were elicited in single and random sound conditions. The data did not provide conclusive evidence whether amplitudes were different between conditions for the first subcomponent (oP3-1),

whereas in the later subcomponents (oP3-2, oP3-3) the single condition demonstrated larger amplitudes than the random condition. Thus, at least oP3-2 and oP3-3 seem to indicate increased higher-order processing in reaction to an increased prediction error response. Although the precise functions of P300 subcomponents are still debated, some observations can be made regarding the resemblance of the P300 subcomponents found in the current study to subcomponents found in non-omission studies. The first subcomponent (oP3-1) peaks at 258 ms and is fronto-centrally oriented, reflecting characteristics of the early P3a component (Escera et al., 1998; Polich, 2007). This component is discussed to be related to the phasic activation of the locus coeruleus-norepinephrine-system and the processing of motivationally significant sounds (Nieuwenhuis et al., 2011a) and the enhanced evaluation of deviant or novel stimuli. The subsequent subcomponents peaking at 314 ms over posterior sites (oP3-2) and 366 ms over frontal sites (oP3-3) reflect characteristics of the late P3a component (Escera et al., 1998) and the novelty-P3a (Barry et al., 2016), that are discussed to reflect aspects of the orienting of attention. The notion that also the omission of a sound might possibly reflect surprising and in some sense novel information might provide interesting insights into cognition and inspire future research.

3.5 Conclusions

This replication study shows that the omission responses obtained from the single condition in this paradigm are robust. Furthermore, it replicates the increased omission responses in the single compared to the random condition, confirming the important role identity specific predictions play in perception. Increased power revealed additional omission responses in the random condition, suggesting that predictions do not necessarily have to be identity specific in order to elicit a prediction error. These results suggest the existence of both specific and unspecific predictions along the sound processing hierarchy, where precision weighting possibly influences the strength of prediction error. Compared to earlier studies, these results appear to be more compatible with everyday life, in which uncertain predictions seem highly prevalent. Additionally, this study bridges the gap between omission studies and N1 suppression studies that show suppression also without knowledge of sound identity.

3.6 Acknowledgements

We thank all participants that took part in this study. We thank Dunja Kunke, Gabriele Schöps, Celine Jakel and Luisa Kocherscheid for support in data acquisition.

3.7 Funding

This work was supported by the Center for Behavioral Brain Sciences Magdeburg financed by the European Regional Development Fund (ZS/2016/04/78120) and Leibniz Association (P58/2017).

3.8 Supplementary data

Table 3: Sensitivity analysis for all Bayesian t-tests with scale r = 0.707, r = 1, and r = 1.414 ("medium", "wide", and "ultrawide" effect size priors in the BayesFactor R package) changing the spread of the Cauchy distribution reflecting the prior belief on the size of the expected effect sizes. Prior scaling did not affect the conclusions in any of the analyses.

		BF_{10} original study			BF_{10} replication study - Replication analysis			BF_{10} replication study - PCA analysis		
Compo-nent	Contrast	*r* = 0.707	*r* = 1	*r* = 1.414	*r* = 0.707	*r* = 1	*r* = 1.414	*r* = 0.707	*r* = 1	*r* = 1.414
oN1	SO vs. M	10.27	9.84	8.65	13146	14031	13457	8104	8557	8121
	RO vs. M	1.14	0.95	0.75	575	569	508	87.3	81.4	69.4
	SO vs. RO	2.9	2.57	2.12	79.3	73.7	62.6	8.46	7.26	5.81
oN2	SO vs. M	35.3	36.2	33.7	972	974	880	13.1	11.5	9.27
	RO vs. M	0.27	0.2	0.15	40	36.3	30.3	0.20	0.15	0.11
	SO vs. RO	118	128	125	151	144	124	180	172	149
oP3-1	SO vs. M	302	339	345	121965	136118	136697	34.3	31	25.7
	RO vs. M	0.29	0.21	0.16	760	757	680	21.9	19.5	16
	SO vs. RO	41.2	42.5	39.9	645	639	572	0.76	0.59	0.44
oP3-2	SO vs. M							1460	1479	1350
	RO vs. M							12.8	11.2	9
	SO vs. RO							173	166	143
oP3-3	SO vs. M							43398	47488	46710
	RO vs. M							120	113	97.3
	SO vs. RO							115	108	92.9

Chapter 4: Study 2

SOMATOSENSORY OMISSIONS REVEAL ACTION-RELATED PREDICTIVE PROCESSING

The present chapter is based on the following manuscript that is submitted for publication:
Dercksen, T., Widmann, A., Noesselt, T., & Wetzel, N. (2022). Somatosensory omissions reveal action-related predictive processing.

Abstract

The intricate relation between action and somatosensory perception has been studied extensively in the past decades. Generally, a forward model is thought to predict the somatosensory consequences of an action. These models propose that when an action is reliably coupled to a tactile stimulus, unexpected absence of the stimulus should elicit prediction error. Although such omission responses have been demonstrated in the auditory modality, it remains unknown whether this mechanism generalizes across modalities. This study therefore aimed to record action-induced somatosensory omission responses using EEG in humans. Self-paced button presses were coupled to somatosensory stimuli in 88% of trials, allowing a prediction, or in 50% of trials, not allowing a prediction. In the 88% condition, stimulus omission resulted in a neural response consisting of multiple components, as revealed by temporal principal component analysis. The oN1 response suggests similar sensory sources as stimulus-evoked activity, but an origin outside primary cortex. Subsequent oN2 and oP3 responses, as previously observed in the auditory domain, likely reflect modality-unspecific higher order processes. Together, findings straightforwardly demonstrate somatosensory predictions during action and provide evidence for a partially amodal mechanism of prediction error generation.

4.1 Introduction

Whether mindlessly playing with our pen, or consciously tapping on our phone, it seldomly happens that we are surprised by the tactile sensations that our own actions produce. Several models explain this phenomenon in terms of an action-related sensory prediction that attenuates surprise. For example, motor commands are thought to be accompanied by an efference copy that signals the predicted sensory consequences of the action (Sperry, 1950; von Holst & Mittelstaedt, 1950). Similarly, predictive coding assumes a cortical hierarchy where higher cortical levels predict lower levels (Friston, 2005; Rao & Ballard, 1999). As action unfolds, motor areas are thought to send predictions to sensory areas, where they are compared to actual input (Adams et al., 2013; Friston et al., 2017). Where predictions are incorrect, a prediction error is propagated back up the hierarchy that corrects higher-level models, while correct predictions result in diminished prediction error or surprise compared to external stimuli.

Efference copy and predictive coding, along with comparable forward models, explain a variety of behavioral (e.g., Bays et al., 2005, 2006; Kilteni & Ehrsson, 2017a, b; Walsh et al., 2011) and neuroimaging findings of perceptual phenomena (De Lange et al., 2018; Horváth, 2015; Schröger et al., 2015; Shadmehr et al., 2010; Imamizu, 2010; Shin et al., 2010). For example, sensory attenuation or suppression has consistently been reported in several modalities, with diminished neural activity for self-generated versus externally generated stimuli (Bäß et al., 2008; Bednark et al., 2015; Blakemore et al., 1998, 1999, 2000; Kilteni & Ehrsson, 2020; Knolle et al., 2013b, 2019; Roussel et al., 2013, 2014; Shergill et al., 2013). However, the observed attenuation in these studies is only indirect evidence of a hypothetical sensory prediction, leaving room for explanations other than prediction-related effects such as neural adaptation (Schröger et al., 2015). A more explicit demonstration of motor-induced sensory predictions is found in studies using auditory stimulus omissions. Here, an action is reliably coupled to a sound that is sometimes unexpectedly omitted. An increasing number of studies have demonstrated omission-related brain responses when auditory stimuli were coupled to an action (SanMiguel et al., 2013a, c; Dercksen et al., 2020, 2022; Korka et al., 2020) or another stimulus (Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). Event-related potentials (ERPs) in these studies show a consistent pattern of omission responses: an initial oN1 component (~100 ms) potentially reflecting sensory prediction error, followed by a later oN2 and possibly several oP3 components likely reflecting higher-level processing. Explaining this sensory-related neural activity in the absence of a stimulus is not possible without the notion of an internal process that triggers this activity, which is often interpreted in terms of prediction and prediction error.

Stimulus omission paradigms avoid confounding bottom-up activity caused by unexpected deviant stimuli and are thus well suited to investigate motor-induced sensory predictions (Heilbron & Chait, 2018; Korka et al., 2022; Schröger et al., 2015). Moreover, the cascade of subsequent omission components as observed in auditory studies offers a detailed insight into the subprocesses related to prediction error computation. Despite these advantages, omission studies are still scarce compared to other paradigms investigating predictions and the omission response has barely been studied outside the auditory modality. Three studies have demonstrated somatosensory omission responses, all using MEG (Andersen & Dalal, 2021; Andersen & Lundqvist, 2019; Tesche & Karhu, 2000). These studies did not involve action but used a fixed inter-stimulus-interval (ISI) to induce stimulus predictions, all reporting only a single omission-related component. Possibly, the lack of a time-locking cue might have led to decreased power hindering the observation of all components of the omission response.

In the current study we therefore aimed to characterize the full omission-related response. To this end, we recorded action-induced somatosensory omission responses using ERPs. The paradigm was similar to aforementioned auditory studies. A two-step approach was used to analyze ERPs, starting with cluster-based permutation tests to determine significant variation of the signal between conditions and following up with temporal principal component analysis (PCA) for a more detailed examination of the effects. PCA, as compared to conventional ERP analysis, mitigates the problem that the observed peaks of the recorded ERP waveform are a poor indication of its underlying components (Scharf et al., 2022). It achieves this by decomposing the waveform into components using a factor analytic approach. An added advantage of applying PCA in the current study is that it facilitates a comparison of omission responses across modalities, as this method was also used in previous auditory omission studies (Dercksen et al. 2020, 2022; Korka et al., 2020).

4.2 Material and methods

4.2.1 Participants

EEG and behavioral data were acquired from a total of 30 participants (17 female; age range=19-39; mean age=25 years, SD=5 years; 1 left-handed as measured by an adapted German version of the Oldfield Scale; Oldfield, 1971; the left-handed participant performed the task with the same hand as did right-handed participants). All participants reported normal hearing and were compensated either financially or in the form of credit points. Participants gave written consent prior to the experiment. The project was approved by the local ethical committee.

4.2.2 Apparatus and stimuli

Participants were seated in a dimly lit, electrically shielded and acoustically attenuated chamber, while EEG was continuously recorded. The experiment was programmed using Psychtoolbox (version 3.0.15; Brainard, 1997) and ran on a Linux-based system using GNU Octave (version 4.0.0). A white fixation cross was presented using a VIEWPixx/EEG Display (Resolution 1920(H) x 1080(V) - 23.6-inch display size). The fixation cross was presented in the middle of a grey screen, at about 60 cm from the participants' eyes (0.67° × 0.67° visual angle). To trigger the stimuli (or omissions), a custom-built button was used in order to ensure a completely silent button press. The button used an infrared photoelectric mechanism and was additionally padded with sound absorbing material. To ensure that no residual sound (e.g. contact of the skin of the fingertip with the button surface) was correlated with the button press and membrane inflation, participants wore Sennheiser HD-25 headphones during the experiment (no sound was presented). Tactile stimuli were presented using pulses of pressurized air (3 bar) that inflated a membrane, which was controlled using a somatosensory stimulus generator (University of Münster, Germany) that was placed outside the chamber. Stimulus duration was approximately 30 ms. Two membranes were placed on the left middle and index fingers at the volar aspect of the distal phalanx. The stimulation of two fingers was chosen because this generates a stronger signal compared to one finger (Severens et al., 2010) but at the same time is still focused to a limited part of the cortex. The tactile stimulus always consisted of simultaneous stimulation of both fingers. Because of the travel time of the air pulse, there was a slight time delay between button press and inflation of the membrane (onset of the tactile stimulus) of approximately 40 ms (which was corrected during data preprocessing of the ERPs, see section 2.5). The delay varied over a range of max. 4 ms.

4.2.3 Experimental design

The experimental task was adapted from an auditory omission study by SanMiguel et al. (2013c). Participants sat approximately 60 cm from a screen, having their right index finger on a button, and their left hand (where the tactile stimulus was applied) on a table. Distance between hands was approximately shoulder width (see Figure 7A for experimental layout). In all conditions, participants were asked to press a button every 600–1200 ms while looking at the fixation cross (Figure 7B). Two distinct tactile conditions (88%-condition, 50%-condition) and a motor control condition were presented (Figure 7C). In the tactile conditions, a button press resulted in a tactile stimulus either 88% (88%-condition) or 50% (50%-condition) of the time. In the remaining percentage of the button presses the tactile stimulus was omitted. In the motor control condition only the button was pressed, never resulting in a tactile stimulus. This condition was included to be able to subtract the neural activity related to the pressing of the button. A total of 160 omissions and 1120 tactile stimuli were presented in the 88%-condition, a total of 160 omission and 160 tactile stimuli were presented in the 50%-condition, and a total of 320 trials were presented in the motor control block. Blocks in the 88%-condition consisted of 20 omissions and 140 tactile stimuli, blocks in the 50%-condition consisted of 80 omissions and 80 tactile stimuli, and motor control blocks consisted of 160 trials. In the 88%-condition, omissions were randomly placed, under the restricting conditions that the first five trials of every block were always tactile trials, and every two trials following an omission were always tactile trials. In the 50%-condition, omission and tactile trials were randomly mixed. Before the experiment, two short training blocks (60 trials each block) were completed where participants trained to press the button every 600–1200 ms. In these training blocks, feedback was presented visually after every button press, displaying the number of milliseconds that was in between the last button presses. In the first training block, no tactile stimuli were presented when pressing the button, while in the second training block a tactile stimulus was always presented when pressing the button. After this training, 12 experimental blocks were presented. Block order was identical for all participants, first presenting a motor control block, followed by 8 blocks of the 88%-condition, then 2 blocks of the 50%-condition, and ending with another motor control block. The order of blocks was chosen with possible transfer effects in mind (SanMiguel et al., 2013c). The 50%-block could have induced a learning effect that there is no reliable coupling between button-press and stimulus, possibly resulting in absent omission responses if the 88%-blocks were presented after the 50%-blocks. Therefore, it was decided to always present 50%-blocks after 88%-blocks, since learning effects from 88% to 50%-blocks would be less problematic. If learning effects would be present, resulting in a significant omission result in the 50% condition, more participants would have been measured where the block order would be reversed (50%-condition before 88%-condition). However, this was not necessary as no significant omission responses were measured in the 50%-condition after 30 subjects. Total experiment time was about 45 minutes including breaks.

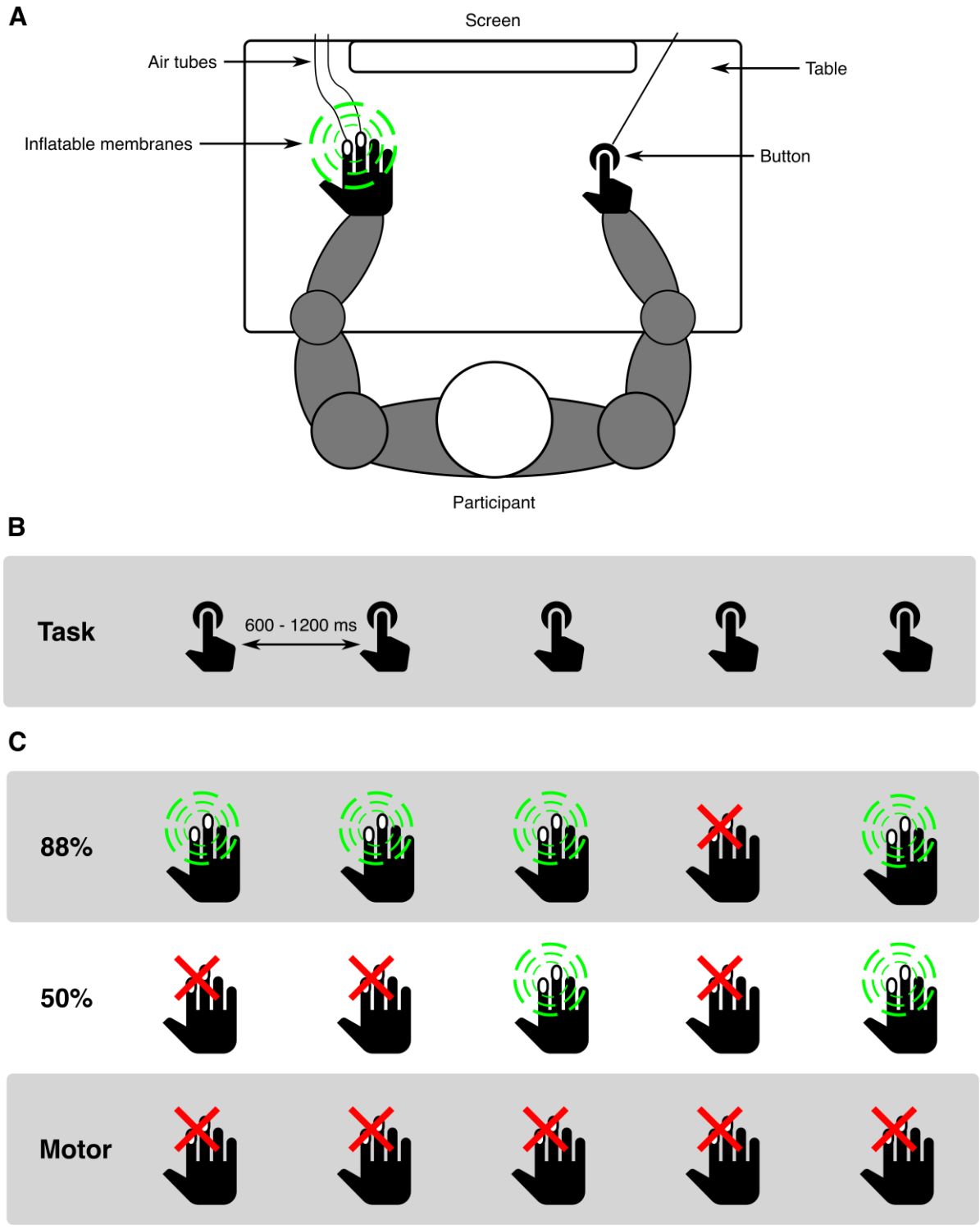

Figure 7: Schematic representation of the experimental design. Panel A shows the experimental set-up: a participant sat in front of a screen with both arms on a table. With the right hand a button was pressed, possibly resulting in a stimulus on the left hand (indicated with green circles). Stimuli were applied by a puff of air traveling through air tubes and inflating a membrane on the left middle- and index-finger. Panel B depicts the task over time, where participants pressed a button every 600 – 1200 ms. Panel C shows examples of the tactile effects of the button presses for all three conditions. In the 88%-condition, there was an 88% chance of a button press resulting in a stimulus. In the 50%-condition, the chance was 50%. In the motor condition, button presses never resulted in a tactile stimulus.

4.2.4 Data recording

EEG was recorded from a total of 63 active electrodes, placed according to the extended international 10-10 system at the following positions: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, O1, O2, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2, and the left (M1) and right (M2) mastoids. Furthermore, EOG was recorded from three electrodes placed left and right of the outer canthi of the eyes and below the left eye. The reference electrode was placed on the tip of the nose. An Actichamp amplifier (BrainProducts, Gilching, Germany) was used, recording at 500 Hz and without filtering using Vision Recorder software (version 1.21). Data is available on request to the corresponding author without further conditions.

4.2.5 EEG data preprocessing

EEG data analysis was performed with MATLAB software using the EEGLAB toolbox (Delorme & Makeig, 2004). Timestamps of the triggers were corrected for the delay between button press and stimulus by adding 40 ms to each timestamp. Data was filtered offline with a 0.1 Hz high-pass filter (-6 dB, Kaiser windowed sinc FIR filter, order=8024, beta=5, transition band width=0.2 Hz) and a 48 Hz low-pass filter (-6 dB, Kaiser windowed sinc FIR filter, order=402, beta=5, transition band width=4 Hz, this low-pass filter has full attenuation at 50 Hz power line frequency). Data was segmented into epochs starting 200 ms before and ending 500 ms after button press. A trial was excluded when time between button presses was less than 600 ms or more than 2000 ms. Although subjects aimed to press between 600 – 1200 ms, there was no reason to discard trials pressed slightly later. Only a 2000 ms cut-off was applied to eliminate trials where subjects would forget to press the button. Based on this criteria, on average 14 trials were rejected per participant (median=1, min/max=0/218, SD=46). Noisy channels were removed from the data, which were defined as having a robust z-score of the robust standard deviation (0.7413 times the interquartile range) larger than 3 (Bigdely-Shamlo et al., 2015). These channels were removed from analysis and interpolated after Independent Component Analysis (ICA). Epochs exceeding a 500 µV signal-change per epoch threshold were removed. Based on this criteria, on average 17 trials were rejected per participant (median=5, min/max=0/116, SD=29). ICA was performed to correct for artifacts. This was done on data which were 1 Hz high-pass filtered (-6 dB, Kaiser, order=1604, beta=5, transition band width=1 Hz) and 48 Hz low-pass filtered (same as above), as 1-2 Hz high-pass filters improve ICA performance (Klug & Gramann, 2020; Winkler et al., 2015). Epoching and channel and trial removal were identical to the 0.1 Hz filtered dataset. After ICA, the obtained demixing matrix was subsequently applied to the 0.1–48 Hz filtered data. Two independent raters judged components, aiming to remove all heart-, eye- and muscle-related components. Raters specifically paid attention to not remove components that indicated neural activity, considering the frequency spectrum (in particular alpha peak; Chaumon et al., 2015; Winkler et al., 2011), topography and event-related average of the components. Selected components were then discussed to come to a final judgement of components to be removed. Artifact independent components (ICs) were detected with support of the IClabel plugin (Pion-Tonachini et al., 2019). On average, 15 components were rejected per participant (median=15, min/max=11/21, SD=4). Each epoch was baseline corrected by subtracting the mean amplitude of the -200 to -100 ms window preceding stimulus onset (corrected for delay between button press and stimulus). Although this window might include motor-related activity (e.g. planning, execution), this should be common to all conditions. The first five trials of each block and the two trials following an omission in the 88% condition were excluded from analysis to prevent confounding activity unrelated to the stimulus (e.g.

attention-related activity). Finally, trials that exceeded 125 µV signal-change per epoch were excluded from analysis. Based on this criteria, on average 26 trials were rejected per participant (median=7, min/max=0/405, SD=73). In total, on average 1802 trials were left per participant after preprocessing (median=1838, min/max=1451/1856, SD=87). Condition-specific ERPs were computed for each participant.

4.2.6 Behavioral data

Behavioral data were analyzed to check for systemic differences between conditions regarding the time asynchrony between button presses. The asynchrony was determined on the basis of the behavioral data from which any too early/late button presses were removed. Trials were defined as too early when time between button presses was less than 600 ms, and as too late when time between button presses exceeded more than 2000 ms.

4.2.7 Cluster-based permutation tests

Cluster-based permutation tests were performed using the FieldTrip toolbox (Oostenveld et al., 2011) on a time-window of -200 ms to 500 ms around the button press. Parameters were kept as suggested by the Fieldtrip tutorial on cluster-based permutation tests, with temporo-spatial clusters defined by a minimum of 3 neighbouring channels, using Monte Carlo method to calculate the p-value, dependent samples *t*-test as statistic, "cluster" as correction method, "maxsum" as cluster statistic, .025 as alpha, and 1000 randomizations. For omission responses, the following contrasts were tested: 88%-condition vs. motor-control, 50%-condition vs. motor-control, and 88%-condition vs. 50%-condition. For somatosensory responses, only the 88%-condition vs. 50%-condition contrast was tested in order to obtain insights regarding sensory attenuation. A cluster was considered statistically significant when the *p*-value was below 0.05.

4.2.8 PCA

Although cluster-based permutation tests can reveal differences between conditions, more detailed inferences about latency and location (at sensor level) are unjustified (Sassenhagen & Draschkow, 2019). Therefore, we computed temporal principal component analysis (PCA) on the grand-average ERP data (including one individual average waveform per participant, condition, and electrode) to analyze ERPs in greater detail. This method aims to statistically decompose ERP waveforms into the constituent components that constitute the resulting waveform (see Dien, 2012 or Scharf et al., 2022 for tutorial treatments). The number of retained components was determined using Horn's parallel test, which compares the variance explained by each factor with the variance explained by the corresponding factor from a simulated dataset of uncorrelated (noise) variables (Scharf et al., 2022). An R (R 4.1.2; R Core Team, 2021) implementation of the Geomin rotation (Yates, 1987) method with $\varepsilon = 0.01$ was applied to the initial PCA solution as described in the tutorial of Scharf et al. (2022). Geomin rotation is less prone to conflating components (representing separate components in a single factor) with strong temporal and spatial overlap than other rotation methods like Promax (Scharf & Nestler, 2018, 2019). Two separate PCAs were computed, one to analyze ERP responses to tactile omissions and one to analyze ERP responses to tactile stimuli. The motor-control condition was included in both PCAs to control for the neural activity associated with the pressing of the button. Note that by including the motor-control condition in both PCAs, there is a possibility of artificial similarities between the results of both PCAs. The PCA of omission responses (plus motor-control) was computed on the individual averages of the motor control, 88%-condition omissions, and 50%-condition omissions together, resulting in identical components for all experimental conditions which could vary

in amplitude across conditions. The PCA of tactile stimuli responses (plus motor-control) was again computed on the individual averages of the motor control, 88%-condition stimuli, and 50%-condition stimuli together. From a theoretical perspective, only the stimulus responses in the time-window of the initial sensory omission responses were of interest to this study. Components outside this time-window were not considered for further analysis. As no prior information was available, statistical regions of interest for both PCAs were based on visual inspection of the topographies of the individual components. For early oN1 using right temporal electrodes: C6, CP6. For late oN1 using bilateral temporal electrodes: C4, C6, FT7. For oN2 using frontal electrodes: Fz, F2. For oN3 using occipital electrodes: P5, P6, P7, P8. For oP3-1 using central electrode: Cz. For oP3-2 using central electrode: Cz. For oP3-3 using frontal electrode: FC2. For oP3-4 using right temporal electrode: C4. For oP3-5 using right temporal electrodes: C2, CP2, C4, CP4. For tactile component 8 using right temporal electrode: CP6. For tactile component 5 using right temporal electrodes: C4, C6. For tactile component 2 using central/parietal electrodes: Cz, CPz. Resulting PCA components are ordered by explained variance with the first component explaining most variance. Explained factor variance is computed as the ratio of variance accounted for by a factor (sum of the variance multiplied by the factors' loading matrix and correlation matrix) and the overall total variance (sum of the variance).

Although in this study the analysis used for component separation is referred to as PCA, technically the algorithm estimates an exploratory factor analysis (EFA). Because differences between PCA and EFA estimates are negligible (see Scharf et al., footnote 11) and the term PCA is dominant in the field, this paper will keep referring to PCA with this technicality in mind. Additionally, note that PCA is an analysis at the sensor level and does not allow inferences about the specific brain areas involved.

4.2.9 Statistical analysis

Statistical testing was done using a Bayesian approach. Additionally, we report frequentist statistics. This way, readers familiar with Bayesian statistics can benefit from its advantages (Rouder et al., 2009; Wagenmakers, 2007), for example direct interpretability and the evaluation of the evidence for the null model provided by the data, while still keeping our results interpretable for readers preferring frequentist statistics and allowing a simple comparison with frequentist results from previous publications.

Behavioral data was tested for differences between conditions regarding the time asynchrony between button presses. A one-way repeated-measures ANOVA was performed using condition (motor, 88%-condition, 50%-condition) as independent variable and mean asynchrony between button presses as dependent variable. Equivalent variables (condition, mean asynchrony between button presses) were used for the Bayesian repeated measures ANOVA. Follow-ups were performed using paired samples *t*-tests, corrected for multiple comparisons using Bonferroni correction (Bonferroni, 1936) correcting for a family of 3 (motor, 88%-condition, 50%-condition), as well as Bayesian paired samples *t*-tests.

PCA omission and stimulus components were tested for differences between conditions using separate paired samples *t*-tests (88%-condition vs. motor control, 50%-condition vs. motor control, 88%-condition vs. 50%-condition). Equivalent comparisons were tested using Bayesian paired samples *t*-tests (88%-condition vs. motor control, 50%-condition vs. motor control, 88%-condition vs. 50%-condition).

All statistical tests were performed in JASP (version 0.16.0 JASP Team, 2021). For Bayesian statistics, the null hypothesis corresponded to a standardized effect size δ = 0, while the alternative hypothesis was defined as a Cauchy prior distribution centered around 0 with a scaling factor of r = 0.707 (the default "medium" effect size prior scaling). Additionally, for the Bayesian repeated measures ANOVA (see Rouder et al., 2017 for more information on Bayesian ANOVA), the JASP default fixed (condition) and random (participant variability) effects priors were used, defined as respectively r = 0.5 and r = 1. Resulting Bayes Factors (BF_{10}) were interpreted following Lee & Wagenmakers (2013), who give the labels anecdotal (0.33-3), moderate (3-10 or 0.33-0.1), strong (10-30 or 0.1-0.033), and very strong (>30 or <0.033) for specific ranges of the Bayes Factor. We replaced the label "anecdotal" with "weak", and "very strong" with "decisive" to aid interpretation.

4.3 Results

This paradigm compared physically identical stimuli (a silent button press) between conditions that manipulate the prediction related to the button press. Assuming that the motor-control condition does not predict a somatosensory stimulus on the left fingers, any additional activity in the other conditions (88%- and 50%-conditions) was considered prediction-related activity. Uncorrected ERP results are shown in Figure 8. As prediction-related activity is the main focus of this study, Figures 10, 11, and 12 show difference waves where the motor-control condition was subtracted from the other conditions.

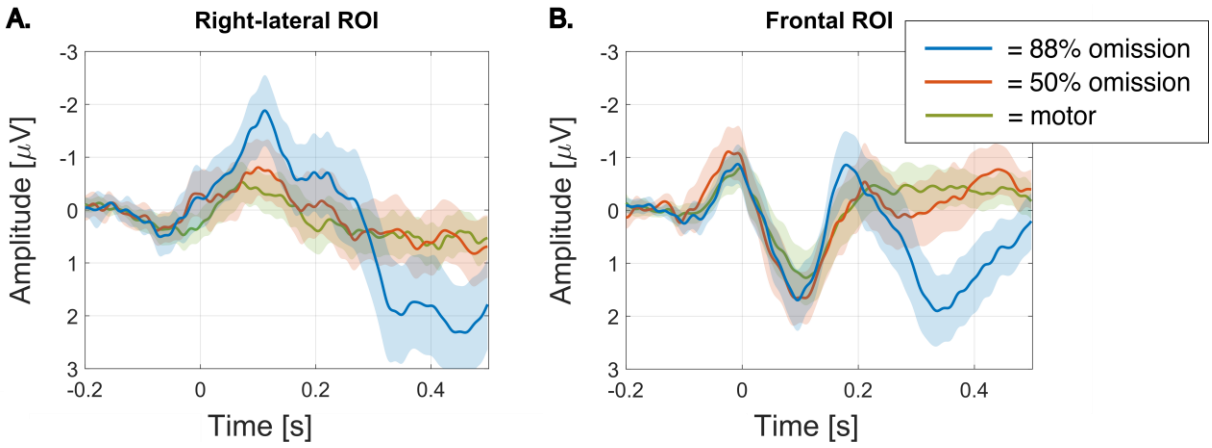

Figure 8: Uncorrected ERPs for right-lateral ROI (A: channels C6, CP6) and frontal ROI (B: channels Fz, F2). Plots show ERPs incl. 95% CIs for 88% omission, 50% omission and motor-control conditions.

4.3.1 Behavior

Participants were generally able to keep a stable pace between button presses throughout the experiment, where the aim was to keep inter-press-interval (IPI) between 600-1200 ms. Group average was 1001 ms (SD=112 ms) for motor-control, 965 ms (SD=120 ms) for 88%-condition, and 937 ms (SD=122 ms) for 50%-condition. Repeated measures ANOVAs showed decisive evidence for a difference between conditions (BF_{10}=427, $F_{(2,58)}$=11.862, p<.001, η^2=0.290). Post-hoc t-tests showed moderate evidence for longer IPI in motor versus 88%-conditions (BF_{10}=5.096, d=0.50, t(29)=2.760, p_{bonf}=.023), decisive evidence for longer IPI in motor versus 50%-conditions (BF_{10}=258, d=0.89, t(29)=4.856, p_{bonf}<.001), and weak evidence for longer IPI in 88%- versus 50%-conditions (BF_{10}=1.667, d=0.38, t(29)=2.095, p_{bonf} =.122).

4.3.2 Cluster-based permutation tests

Cluster-based permutation testing of the 88%-condition (omission) vs. the motor-control condition indicated an effect of condition, showing 2 significant clusters (Figure 9A). The range of the first cluster (p=.008) was around 80 - 250 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, P3, P7, O1, O2, P4, P8, CP6, CP2, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C5, TP7, CP3, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2. The range of the second cluster (p<.001) was around 270-500 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, O1, O2, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2.

Cluster-based permutation testing of the 50%-condition (omission) vs. the motor-control condition indicated no effect of condition.

Cluster-based permutation testing of the 88%-condition (omission) vs. the 50%-condition (omission) indicated an effect of condition, showing 2 significant clusters (Figure 9B). The range of the first cluster (p=.024) was around 80 - 200 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, POz, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2. The range of the second cluster (p<.001) was around 290 and 500 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, O1, O2, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2.

Finally, cluster-based permutation testing of the 88%-condition (stimulus) vs. the 50%-condition (stimulus) indicated an effect of condition, showing 2 significant clusters (Figure 9C). The range of the first cluster (p=.013) was around 30 – 170 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, O1, O2, P4, P8, CP6, CP2, Cz, C4, FC2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2. The range of the second cluster (p<.001) was around 180 - 410 ms and included electrodes: Fp1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, O1, O2, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, Fp2, AF7, AF3, AFz, F1, F5, FT7, FC3, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, AF8, AF4, F2.

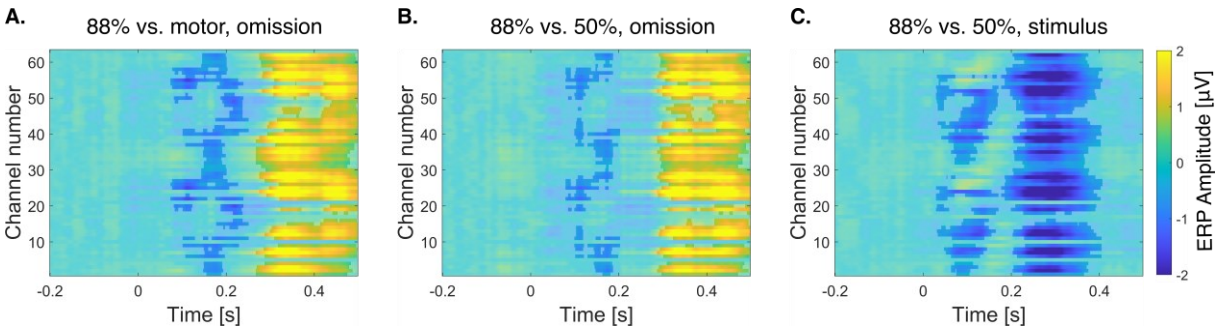

Figure 9: ERP amplitudes (colour map) and cluster statistics (transparency maps) for the difference between motor- vs. 88%-condition in omission trials (panel A), 88%- vs. 50%-condition in omission trials (panel B) and 88%- vs. 50%-condition in stimulus trials (panel C). Color maps display the difference in ERP amplitude over time, broken down by electrode. Electrode numbers, broadly, begin at left frontal sites, ascending counter clockwise, first to posterior sites and then to right frontal sites. Statistically significant clusters (p<.05) are shown as opaque, while non-significant sampling points are shown as transparent.

4.3.3 Omission PCA

After we established that the ERPs of the different experimental conditions differed significantly, we used PCA for signal decomposition to identify the components which carried the crucial information. PCA of the omission ERPs extracted a total of 16 components (as determined by Horn's parallel test) explaining 96.7% of variance. As no prior information was available regarding PCA separation of somatosensory omission components, selection of relevant components was based on visual inspection. Relevant components were selected based on localized peaks in the topographies of either the 88%-condition or the 50%-condition (although no omission components were observed in the 50%-condition). Components were named analogous to auditory omission studies, that is, based on latency and polarity. Results of this process are summarized in Table 4 in chronological order.

Table 4: Results of PCA in chronological order. Displayed are the name of the component, the component number in the PCA, the explained variance of the PCA component, peak latency of the PCA component, and PCA component topography.

Component name	Component number	Explained variance	Peak Latency	Activation topography
Early oN1	1	11.7%	90 ms	Right centrotemporal
Late oN1	10	5.9%	138 ms	Right centrotemporal
oN2	8	7.2%	172 ms	Frontal
oN3	6	7.6%	214 ms	Posterior-temporal
oP3-1	5	8.5%	304 ms	Fronto-central
oP3-2	3	9.0%	348 ms	Central
oP3-3	4	8.7%	394 ms	Fronto-central
oP3-4	13	2.8%	430 ms	Right centrotemporal
oP3-5	2	10.8%	466 ms	Right centrotemporal

Early oN1. PCA extracted two separate components from the first negative wave in the omission ERP. These were termed early and late oN1 (Figure 10A, B), analogous to auditory findings, where o stands for omission and N for the polarity (negative). The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=156, d=0.79, t(29)=4.300, p<.001). In contrast, data provided weak evidence against elicitation of the component in the 50%-condition (BF_{10}=0.491, d=0.26, t(29)=1.438, p=.161). Finally, data provided moderate evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=8.54, d=0.56, t(29)=3.061, p=.005).

Late oN1. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=93, d=0.75, t(29)=4.089, p<.001). In contrast, data provided weak evidence against elicitation of the component in the 50%-condition (BF_{10}=0.547, d=0.28, t(29)=1.521, p=.139). Finally, data provided strong evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=15.0, d=0.61, t(29)=3.316, p=.002).

oN2. Analogous to auditory findings, a frontal negativity was observed around 170 ms (Figure 10C). For this reason the same naming was applied. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=313, d=0.84, t(29)=4.580, p<.001). In contrast, data provided moderate evidence against elicitation of the component in the 50%-condition (BF_{10}=0.199, d=0.043, t(29)=0.235, p=.816). Finally, data provided moderate evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=7.585, d=0.55, t(29)=3.005, p=.005).

oN3. Contrary to earlier findings in auditory modality (e.g. Dercksen et al., 2020; Korka et al., 2020), PCA extracted another negativity which we termed omission N3 (oN3; Figure 10D). The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=40, d=0.68, t(29)=3.743, p<.001). In contrast, data provided weak evidence against elicitation of the component in the 50%-condition (BF_{10}=0.560, d=0.28, t(29)=1.539, p=.135). Finally, data provided moderate evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=7.900, d=0.55, t(29)=3.024, p=.005).

oP3-1. The negative polarity components were followed by a positivity (oP3), which PCA separated in 5 components that we termed oP3-1 to oP3-5 (Figure 10E-I). This naming convention was adapted from Dercksen et al. (2020), where PCA also separated the oP3 in different subcomponents. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=54, d=0.71, t(29)=3.867, p<.001). In contrast, data provided moderate evidence against elicitation of the component in the 50%-condition (BF_{10}=0.216, d=0.09, t(29)=0.473, p=.640). Finally, data provided decisive evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=58, d=0.71, t(29)=3.892, p<.001).

oP3-2. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=8394, d=1.07, t(29)=5.877, p<.001). In contrast, data provided moderate evidence against elicitation of the component in the 50%-condition (BF_{10}=0.225, d=0.10, t(29)=0.566, p=.575). Finally, data provided decisive evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=1596, d=0.95, t(29)=5.225, p<.001).

oP3-3. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=471, d=0.87, t(29)=4.743, p<.001). In contrast, data provided moderate evidence against elicitation of the component in the 50%-condition (BF_{10}=0.205, d=0.06, t(29)=0.340, p=.736). Finally, data provided decisive evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=228, d=0.81, t(29)=4.454, p<.001).

oP3-4. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=58, d=0.71, t(29)=3.892, p<.001). In contrast, data provided weak evidence against elicitation of the component in the 50%-condition (BF_{10}=0.760, d=0.32, t(29)=1.757, p=.09). Finally, data provided decisive evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=2563, d=1.00, t(29)=5.411, p<.001).

oP3-5. The observed data provided decisive evidence for elicitation of the component in the 88%-condition (BF_{10}=13411, d=1.11, t(29)=6.062, p<.001). In contrast, data provided moderate evidence against elicitation of the component in the 50%-condition (BF_{10}=0.200, d=0.05, t(29)=0.250, p=.804). Finally, data provided decisive evidence in favor of a difference between 88%- and 50%-conditions (BF_{10}=1537, d=0.95, t(29)=5.210, p<.001).

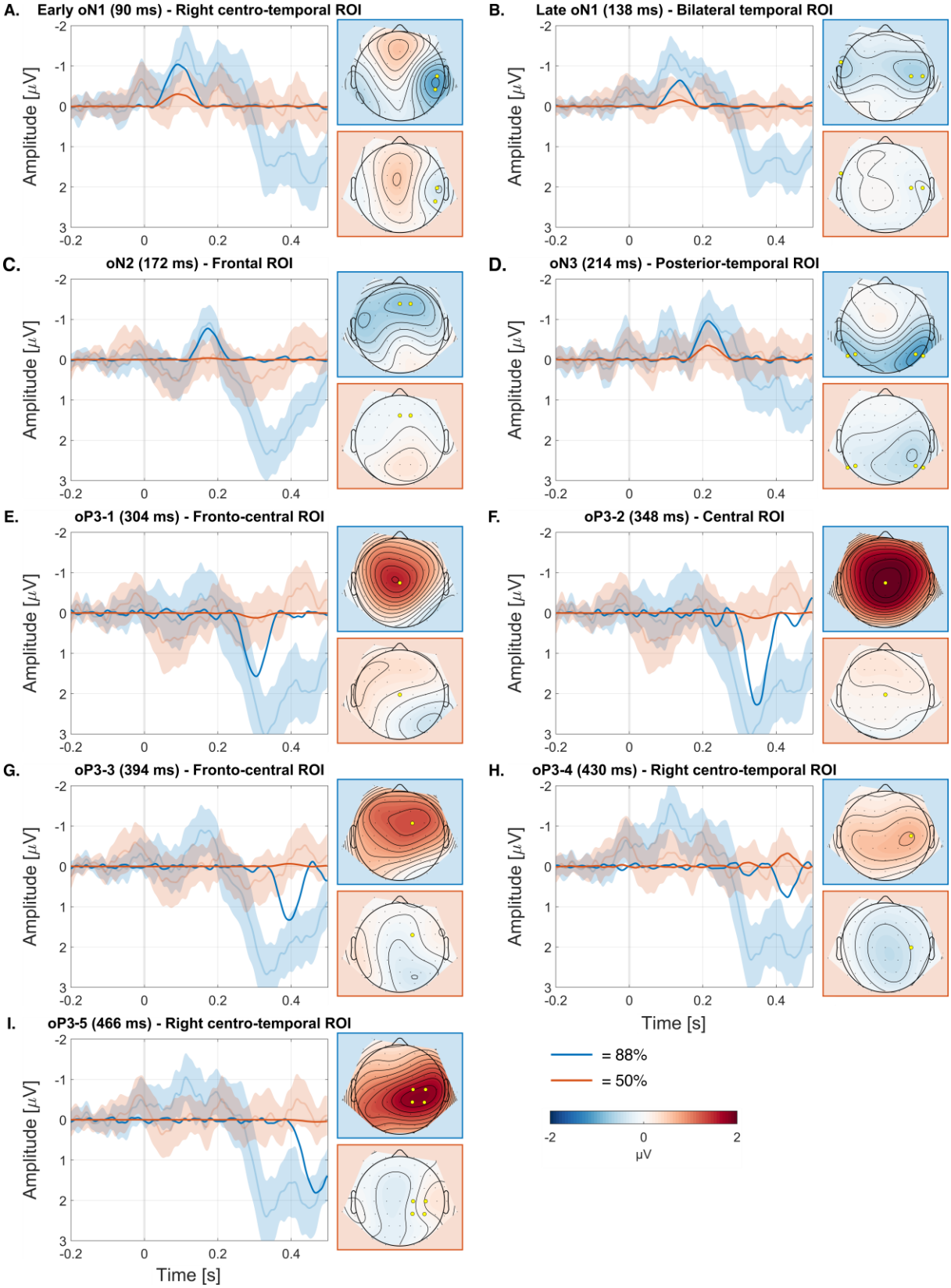

Figure 10: PCA omission components in chronological order (A-I). Plots show difference waves (condition minus motor) for reconstructed PCA (opaque) and the original ERPs incl. 95% CIs (transparent) at highlighted (yellow) electrodes.

4.3.4 Somatosensory PCA

A second PCA analyzed the ERPs of the somatosensory evoked components. The somatosensory PCA extracted 15 components (as determined by Horn's parallel test) explaining 97.0% of variance. Of interest to the current study was the comparison of the chronologically first stimulus-evoked components with the chronologically first omission components. Therefore, relevant stimulus-evoked components were those that occurred from the start of the trial until, and including, the elicitation of the first omission responses (early and late oN1 at respectively 90 and 138 ms) in the omission PCA. This narrowed down the analysis to 3 stimulus-evoked components ranging from 42 ms to 130 ms.

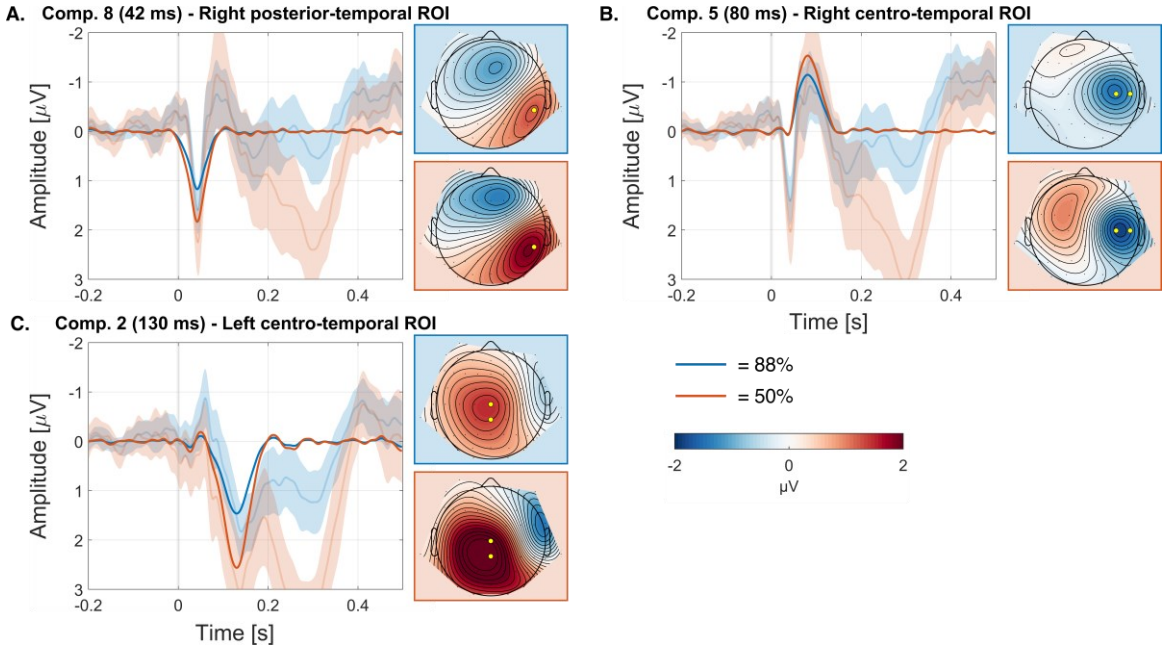

Figure 11: First stimulus-evoked components in chronological order (A-C). Plots show difference wave (condition minus motor) for reconstructed PCA (opaque) and the original ERPs incl. 95% CIs (transparent) at highlighted (yellow) electrodes.

Component 8 was the temporally first elicited component at 42 ms, explaining 5.0% of variance, showing a dipolar topography over right somatosensory areas (Figure 11A). The observed data provided decisive evidence for elicitation of the component in both 88%- and 50%-conditions (88%-condition: BF_{10}=1830, d=0.96, t(29)=5.279, p<.001; 50%-condition: BF_{10}=8013, d=1.070, t(29)=5.859, p<.001). Data provided strong evidence for attenuation in 88%-condition compared to 50%-condition (BF_{10}=19.3, d=0.63, t(29)=3.427, p=.002).

Component 5 was the second elicited component at 80 ms, explaining 9.6% of variance, showing a negativity over right somatosensory areas (Figure 11B). The observed data provided decisive evidence for elicitation of the component in both 88%- and 50%-conditions (88%-condition: BF_{10}=75.5, d=0.73, t(29)=4.004, p<.001; 50%-condition: BF_{10}=52.6, d=0.70, t(29)=3.854, p<.001). Data provided weak evidence for attenuation in 88%-condition compared to 50%-condition (BF_{10}=1.121, d=0.37, t(29)=2.006, p=.054).

Component 2 was the third elicited component at 130 ms, explaining 13.7% of variance, showing a dipolar topography over right somatosensory areas (Figure 11C). The observed data provided decisive evidence for elicitation of the component in both 88%- and 50%-conditions (88%-condition: BF_{10}=2008, d=0.97, t(29)=5.315, p<.001; 50%-condition: BF_{10}=656, d=0.89, t(29)=4.875, p<.001). Data provided

strong evidence for attenuation in 88%-condition compared to 50%-condition (BF_{10}=11.6, d=0.59, t(29)=3.202, p=.003).

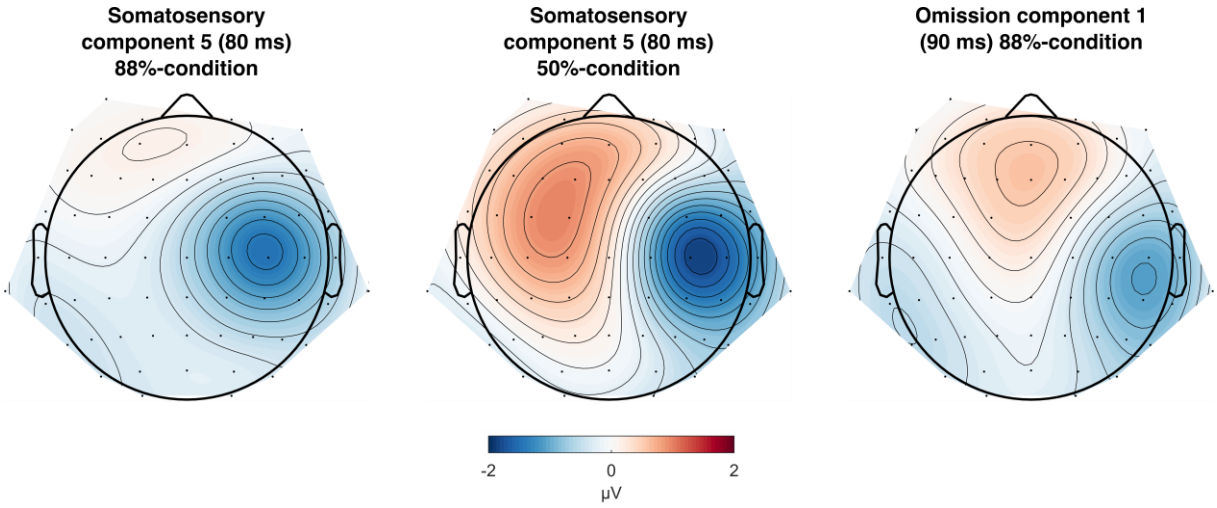

Figure 12: Comparison of topographies between stimulus-evoked component 5 (88%-condition and 50%-condition) and omission component 1 (88%-condition). Topographies show PCA activations at peak latency.

4.4 Discussion

The current study tested whether an omission response would be elicited if an action-related somatosensory prediction was violated by unexpected stimulus omission. To this end, tactile stimulation was either reliably (88%-condition) or unreliably (50%-condition) coupled to a self-paced button press. Stimulus omission elicited a response in the 88%-condition but not in the 50%-condition. Cluster-based permutation tests show an omission response in the 88%-condition starting with a cluster around 80 ms that shows negative polarity in the ERP which is followed by a cluster that shows a positive ERP polarity. Temporal PCA shows a first omission component peaking at 90 ms and reveals several subcomponents within the broad negative-positive distribution of the omission ERP. We will discuss our findings in the context of somatosensory prediction, action-effect couplings, and in comparison with studies reporting auditory omission responses.

Similar to auditory studies, a negativity around 80-100 ms is the first response to omission in the current study (Dercksen et al., 2020, 2022; Korka et al., 2020; SanMiguel et al., 2013a, c; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). PCA separates the negative peak into an early (90 ms) and late (138 ms) component (Figure 10A, B). Similar results were observed in auditory studies, but whether one or two components are extracted might be dependent on the morphology of the ERP and the rotation method used for PCA (Dercksen et al., 2022). The oN1 is mainly elicited on the contralateral side of (omitted) stimulation, suggesting an origin in somatosensory-specific areas of the left hand. This is in accordance with predictive coding: a reliable coupling between action and a sensory consequence on the left hand (88%-condition) builds a sensory prediction, which is thought to be carried by the descending motor signal to contralateral somatosensory areas either through cortical (Jo et al., 2019, Lima et al., 2016, Pazen et al., 2020, Reznik et al., 2015, Schneider & Mooney, 2018) or subcortical (Baumann et al., 2015, Kilteni & Ehrsson, 2020, Knolle et al., 2013a, Pazen et al., 2020) connections. In case of unexpected stimulus omission, comparison of prediction and actual input results in a prediction error signal first elicited in these sensory areas, which serves to correct perception and update higher-level models. The oN1 is assumed to represent this prediction error

signal, and the fact that in both auditory and somatosensory modalities the oN1 seems to be elicited in sensory areas further supports this interpretation.

Cortical implementations of predictive coding assume that deeper layers of the cortical column encode prediction, while superficial layers elicit prediction error. That is, brain areas responsible for stimulus processing also generate corresponding prediction errors (Bastos et al., 2012; Jiang & Rao, 2021; Shipp, 2016). Results in the current study seem to provide some support for this hypothesis, as the early oN1 shows a similar topography and latency relative to the stimulus-evoked component (see Figure 12 for a comparison). This component (Figure 11B), peaking around 80 ms, presumably reflects the N80 given its latency and similar topographical features compared to earlier studies (Montoya & Sitges, 2006; Schubert et al., 2008). However, the N80 is not the first cortical component that is elicited in the stimulus evoked potential (SEP). An earlier component around 42 ms (Figure 11A), showing topographical activation congruent with the P45 (Montoya & Sitges, 2006; Schubert et al., 2008; Van de Wassenberg et al., 2008), is elicited by tactile stimuli but does not have a counterpart in the omission response. The propagation of somatosensory predictions in this study thus seems to be limited to specific parts of the cortex. While the P45 is thought to originate from area 3b in primary somatosensory cortex (SI; Allison et al., 1992; Kakigi et al., 1995; Xiang et al., 1997), generators of the N80 have been placed in both the posterior parietal cortex (PPC) and secondary somatosensory cortex (SII; Forss et al., 1994a, b, 1995; Hoshiyama et al., 1997). The early and late oN1 therefore seem to rather reflect activity in these latter areas, while no omission component is elicited with a latency or topography that would suggest activity from SI. Somatosensory omission results from Andersen and Dalal (2021) and Andersen and Lundqvist (2019) support this conclusion, as they observed omission responses around 135 ms with MEG showing generators localized in SII. This omission response had strong bilateral activation, which in the current study was also more prevalent in the late oN1 (138 ms). Additionally, fMRI studies demonstrate that activity in SII is attenuated when stimuli are self-generated (Arikan et al., 2021; Blakemore et al., 1998, 2000; Kilteni & Ehrsson, 2020; Shergill et al., 2013), further supporting the notion that action-related predictions especially influence secondary areas.

The somatosensory oN1 shows some notably similar characteristics to the auditory oN1, as the auditory oN1 resembles the topography of the T-complex components N1a and N1c that are elicited by auditory stimuli (maximal over temporal electrode locations; Dercksen et al., 2020, 2022; SanMiguel et al., 2013a). The auditory N1a and N1c are thought to originate from the secondary auditory cortex or belt region (Bruneau et al., 1999; Näätänen & Picton, 1987; Ponton et al., 2002; Woods, 1995). As tested in these paradigms, both modalities thus show the areas adjacent to primary areas to be the main generators of prediction error in motor-sensory couplings. This is in line with animal studies suggesting a separation of perception pathways into lemniscal areas (e.g. SI/A1), mainly propagating "raw" sensory information, and nonlemniscal areas (e.g. SII/PPC/A2), which are in comparison more sensitive to stimulus-specific-adaptation (SSA), prediction error generation, and deviance detection (Carbajal & Malmierca, 2018; Parras et al., 2017). The prediction error related to action-effect couplings might therefore primarily be elicited in the rapidly responding and context-sensitive nonlemniscal areas.

It is noteworthy that although the stimulus-evoked P45 does not have an omission counterpart, it does demonstrate a substantial attenuation effect in the 88%-condition. A likely explanation is that in the 88%-condition stimuli were more prevalent, causing stronger adaptation effects (also referred to as

neural fatigue: Grill-Spector et al., 2006; or SSA: Ulanovsky et al., 2003; Malmierca et al., 2014) compared to the 50%-condition. The substantial latency difference between attenuation and omission effects demonstrates that the omission response is not merely a mirror image of sensory attenuation. Instead, the omission response seems to specifically reflect prediction error related to the motor-somatosensory coupling.

After the oN1 components, the next elicited omission response is the oN2 at frontal electrodes around 172 ms after button press (Figure 10C). The oN2 shows remarkable similarities in both topography and latency to the oN2 observed in auditory studies (e.g. Dercksen et al., 2020). Dercksen et al. (2020) argue that the oN2 reflects activity similar to the Mismatch Negativity (MMN). Extensive study of the auditory MMN has revealed separate contributing sources from temporal and frontal generators (see Deouell, 2007 for a review). The somatosensory MMN (sMMN), although not studied in as much detail, also shows evidence of both sensory-specific and frontal generators (Kekoni et al., 1997; Naeije et al., 2018; Shinozaki et al., 1998; Kida et al., 2004). Moreover, an intracranial study of Spackman et al. (2010) found frontal contributions to the sMMN after initial mismatch responses in somatosensory cortex. This modality-independent, preattentive component is thought to be involved in involuntary attention switching. The oN2 fits well to this description, as it resembles a modality-independent frontal mismatch response that is elicited between initial prediction error (oN1) and attention reorienting (oP3) responses. Additionally, this is in line with computational models that assume MMN and omission responses to be elicited by shared local circuitry (Braga & Schönwiesner, 2022).

Contrary to auditory omission studies, a third negative component was observed after the oN2, which was termed the oN3 (Figure 10D). The oN3 was elicited around 214 ms with a bilateral occipital topography that was stronger on the contralateral side of stimulation, indicating somatosensory-specific contributions. A straightforward interpretation of this component is difficult given its absence in earlier studies and posterior topography. Studies more suited to source localization would be helpful for understanding its possible role.

Parallel to auditory omission studies, the earlier negative components are followed by an oP3 including several subcomponents. The oP3 has been associated with the stimulus-evoked P300 response (Dercksen et al., 2020; SanMiguel et al., 2013a; Van Laarhoven et al., 2017). The P300 is a well-documented component, reflecting higher-order processes related to attention reorienting and knowledge updating (e.g. Barry et al., 2016; Escera et al., 1998; Polich, 2007) and is related to the phasic activation of the Locus Coeruleus-Norepinephrine-system (Nieuwenhuis et al., 2011a). PCA separates the large oP3 peak in the ERP into 5 components (Figure 10E-I), which is a plausible result given earlier omission studies and the observed subdivision of the stimulus-evoked P300 response into several subcomponents (e.g. Polich, 2007). What stands out in the PCA separation of the oP3 are the evident similarities of the first three components to the oP3 components observed in the auditory modality by Dercksen et al. (2020) and Korka et al. (2020), who also applied PCA. The similar elicitation of oP3 components across modalities supports that these resemble higher-order and sensory-unspecific cognitive processes. After the third oP3 component, two additional components were identified with similar topography that was contralateral to the stimulus hand. These components presumably reflect additional P300-related activity. Their topographies may be compatible for example with neural generators in the somatosensory cortex (Tarkka & Stokić, 1996).

The current study mainly considers observed omission responses from the perspective of motor-somatosensory prediction. On the one hand, this is in line with the action-based paradigm and the long

history of motor-sensory research that continues up to this day (Kilteni & Ehrsson, 2020; Korka et al., 2022; Shin et al., 2010; Sperry, 1950; von Holst & Mittelstaedt, 1950). On the other hand, research increasingly suggests that the motor system might be part of a more general prediction system. A review of Korka et al. (2022) states that both sensory and motor information likely feed into a common prediction system, where the motor system is one of multiple prediction pathways that result in similar sensory predictions. This explains the observation that similar omission responses are observed whether using motor-sensory (Dercksen et al., 2020, 2021; Korka et al., 2020; SanMiguel et al., 2013a, c; Stekelenburg & Vroomen, 2015) or sensory-sensory (Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017) couplings. It also explains the similar omission response around 135 ms between the current study and studies only using rhythm to induce predictions (Andersen & Dalal, 2021; Andersen & Lundqvist, 2019). To what degree and under which circumstances the motor system plays a unique role in sensory prediction is an ongoing question. Current results suggest that an omission approach might be particularly suitable to study this question given the well-defined subcomponents and robust activations.

4.5 Conclusions

This study investigated the prediction of tactile consequences of self-paced actions and shows for the first time an action-related omission response in the somatosensory modality. When a somatosensory prediction is present when pressing a button, omission of the somatosensory stimulus results in a neural response consisting of multiple consecutive components. First oN1 responses are likely elicited in secondary sensory areas. Furthermore, most of subsequent oN2 and oP3 responses are likely modality-unspecific and presumably reflect higher order processes. The observed omission response supports the long-standing idea that motor acts are paired with forwarded predictions of their somatosensory consequences.

4.6 Acknowledgements

We thank all participants that took part in this study. We thank Dunja Kunke, Gabriele Schöps, Marit Giechau and Cora Bittorf for support in data acquisition

4.7 Funding

This work was supported by the Center for Behavioral Brain Sciences Magdeburg financed by the European Regional Development Fund (ZS/2016/04/78120) and Leibniz Association (P58/2017). TN was funded by the Deutsche Forschungsgemeinschaft (DFG-SFB1436-TPB06). Funding sources did not have any involvement in study design, data collection/analysis/interpretation, writing of the report, or decision to submit for publication.

Chapter 5: Study 3

SALIENT OMISSIONS - PUPIL DILATION IN RESPONSE TO UNEXPECTED OMISSIONS OF SOUND AND TOUCH

The present chapter is based on the following publication:
Dercksen, T. T., Widmann, A., & Wetzel, N. (2023). Salient omissions-pupil dilation in response to unexpected omissions of sound and touch. *Frontiers in Psychiatry*, *14*, 367.

Abstract

Introduction
Recent theories describe perception as an inferential process based on internal predictive models adjusted by means of prediction violations (prediction error). To study and demonstrate predictive processing in the brain the use of unexpected stimulus omissions has been suggested as a promising approach as the evoked brain responses are uncontaminated by responses to stimuli. Here, we aimed to investigate the pupil's response to unexpected stimulus omissions in order to better understand surprise and orienting of attention resulting from prediction violation. So far only few studies have used omission in pupillometry research and results have been inconsistent.

Methods
This study adapted an EEG paradigm that has been shown to elicit omission responses in auditory and somatosensory modalities. Healthy adults pressed a button at their own pace, which resulted in the presentation of sounds or tactile stimuli in either 88%, 50% or 0% (motor-control) of cases. Pupil size was recorded continuously and averaged to analyze the pupil dilation response associated with each condition.

Results
Results revealed that omission responses were observed in both modalities in the 88%-condition compared to motor-control. Similar pupil omission responses were observed between modalities, suggesting modality-unspecific activation of the underlying brain circuits.

Discussion
In combination with previous omission studies using EEG, the findings demonstrate predictive models in brain processing and point to the involvement of subcortical structures in the omission response. Our pupillometry approach is especially suitable to study sensory prediction in vulnerable populations within the psychiatric field.

5.1 Introduction

Unexpected events, such as a loud noise (Liao et al., 2016), a sudden plane engine failure (Kinney & O'Hare, 2020), or a sports match that takes an unexpected turn (Antony et al., 2021), are typically followed by a dilation of the pupil. This pupil dilation response (PDR) is thought to reflect a physiological reaction to surprise and has been observed in a wide range of contexts (Einhäuser, 2017; Kloosterman et al., 2015; Mathôt, 2018; Preuschoff et al., 2011; Strauch et al., 2022; Wang & Munoz, 2015). Surprise responses have played a principal role in traditional and modern theories of brain function, for instance as a reflection of the orienting response (Pavlov, 1927; Sokolov, 1963) or as a consequence of prediction error in the predictive coding framework (Friston, 2005). The "oddball" paradigm is commonly used to elicit surprise in controlled settings, in which a repeated standard stimulus is occasionally interrupted by a rare and unexpected deviant stimulus. Numerous studies have shown an increased PDR in deviant compared to standard stimuli (Bonmassar et al., 2020; Friedman et al., 1973; Wetzel et al., 2016) which is associated with increased activity in the locus coeruleus norepinephrine (LC-NE) system and the superior colliculus (Aston-Jones & Cohen, 2005; Joshi et al., 2016, 2020; Murphy et al., 2011, 2014; Wang & Munoz, 2021).

One challenge in using pupil dilation as a measure of surprise in response to deviant stimuli is that these stimuli may also affect pupil size through various other mechanisms. For example, a novel sound in a series of standard sounds may require additional cognitive resources for processing, or an unfamiliar environmental sound may elicit encoding of new memories. These and other stimulus-related factors can impact pupil dilation (Mathôt, 2018; Zekveld, 2018), but may not necessarily be related to surprise. As a result, the conflation of stimulus- and surprise-related factors on the low-dimensional measure of pupil dilation can make it difficult to draw conclusions about surprise alone when analyzing the PDR.

An innovative approach to studying surprise is through the use of stimulus omissions, where expected standard stimuli are occasionally replaced by an unexpected stimulus absence to elicit surprise. The surprise response to omission can be explained in terms of predictive coding, a neurocognitive theory that posits that the brain uses prior knowledge to continually generate predictions about incoming sensory information. When these predictions are incorrect compared to actual sensory input, this results in a prediction error or surprise response that is used to update and refine the brain's internal models, allowing for more accurate predictions in the future (Clark, 2013; Feldman & Friston, 2010; Friston, 2005). Omission studies use these principles to construct experiments in which a prediction of a stimulus is built and then the stimulus is unexpectedly omitted, resulting in a discrepancy between prediction and input and therefore a surprise response. This approach avoids confounding factors related to the stimulus itself, allowing for a more precise analysis of the effects of surprise on neural processing or behavior.

While theoretically appealing, the use of stimulus omissions has produced somewhat inconsistent results in previous pupillometry research. Cooper et al. (1978) observed only rare pupil responses to auditory omissions in paralyzed cats (but note that the relationship between subcortical activity and pupil responses differs substantially between species, e.g. Joshi et al., 2016, Liu et al., 2017). Stemmerding et al. (2022) observed responses to the omission of fear stimuli in the skin conductance response but not in the PDR. Damsma and Van Rijn (2017) observed an amplified PDR only for omission of the most salient sound on the first beat of a drum sequence but not for the second beat or hi-hat sounds. Zhang et al. (2019), on the other hand, show convincing pupillary omission responses when

coupling visual and auditory stimuli where occasionally the visual stimulus was omitted. This suggests that pupil responses to omissions can be observed under the right conditions. However, it is not yet clear what these conditions may be. In contrast, studies using EEG have consistently demonstrated robust activations in response to omissions over the past years (Dercksen et al., 2020, 2022a, b; Korka et al., 2020; SanMiguel et al., 2013a, c; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). Moreover, the omission P3 (oP3) component that is elicited in response to omissions in the EEG seems to resemble the novelty or surprise evoked P3a. This component is typically also associated with pupil dilation in response to unexpected stimuli and presumably reflects processes related to attention orienting (Nieuwenhuis et al., 2005, 2011a). An important difference between pupillometry and EEG omission studies is the condition to which the omission is compared. In pupillometry studies, unexpected omissions have typically been compared to standard stimuli (Damsma & Van Rijn, 2017; Stemmerding et al., 2022; Zhang et al., 2019), while in EEG studies, unexpected omissions are compared to expected omissions. This reintroduces stimulus-specific confounds to pupillometry studies and may have contributed to inconsistent results in the past. Furthermore, recent omission studies using EEG typically use a time-locking cue, such as the action of a button press, to indicate the exact moment when a stimulus should have occurred. Actions have repeatedly shown to trigger strong predictions of associated effects (see Korka et al., 2022 for a review), but stimuli in different modalities seem to be able to serve the same purpose (Stekelenburg & Vroomen, 2015). Using such time-locking cues likely avoids temporal shifts in the omission response, which may have led to null results in previous studies (Hughes et al., 2001).

Pupil dilation studies have predominantly focused on the visual and auditory modalities, with comparatively few examining the somatosensory modality (Gusso et al., 2021). Similar to other modalities, the pupil responds to tactile stimuli (e.g. Van Hooijdonk et al., 2019). While some pupillometry studies have investigated surprise responses to tactile stimuli (Geuter et al., 2017; Sokolov, 1963), these have largely been in the context of pain research and little is known about more general tactile surprise processes. To the best of the authors' knowledge, surprise responses have not yet been directly compared across the auditory and somatosensory modalities using pupillometry. This is particularly interesting given that Dercksen et al. (2022a) recently identified similar omission components in the EEG using tactile stimuli as those previously recorded using auditory stimuli.

The current study utilizes a tried-and-tested paradigm adapted from EEG studies to examine omission responses in the auditory and somatosensory modalities using pupillometry. This paradigm has been proven to consistently elicit EEG responses to omission in both modalities (Dercksen et al., 2022a ; SanMiguel et al., 2013a). The study presents three conditions, in which participants are asked to repeatedly press a button. In one condition, the stimulus is coupled with the button press most of the time (88%-condition). In the other two conditions, the coupling is either unpredictable (50%-condition) or absent (motor-control condition). Omission responses are expected to occur only in the 88%-condition, as there is a prediction of a stimulus, resulting in surprise when it is omitted. The other two conditions serve as proper comparisons by examining equivalent actions (button presses without a stimulus) where only the surprise associated with the omission is varied.

5.2 Material and methods

5.2.1 Participants

A total of 40 participants took part in the experiment (29 female; age range=18 – 35; mean age=24 ; SD=4.4 years). All participants were right-handed, as measured by a German version of the Oldfield Scale (Oldfield, 1971). All participants reported normal hearing and touch and were compensated either financially or in the form of course credit points. Participants gave written consent prior to the experiment. The project was approved by the local ethics committee.

5.2.2 Stimuli and apparatus

Sound stimuli. A total of 48 different common environmental sounds (e.g., dog, car-horn, trumpet) rated as identifiable by an independent sample of participants (in 200 ms form, see Wetzel et al., 2011) were used as sound stimuli. Sounds were presented binaurally for 200 ms using Sennheiser HD-25 headphones and were tapered-cosine windowed (10 ms rise- and 10 ms fall-time) and root mean square (RMS) matched. Loudness was set at 70.4 dB SPL for all participants (identical to Dercksen et al., 2022b). A new sound was presented for each auditory experimental block, where all 48 sounds were balanced across participants.

Tactile stimuli. Presentation of tactile stimuli was performed using pulses of pressurized air (3 bar) that inflated a membrane, which was controlled using a somatosensory stimulus generator (University of Münster, Germany) that was placed outside the chamber. Tactile stimulus duration was approximately 30 ms. Two membranes were placed on the left middle and index fingers at the volar aspect of the distal phalanx (identical to Dercksen et al., 2022a). The tactile stimulus always consisted of simultaneous stimulation of both fingers. Because of the travel time of the air pulse, there was a slight time delay between button press and inflation of the membrane (onset of the tactile stimulus) of approximately 40 ms.

Apparatus. Participants were seated in an electrically shielded and acoustically attenuated chamber, where a constant luminance of 48.9 lx (measured with MAVOLUX 5032B USB, GOSSEN Foto- and Lichtmesstechnik GmbH, Nürnberg, Germany) was maintained. Pupil diameter of both eyes was recorded with an infrared EyeLink Portable Duo eye-tracker (SR Research Ltd., Mississauga, Ontario, Canada). The eye tracker was set up in remote mode at a sampling rate of 500 Hz. The experiment was programmed using Psychtoolbox (version 3.0.15; Brainard, 1997) and ran on a Linux-based system using GNU Octave (version 4.0.0). A white fixation cross was presented using a VIEWPixx/EEG Display (Resolution 1920(H) x 1080(V) - 23.6-inch display size). The fixation cross was presented in the middle of a grey screen (illuminance: 13.1 cd/m^2), at about 60 cm from the participants' eyes (0.67° × 0.67° visual angle). To trigger the stimuli (or omissions), a custom-built button was used in order to ensure a completely silent button press. The button used an infrared photoelectric mechanism and was additionally padded with sound absorbing material. To ensure that no residual sound (e.g. contact of the skin of the fingertip with the button surface) was correlated with the button press and membrane inflation, participants wore the above mentioned Sennheiser HD-25 headphones throughout the experiment (also when no sounds were presented).

5.2.3 Procedure

Participants were seated approximately 60 cm from a screen, having their right index finger on a button, their left hand on a table (with membranes attached for applying tactile stimuli), and wearing headphones (see Figure 13 for experimental set-up). In all conditions, participants were asked to press

a button every 3000 ms while looking at a fixation cross that was presented on a screen. For both modalities (auditory and somatosensory), two distinct conditions (88%-condition and 50%-condition) were presented. An experimental block always presented only one modality and condition (e.g. auditory 88%-condition). In the 88%-condition, 88% of button presses resulted in a stimulus, while the remaining 12% of button presses resulted in omissions. Omissions were randomly placed within the block to ensure unpredictability, with the only restricting conditions that the first two button presses of every block and the two button presses following an omission always resulted in a stimulus. This was done to avoid any persisting attention- or deviance-related effects in responses to standard stimuli (similar to e.g. Dercksen et al., 2022a). In the 50%-condition, 50% of button presses resulted in a stimulus and the other 50% in omissions. For this condition no restrictions were applied. Additional to the 88%- and 50%-conditions, a motor-control condition was applied to analyze the effect of pressing the button on the pupil. In this condition only the button was pressed, never resulting in a stimulus (i.e., 100% omission). Before the experiment, two short training blocks (15 trials each block) were completed where participants trained to press the button every three seconds. In the first training block, visual feedback on the screen was given after each button press about the time between the current and previous button presses. In the second training block, the participant practiced to keep the correct time between button presses without visual feedback. If participants did not report confidence in their ability to press in the appropriate rhythm, training blocks were repeated to provide additional practice in keeping the time between button presses around three seconds. After training, 12 experimental blocks were presented. Modalities were always presented separately, i.e., first all blocks for one modality were presented, followed by all blocks presenting the other modality, which was balanced across participants. Within a modality, five 88%-condition blocks, one 50%-condition block, and one motor-control condition block were presented. The five 88%-condition blocks were always presented in direct succession. The modality would start with either a 88%-condition or 50%-condition block (balanced across participants), which was followed by a motor-control block, which was then followed by the remaining condition (either 88%- or 50%-condition). The separation between 88%- and 50%-conditions by a motor-control block was implemented to minimize possible carry-over effects between conditions within a modality. Blocks in the 88%-condition consisted of 66 trials, presenting 58 stimulus (sound or tactile) and 8 omission trials. Blocks in the 50%-condition consisted of 80 trials, presenting 40 stimulus (sound or tactile) and 40 omission trials. Blocks in the motor-control condition consisted of 40 trials. The slight increase in the number of trials for the 50%-condition block compared to the 88%-condition block was chosen so that all required trials in the 50%-condition could be presented in a single block. The decrease in the number of trials for the motor-control condition block compared to the 88%-condition block was chosen so that all required trials in the motor-control condition could be presented in 2 blocks that were spread out in the experiment. A total of 768 trials were presented: 528 for 88%-condition (64 omissions), 160 for 50%-condition (80 omissions) and 80 for motor-control (80 omissions). Participants were instructed about the details of the upcoming condition (whether auditory or somatosensory and 88%, 50% or motor condition was presented) before the respective block started. Total experiment time was around 70 minutes including breaks.

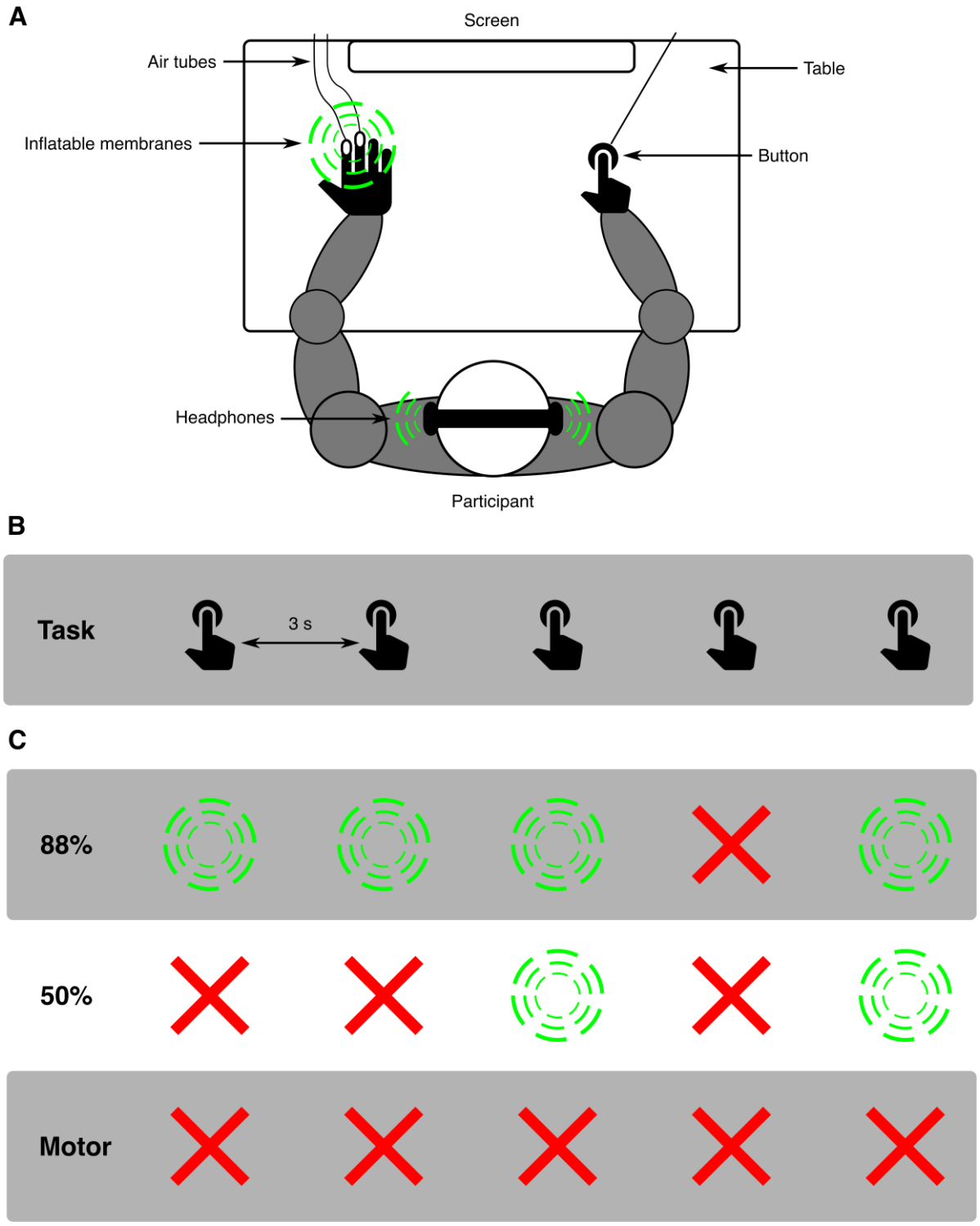

Figure 13: Schematic representation of the experimental design. (A) shows the experimental set-up: a participant sat in front of a screen with both arms on a table. With the right hand a button was pressed, possibly resulting in a stimulus (indicated with green circles). The same stimulus modality was always presented in one experimental block, either auditory or somatosensory. Auditory stimuli were presented using headphones. Somatosensory stimuli were applied by a puff of air traveling through air tubes and inflating a membrane on the left middle- and index-fingers. (B) depicts the task over time, where participants aimed to press a button every 3000 ms. (C) shows examples of the effects of the button presses for all three conditions (green circles are stimulus presentations, red crosses are omissions). In the 88%-condition, there was an 88% chance of a button press resulting in a stimulus.

5.2.4 Pupil data preprocessing

Pupil diameter measurements were converted to mm as suggested by Steinhauer et al. (2022). Eye saccade and blink information were provided by the eye tracker. Partial blinks were detected during post-processing from the smoothed velocity times series by an additional custom function. This function detected pupil diameter changes exceeding 20 mm/s including a 50 ms pre-blink and a 100 ms post-blink interval (as suggested by Merritt et al., 1994). Data from both eyes was averaged using the dynamic offset algorithm (Kret & Sjak-Shie, 2019). Blinks and other intervals with signal loss longer than 1 s were discarded from the data, while shorter intervals were interpolated (using the Matlab 1-D interpolation function with shape-preserving piecewise cubic interpolation). Data was segmented in 2 s epochs around the triggers of interest including a 0.2 s pre-stimulus baseline period (total time window: - 0.2 s to 1.8 s). Epochs were baseline corrected by subtracting the mean amplitude from the baseline period (- 0.2 s to 0 s, similar to Bonmassar et al., 2020 and Widmann et al., 2018). The first 2 trials for all blocks and the 2 trials immediately following an omission in the 88%-condition were removed from further analysis. Individual mean PDRs were computed per participant and condition. For statistical testing, mean PDRs were computed from a time window around the peak between 0.6 s and 0.8 s after button press, which is similar to time windows where other omission studies have found effects (Damsa & Van Rijn, 2017; Qiyuan et al., 1985; Zhang et al., 2019).

5.2.5 Statistical and data analyses

Statistics. Statistical analyses were performed on the PDR data using a Bayesian approach. Additionally, we report frequentist statistics for informational purposes. This way, readers familiar with Bayesian statistics can benefit from its advantages (Rouder et al., 2009; Wagenmakers, 2007) while still keeping results interpretable for readers more familiar with frequentist statistics. Statistical testing was done using JASP (version 0.16.4, JASP Team, 2021). For Bayesian *t*-tests, either a one sample test (to compare with motor activity) or two-tailed paired test (to compare between modalities) were used where the null hypothesis corresponded to a standardized effect size $\delta = 0$, while the alternative hypothesis was defined as a Cauchy prior distribution centered around 0 with a scaling factor of $r = 0.707$ (the default "medium" effect size prior scaling). For Bayesian repeated-measures ANOVA (rANOVA; see Rouder et al., 2017 for more information on Bayesian ANOVA), the JASP default fixed effects priors, random effects priors and covariates priors were used, defined as respectively $r = 0.5$, $r = 1$ and $r = 0.354$. Bayesian rANOVA tested all alternative models (main effects and interactions) against the null model, which included subjects and random slopes. The $BF_{inclusion}$ factor across matched models was calculated for all variables to determine the evidence provided by the data for an effect if comparing all matched models including vs. excluding the effect. Bayes Factor (BF_{10}) was calculated using 10.000 sample repetitions (the JASP default) and was interpreted following Lee & Wagenmakers (2013), who give the labels anecdotal (0.33-3), moderate (3-10 or 0.33-0.1), strong (10-30 or 0.1-0.033), and very strong (>30 or <0.033) for specific ranges of the Bayes Factor. We replaced the label "anecdotal" with "weak", and "very strong" with "decisive" to aid interpretation. The direction of the effect was only reported if the alternative model was preferred over the null model by the data (i.e., $BF_{10} > 1$). For frequentist *t*-tests and rANOVA effect size was reported using Cohens *d* and the generalized η^2 (η_G^2; Bakeman, 2005) respectively.

Planned data analysis. An initial data analysis was planned a priori and aimed to replicate the analysis strategy from preceding EEG studies (SanMiguel et al., 2013a, c; Dercksen et al., 2020, 2022a, b). These studies in a first step typically compared omissions in the 88%-condition to the motor-control condition

as well as omissions in the 50%-condition to the motor-control condition to confirm whether omission responses were elicited in the respective conditions. Presence of an effect in one and absence in another condition does not necessarily indicate a significant difference of the effect between conditions (see, Nieuwenhuis et al. 2011b for discussion), which is why in a second step typically omission responses were directly compared between the 88%-condition and the 50%-condition to confirm that larger omission responses were elicited in the 88% condition. In comparison to the preceding EEG studies in the present study, the additional factor modality (auditory and somatosensory) was introduced. In the first step we therefore tested the omission PDR amplitudes averaged over modalities against the PDR amplitudes in the motor-control condition separately for each probability condition (88% and 50%) and next the omission PDR amplitudes in the auditory against the somatosensory condition separately for each probability condition[1]. In the second step, we then tested differences between 88%-condition and 50%-condition using a 2 x 2 rANOVA including the factors probability condition (88% and 50%) and modality (auditory, somatosensory).

Post-hoc data analysis. A second, post-hoc data analysis of omission results was decided upon a posteriori. We could not help but notice block-specific effects in the 88% and motor-control conditions, showing a substantial attenuation of the PDR after the first block. This observation implies a confounded comparison between omission conditions in the planned data analysis, as the 88%-condition was presented in five consecutive blocks whereas the 50%-condition was presented in a single block. Therefore, we performed another, post-hoc data analysis that took habituation effects into account. First, we tested PDR amplitudes in the 88% and motor-control condition observed in the first block against the PDR amplitudes in the following blocks (second block in motor-control and second to fifth block in 88% condition) to confirm the habituation effects. Next, we replicated all analyses of the planned data analysis (see above) on the data observed in the first block per condition only.

5.3 Results

5.3.1 Behavior

Participants were generally able to keep a stable pace between button presses throughout the experiment, where the aim was to keep inter-press interval around 3 s. Group average for motor-control condition was 2.77 s (SD=0.41 s), for auditory 88%-condition 2.75 s (SD=0.38 s), for auditory 50%-condition 2.85 s (SD=0.44 s), for somatosensory 88%-condition 2.80 s (SD=0.43 s) and for somatosensory 50%-condition 2.82 s (SD=0.43 s).

5.3.2 PDR planned data analysis

88%-condition versus motor-control. In line with our hypothesis, we observed larger PDR amplitudes in response to omissions in the 88%-condition compared to the motor-control condition (Figure 14). The data provided decisive evidence for a condition effect (88%-condition vs. motor-control: BF_{10}=63, d=.607 , t(39)=3.839 , p<.001). PDR amplitudes in response to omissions in the 88%-condition were similar between modalities. The data provided moderate evidence against an effect of modality (88%-condition, auditory vs. somatosensory: BF_{10}=0.241, d=.136 , t(39)=0.860, p=.395).

[1] Note that the preferable 2 x 2 ANOVA design including the factors expectation (omission vs. motor-control) and modality (auditory vs. somatosensory) would result in an unbalanced design as the motor-control condition was modality unspecific. Therefore, we replaced it by an analogous design including two *t*-tests.

50%-condition versus motor-control. Although we hypothesized similar PDR amplitudes between omissions in the 50%-condition compared to the motor-control condition, results were not clear, showing slightly larger PDR amplitudes in response to omissions in the 50%-condition compared to the motor-control condition. The data provided inconclusive evidence for a condition effect (50%-condition vs. motor-control: BF_{10}=1.194, d=.330 , t(39)=2.086 , p=.044). PDR amplitudes in response to omissions in the 50%-condition were similar between modalities. The data provided weak evidence against an effect of modality (50%-condition, auditory vs. somatosensory: BF_{10}=0.411, d=.218 , t(39)=1.382 , p=.175).

88%-condition versus 50%-condition. Contrary to our hypothesis, we observed similar PDR amplitudes in response to omissions in the 88%-condition compared to omissions in the 50%-condition. PDR amplitudes were similar between modalities. The probability condition (88%-condition vs. 50%-condition) by modality (auditory vs. somatosensory) rANOVA favored the null model. The frequentist rANOVA showed no effects for probability condition ($F_{(1,39)}$=3.218, p=.081, η_G^2=.013), modality ($F_{(1,39)}$=1.790, p=.189, η_G^2=.009), or the probability condition by modality interaction ($F_{(1,39)}$=0.246, p=.623, η_G^2=.000).

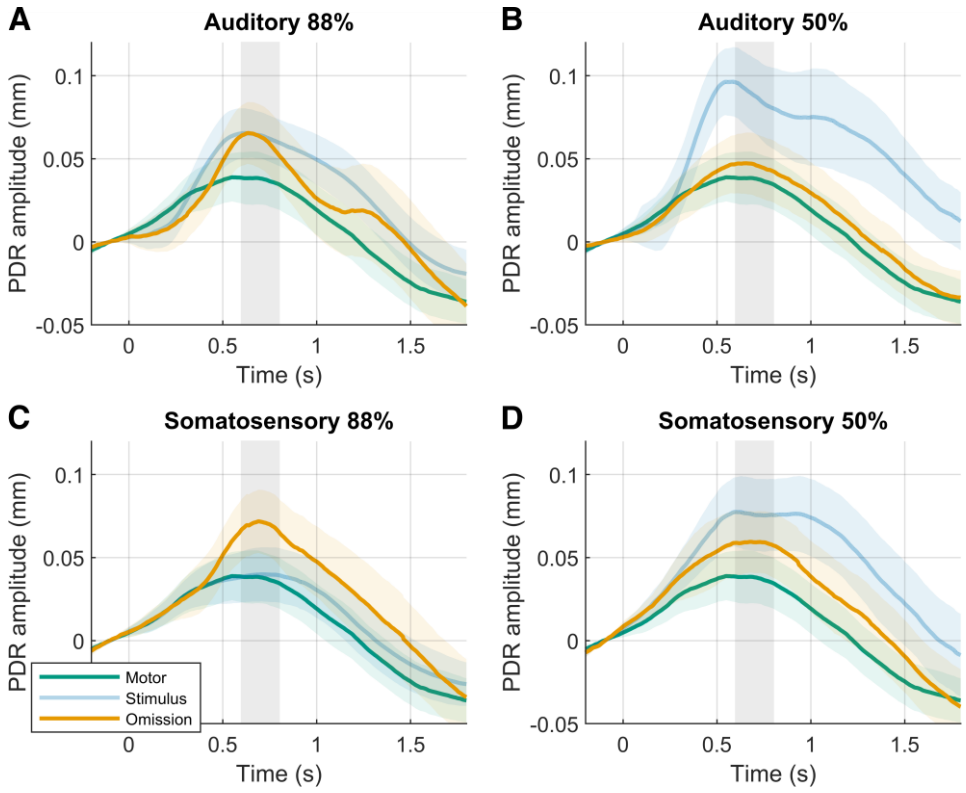

Figure 14: Results of planned analysis. PDRs + 95% confidence intervals of motor-control (green), stimulus (blue, transparent) and omission (orange) trials. The button was pressed at time zero. (A) Auditory 88%-condition. (B) auditory 50%-condition. (C) Somatosensory 88%-condition. (D) Somatosensory 50%-condition. Time-window for statistical analysis shown in grey.

5.3.3 PDR post-hoc data analysis

88%-condition 1st block versus 88%-condition 2+ blocks. Larger PDR amplitudes in response to omissions were observed in the first block of the 88%-condition compared to later blocks in the 88%-condition (Figure 15). PDR amplitudes were similar between modalities. The block (88%-condition 1st block vs. 88%-condition 2+ blocks) by modality (auditory vs. somatosensory) rANOVA favored the model including block, providing moderate evidence (BF_{10}=5.452). The frequentist rANOVA showed a

significant effect for block ($F_{(1,39)}$=9.091, p=.005, η_G^2=.032), no effect for modality ($F_{(1,39)}$=0.433, p=.514, η_G^2=.003), and no modality by block interaction effect ($F_{(1,39)}$=0.035, p=.853, η_G^2=.000).

Motor-control 1st block versus motor-control 2nd block. Slightly larger PDR amplitudes were observed in the first block of the motor-control condition compared to the second block of the motor-control condition. The data provided weak evidence for a block effect (BF_{10}=1.744, d=.362 , t(39)=2.291, p=.027).

88%-condition 1st block versus motor-control 1st block. In line with earlier hypotheses, we still observed larger PDR amplitudes in response to omissions in the first block of the 88%-condition compared with the first block of the motor-control condition. The data provided decisive evidence for a condition effect (BF_{10}=135, d=.651 , t(39)=4.120 , p<.001). PDR amplitudes in response to omissions in the first block of the 88%-condition were similar between modalities. The data provided moderate evidence against an effect of modality (BF_{10}=0.189, d=.074 , t(39)=0.469, p=.641).

50%-condition versus motor-control 1st block. In line with earlier hypotheses, we now observed similar PDR amplitudes in response to omissions in the 50%-condition compared to the motor-control condition. The data provided moderate evidence against an effect of condition (BF_{10}=0.219, d=.116 , t(39)=0.731 , p=.469). For differences between modalities, see section 3.2.1: 50% omission versus motor control.

88%-condition 1st block versus 50%-condition. In line with earlier hypotheses, we now observed larger PDR amplitudes in response to omissions in the first block of the 88%-condition compared to omissions in the 50%-condition. PDR amplitudes were similar between modalities. The probability condition (88%-condition 1st block vs. 50%-condition) by modality (auditory vs. somatosensory) rANOVA favored the model including probability condition, providing strong evidence for a larger PDR in the first block of the 88%-condition compared to the 50%-condition (BF_{10}=12.741). Inclusion Bayes Factor provided strong evidence in favor of including probability condition ($BF_{inclusion}$=12.684) but moderate evidence against including modality ($BF_{inclusion}$=0.326) and the modality by probability condition interaction ($BF_{inclusion}$=0.223). The frequentist rANOVA showed a significant effect for probability condition ($F_{(1,39)}$=13.534, p<.001, η_G^2=.049), no effect for modality ($F_{(1,39)}$=0.735, p=.397, η_G^2=.005), and no modality by probability condition interaction effect ($F_{(1,39)}$=0.006, p=.937, η_G^2=.000).

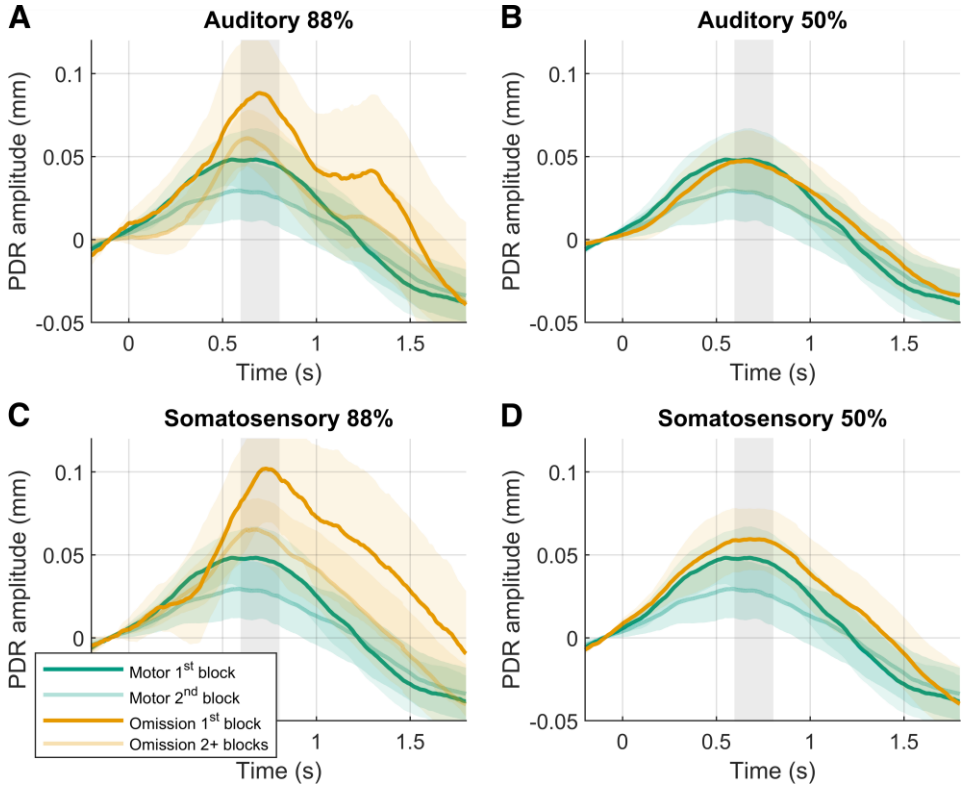

Figure 15: Results of post-hoc analysis. PDRs + 95% confidence intervals of motor-control (green) and omission (orange) trials. The button was pressed at time zero. (A) Auditory 88%-condition. (B) auditory 50%-condition. (C) Somatosensory 88%-condition. (D) Somatosensory 50%-condition. PDRs of first block are shown in opaque to show results of interest, following blocks are transparent. Time-window for statistical analysis shown in grey.

5.4 Discussion

The current study aimed to detect a phasic dilation of the pupil in response to unexpected omissions in the auditory and somatosensory modalities. We manipulated the probability of omissions (88%-condition, 50%-condition, motor-control condition), with the 88%-condition being the only one in which the omission was expected to be surprising. Omission responses were observed in the pupil for both modalities when comparing the 88%-condition with the motor-control condition, showing similar omission PDRs across modalities. In contrast, no omission effects were observed when comparing omissions in the 88%-condition with omissions in the 50%-condition. Further analysis revealed that the amount of exposure to a condition (number of experimental blocks) can impact the amplitude of the omission response, hindering detection of the response in the average over all blocks. When the number of presented blocks was matched between conditions, a clear pupil dilation could be observed in the 88%-condition compared with the 50%-condition. In the following we will discuss these results one by one.

5.4.1 Omission responses in 88%-condition compared to motor-control condition

Similar to EEG studies, the current study used a motor-control condition to determine the elicitation of an omission response. In the motor-control condition, none of the button presses result in a stimulus, making the omissions completely predictable. The comparison of omissions in the 88%-condition with the motor-control condition therefore entails a comparison of two identical events (a button press without a stimulus) where only the associated surprise is manipulated. Controlling for motor activity is important even in pupillometry, as actions are known to be accompanied by a dilation

of the pupil (Hupé et al., 2009; Richer & Beatty, 1985). Also in the current study, a substantial PDR is visible when the button is pressed (Figure 14). The PDR in response to omission in the current study can therefore be defined as the sum of button-press related activity plus a possible surprise response. This can be interpreted as the consequence of high-level executive functions on the one hand and an intermediate-level orienting response on the other in the recent framework proposed by Strauch et al. (2022): button-press related pupil dilation likely reflects a combination of task-related, high-level executive attention processes (e.g. temporal attention, pace keeping, decision-making), while the surprise response likely reflects orienting of attention in response to the salient event (presumably similar to the oP3 observed in EEG omission studies, see Dercksen et al., 2020, 2022a). The surprise response was observed in the 88%-condition compared to motor-control for both auditory and somatosensory stimuli (Figure 14A, C). These results convincingly demonstrate the presence of an omission response in the pupil in both modalities when a stimulus is predicted but unexpectedly omitted. Results also support the notion that the oP3 (presumably belonging to the surprise and orienting-related P3a ERP response family) and omission PDR might reflect at least partly corresponding processes. Indeed, like stimulus deviants, results suggest that surprising omissions can be considered a salient event, with potentially similar effects on behavior like distracted attention (Bendixen et al., 2010; Bonmassar et al., 2021).

This study is the first to directly compare pupillary omission responses between different modalities. Results show evidence against a difference in omission PDRs between the two modalities. This aligns with the EEG findings of Dercksen et al. (2022a), who observed similar oP3 somatosensory omission responses to those seen in auditory studies (e.g. Dercksen et al., 2020). The similarity in pupil responses between the two modalities suggests similar activation in the brain circuits associated with pupil control, which are thought to include the LC-NE system and the superior colliculus (Aston-Jones & Cohen, 2005; Joshi et al., 2016, 2020; Murphy et al., 2011, 2014; Strauch et al., 2022; Wang & Munoz, 2021).

5.4.2 Omission responses in 88%-condition compared to omission responses in 50%-condition

To confirm that the amplified PDR in the 88%-condition was caused by surprise, a 50%-condition included occasional stimuli but, like the motor-control condition, no expectation of stimuli. The cross-condition comparison again involved two identical events (a button press without a stimulus), where now both conditions included stimuli. Contrary to our hypothesis, there was no evidence for a larger omission PDR in the 88%-condition compared to the 50%-condition (Figure 14). This contradicts the results of omission studies using EEG that have consistently reported omission responses when comparing to a 50%-condition (Dercksen et al., 2022a; SanMiguel et al., 2013a). Furthermore, the pattern of results was unclear about whether the PDR was different or the same between the 50%-condition and the motor-control condition. This was unexpected as well, as PDRs between these conditions were expected to be similar rather than different given that theoretically omissions in the 50%-condition are assumed to not elicit a surprise response. To address these surprising results, potential confounds were explored by considering block-specific effects, which are known to severely affect pupil responses. For example, a review of Zekveld et al. (2018) identified 19 pupillometry studies that explicitly mention habituation effects over the course of experimental blocks. In the current study, the 88%-condition included five blocks, while the 50%-condition included only one block (since more 88%-condition blocks were needed to obtain the same number of omission trials given the different presentation rates). Additionally, the motor-control condition included two blocks (spread out across

the experiment). The difference in experimental blocks between conditions carried a risk of disproportionate habituation effects. Post-hoc exploration of the data demonstrated this effect, showing a strong decrease of the omission PDR after the first block of a condition (Figure 15). When only considering the omission trials in the first block of the 88%-condition, the hypothesized larger omission PDR compared with the 50%-condition was observed (Figure 15). The previous effect observed in the 50%-condition compared to the motor-control condition appears to be influenced by block-specific effects as well. When compared with only the first motor-control block, there was evidence against a difference between motor-control and 50%-conditions, in line with the assumption that omissions in the 50%-condition do not elicit surprise. In contrast, a larger omission PDR was still observed when comparing the first block of the 88%-condition with the first block of the motor-control condition. This post-hoc analysis supports the central role of surprise in the omission response and reveals the potential impact of habituation effects. Although habituation effects might be present using other methods than pupillometry (e.g. fMRI, EEG), they are possibly small enough (relative to the omission response) to not interfere with detection of the omission response. Indeed, EEG studies report only small decrements in the P3 elicited by auditory deviants over experimental blocks (Barry et al., 2020; Polich, 1989). These results show that future studies, that aim to study omission responses using pupillometry, should aim to balance experimental blocks across conditions in order to increase statistical power and accuracy. If this is not possible, it is important to consider block-specific effects during analysis to avoid erroneous conclusions. Note that the current post-hoc analysis has the limitation that it only controls for block-specific effects within conditions. This confounding effect was expected to be most influential, as participants were instructed before a new condition and likely needed time to get used to it. However, other effects may also have played a role. For example, on average the presentation of the first block of the 88%-condition occurred earlier in the experiment than the 50%-condition.

Previous pupillometry studies typically compared unexpected omissions with standard stimulus responses to assess the presence of an omission response. This approach may be problematic because the pupil dilates in response to both surprise as well as stimuli. Interestingly, the present study demonstrates how this comparison can be influenced by stimulus-related activity and lead to incorrect conclusions regarding the omission response. In the tactile modality, the relatively small PDR to stimuli is similar to the motor-control and thus allows for the detection of the surprise response in the omission PDR (Figure 14C). However, the sound stimulus produced a PDR that completely masked the omission PDR, potentially leading to the erroneous conclusion that no surprise response is present in the pupil (Figure 14A). The different stimulus responses could be attributed to modality-specific factors, but might also be influenced by stimulus characteristics. For example, the sounds used in the current study changed between blocks, were more complex, longer in duration, and arguably more intense than the tactile stimuli, all of which are factors that are known to affect the PDR to stimuli (Bianchi et al., 2016; Kahnemann & Beatty, 1967; Schlemmer et al., 2005; Oliva & Anikin, 2018; Liao et al., 2016). Controlling for all stimulus-related factors that affect the PDR can be challenging and conflicts with one of the primary benefits of omission paradigms, which aim to minimize the influence of stimulus-related activity. The potential contribution of stimulus activity to inconsistent or null findings in previous pupillometry studies, particularly in the auditory modality, should be carefully considered.

5.4.3 Applications

This study offers a robust and unconfounded approach for investigating the neural mechanisms of surprise. Understanding how the brain responds to surprise has become increasingly relevant not only for a fundamental understanding of the brain, but also in the context of various clinical disorders. For example, several accounts of autism and schizophrenia put the prediction processes that give rise to surprise (or prediction error) at the core of these disorders (Cannon et al., 2021; Van de Cruys et al., 2014; Sterzer et al., 2018). Given the potential differences in stimulus-related processing between patient and control groups (Liss et al., 2006), omission studies, such as the one presented in this study, may be particularly well-suited to isolate and study the effect of surprise (as stimulus-related processing is minimized in the omission response). Additionally, pupillometry offers a number of practical advantages that are especially relevant for clinical populations. These include very good signal-to-noise ratio which reduces recording times compared to other methods such as EEG, reduced physical contact during preparation, reduced preparation time, and minimal attributes that need to be attached to the head. Furthermore, the use of remote eye-trackers does not require movement restrictions as is the case using EEG. This is particularly advantageous when investigating prediction and attention processes in patients with hyperactivity (e.g. ADHD) or tremor (e.g. Parkinson's disease). The combination of a strong indicator of prediction error (the omission response) together with these practical advantages make the current study a useful blueprint for future clinical studies.

5.5 Conclusions

The current study presents conclusive evidence of a pupil response to the unexpected omission of a stimulus, presumably reflecting surprise and the orienting of attention. This finding aligns with the interpretation of the oP3 component observed in EEG omission studies and indicates the involvement of subcortical structures such as the locus coeruleus and superior colliculus in the omission response. There was no indication of an amplitude difference between modalities, suggesting similar, modality-unspecific activation of the involved brain circuits. Additionally, this study was able to identify two important factors that might have contributed to unreliable omission results in past pupillometry studies. First, habituation over experimental blocks apparently plays a substantially larger role in pupillometry compared to EEG studies. Second, stimulus processing effects might mask omission responses when compared with the standard stimulus. These effects should be carefully considered in future study designs. Finally, omission studies using pupillometry may be well suited for use in clinical studies that investigate surprise processing.

5.6 Acknowledgements

We thank all participants that took part in the study. We thank Dunja Kunke, Gabriele Schöps, Marit Giechau, and Cora Bittorf for support in data acquisition.

5.7 Funding

This work was supported by the Center for Behavioral Brain Sciences Magdeburg financed by the European Regional Development Fund (ZS/2016/04/78120) and Leibniz Association (P58/2017). Funding sources did not have any involvement in study design, data collection/analysis/interpretation, writing of the report, or decision to submit for publication.

Chapter 6: Study 4

SOUND OMISSION RELATED BRAIN RESPONSES IN CHILDREN

The present chapter is based on the following publication:
Dercksen, T. T., Widmann, A., Scharf, F., & Wetzel, N. (2022). Sound omission related brain responses in children. *Developmental Cognitive Neuroscience*, *53*, 101045.

Abstract

Action is an important way for children to learn about the world. Recent theories suggest that action is inherently accompanied by the sensory prediction of its effects. Such predictions can be revealed by rarely omitting the expected sensory consequence of the action, resulting in an omission response that is observable in the EEG. Although prediction errors play an important role in models of learning and development, little is known about omission-related brain responses in children.

This study used a motor-auditory omission paradigm, testing a group of 6–8 year old children and an adult group (N = 31 each). In an identity-specific condition, the sound coupled to the motor action was predictable, while in an identity unspecific condition the sound was unpredictable.

Results of a temporal principal component analysis revealed that sound-related brain responses underlying the N1-complex differed considerably between age groups. Despite these developmental differences, omission responses (oN1) were similar between age groups. Two subcomponents of the oN1 were differently affected by specific and unspecific predictions.

Results demonstrate that children, independent from the maturation of sound processing mechanisms, can implement specific and unspecific predictions as flexibly as adults. This supports theories that regard action and prediction error as important drivers of cognitive development.

6.1 Introduction

Infants and children exhibit a strong desire to act in the world. In their first year of life, children voluntarily and repeatedly drop objects, for instance a spoon, and listen highly concentrated to the sound of the impact. A growing body of empirical findings demonstrates the importance of such behavior, showing that action execution forms associations between motor acts and sensory consequences, which are subsequently used to improve perception (Adolph & Hoch, 2019; Hunnius & Bekkering, 2014). Despite the important role of action-effect couplings in development, the maturation of the psychophysiological mechanisms behind this process, their flexibility and specificity, and their interaction with sensory processing are largely unknown. More specifically, the effect of the large developmental changes in the auditory system in middle childhood and its relation to neuronal mechanisms underlying action-effect couplings is largely unexplored.

From a psychophysiological perspective, action-effect couplings are often considered in the context of predictive coding. This theory hypothesizes that higher-level cortical areas send sensory predictions downwards to lower levels. When the predicted input does not match the actual sensory input, a prediction error is generated which is propagated back up the hierarchy, acting as information to update models and generate better predictions (Friston, 2005). An action that is reliably coupled to a sensory consequence (such as dropping a spoon and hearing its impact on the floor) propagates sensory predictions downwards to sensory levels (Arnal & Giraud, 2012). At the moment the action is performed, sensory predictions are compared to actual input, where incorrect predictions result in prediction errors that are propagated back up to higher levels. For infants and children, these prediction errors might be a crucial source of information for learning and development (Emberson, 2017; Köster et al., 2020; Trainor, 2012).

An intriguing example of action-induced prediction error is the electrophysiologically recorded omission response elicited by motor-auditory couplings (Dercksen et al., 2020; SanMiguel et al., 2013a, c). In these experiments, subjects had to press a button every 600–1200 ms, which immediately resulted in a sound most of the time, but where occasionally the sound was unexpectedly omitted. Predictive coding hypothesizes that in these cases, where an auditory prediction is present but auditory input is absent, a prediction error should be elicited in auditory areas. Indeed, a cascade of omission responses is visible in the EEG, where early responses likely originate from auditory areas (SanMiguel et al., 2013c). Similar omission responses have been observed in visual-auditory paradigms (Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). Omission paradigms are a strong tool to investigate prediction as they avoid confounding adaptation effects and can be regarded to solely reflect prediction (error) related activity (SanMiguel et al., 2013c; Schröger et al., 2015). The lack of bottom-up sensory input in these paradigms is particularly beneficial when studying cognitive development, where stimulus processing is still immature (e.g., for auditory processing: Wunderlich & Cone-Wesson, 2006) and could therefore confound inferences regarding the maturation of prediction processes. Several other developmental studies have already demonstrated the benefits of an omission approach using fNIRS (Boldin et al., 2018; Emberson et al., 2015), pupil dilation (Zhang et al., 2019), and EEG (Winkler et al., 2009). These studies were carried out with infants and did not apply motor-sensory couplings that require action. Instead, passive couplings were used, for instance combinations of audio-visual stimuli where occasionally visual stimuli were omitted (e.g. Boldin et al., 2018).

In the paradigm of SanMiguel et al. (2013a), SanMiguel et al. (2013c) and Dercksen et al. (2020) the earliest omission-related component in the event related potential (ERP) is the omission N1 (oN1). As the first indication of (cortical) prediction error, and given its presumed origin in the auditory cortex, the oN1 likely reflects the unconscious comparison between sensory prediction and sensory input (Arnal & Giraud, 2012; Friston, 2005; Knolle et al., 2012; Schröger et al., 2015). According to predictive coding models of perception, the oN1 is related to the N1-family of sound evoked ERP components, as prediction errors are thought to be generated by the sensory processing hierarchy responsible for sound perception (Bastos et al., 2012; Bendixen et al., 2012; Schröger et al., 2015). Significant developmental changes in the sound evoked N1 subcomponents can be observed in middle childhood. The vertex N1 (also termed N1b) takes a long time to fully develop, showing considerable changes until adolescence (Čeponien et al., 1998; Čeponien et al., 2002; Eggermont & Ponton, 2003; Ponton et al., 2000). N1b is often absent in middle childhood, where normally the P1 is the dominant component of the ERP (e.g., Silva et al., 2017; Wetzel & Schröger, 2007), and is sensitive to stimulus presentation and the physical properties of the stimulus (Näätänen & Picton, 1987). The temporal N1 subcomponents – which are considered part of the T-complex (Na and Tb) – are also subject to significant changes throughout development (Rinker et al., 2017; Shafer et al., 2015). The first negative peak, the Na (also termed N1a), is observed in 18-month-olds and is assumed to decrease in both amplitude and latency as the brain matures throughout childhood (Tonnquist-Uhlen et al., 2003; Wunderlich & Cone-Wesson, 2006). The N1a is assumed to reflect the activation of neural generators underlying stimulus detection (Näätänen & Picton, 1987). The later Tb (also termed N1c) emerges after three years of age and decreases in amplitude with age (Albrecht et al., 2000; Ponton et al., 2002), but effects on latency are inconsistent (Albrecht et al., 2000; Mahajan & McArthur, 2013; Ponton et al., 2002). The N1c is assumed to reflect the activation of neural generators underlying stimulus discrimination (Näätänen & Picton, 1987). Generally, the N1 complex is thought to reflect sensory processing (Joos et al., 2014) and is mostly generated by the primary and secondary auditory cortices and auditory association areas (Picton et al., 1999; Woods, 1995).

Given the significant developmental changes of N1 subcomponents, and the discussed relation between auditory omission responses and sound evoked processes, it is unclear whether the oN1 undergoes similar developmental changes. In a broader sense, it is uncertain whether motor-sensory omission responses are present at all in children given the scarce research regarding the development of the responsible prediction pathways. Basirat et al. (2014) found that 3-month-old infants already demonstrate distinct error responses to local sound (deviation from directly successive stimuli, e.g. AAAB, eliciting an early response) and global sound (general rules over multiple sequences, e.g. AAAB AAAB AAAA, eliciting a late response) violations, suggesting that the hierarchical elicitation of prediction error is present from a young age. The responses were, however, very different from adult responses in terms of latency, amplitude, polarity and topography, which might suggest an ongoing development of these components similar to sound evoked processes. Furthermore, action-effect associations have been demonstrated behaviorally in infants around the end of the first year of life (Elsner, 2007). Paulus et al. (2012) additionally observed motor-related EEG activity in 8-month-olds in response to a sound that was associated with the movement of a toy. These findings suggest that action-effect couplings are present from an early age. However, it is unclear whether violations of these couplings elicit sensory error responses in school age children that resemble those of adults given the involvement of an immature auditory system. In particular, the dissociation between the generation of sensory predictions that are specific for the identity of an auditory event, and more

general predictions are barely investigated, even in older children. This knowledge gap regarding the development of action-effect couplings is especially notable given the essential role they play in models of motor control (Shadmehr et al., 2010; Imamizu, 2010), speech production (Hickok & Poeppel, 2007; Pickering & Garrod, 2013), and ideomotor theories in general (for a review see Shin et al., 2010).

The current study aims to investigate the early prediction error (oN1) elicited by motor-auditory couplings, using a child-friendly version of the omission paradigm of SanMiguel et al. (2013a) and Dercksen et al. (2020) that until now was performed in adults only. The study measures a child group aged 6–8 years and an adult control group. This age range ensured that children on the one hand were able to perform the task, and on the other hand demonstrate a comparable, immature brain response to sounds. Our paradigm tests motor-auditory omission responses in two conditions: one where the identity of the sound is known (single sound condition) and one where the identity of the sound is unknown (random sound condition). Dercksen et al. (2020) showed that an oN1 is elicited in both conditions, but that the response is stronger when the sound can be completely predicted (single sound condition). They attributed these findings to possible precision weighting effects: a highly specific prediction (single sound condition) increases the weight that is attributed to the error units, while an unspecific prediction (random sound condition) decreases the weight (Feldman & Friston, 2010). It is unknown whether the children's auditory cortical system, that is not matured in the respective age range, can already differentiate between identity specific and unspecific predictions in a similar way as adults. Therefore, the current study can determine 1) if the oN1 is elicited in children – especially given the developmental processes of its sound evoked counterparts – and 2) whether similar precision weighting effects can also be observed in children.

6.2 Material and methods

6.2.1 Participants

EEG and behavioral data were acquired for a group of adults and a group of children. A total of 39 children and 32 adults were measured. 9 participants were excluded (8 children, 1 adult). 2 children were excluded because they could not perform the task well enough (defined as pressing more than 150 times–out of 1760 trials–too early/late), 3 because of technical problems, and 3 because children switched button-press hand repeatedly during the experiment. 1 adult was excluded because of repeatedly falling asleep and not pressing the button anymore. 31 children were regarded for further analysis (21 female; age range: 6–8; mean age = 7.9, SD = 0.7 years; 2 left-handed as measured by an adapted German version of the Oldfield Scale; Oldfield, 1971; left-handed participants performed experiment with right hand). 31 adults were regarded for further analysis (12 female; age range: 20–35; mean age = 25.3, SD = 4.5 years; 2 left-handed as measured by an adapted German version of the Oldfield Scale; Oldfield, 1971; left-handed participants performed experiment with right hand). All participants reported normal hearing and were compensated with money (for adults) or a voucher for a children's shop (for children). Adults gave written consent prior to the experiment, whereas in the case of children both children and parents gave written consent. For children, it was vocally explained that (translated from German): "I participate voluntarily and if I am tired or would like to stop doing the experiment, it is perfectly ok and we can stop." If the child agreed, they would write their name at the bottom of the form that had the vocally mentioned statement written on it. The project was approved by the local ethical committee.

6.2.2 Stimuli

48 different common environmental sounds (e.g., dog, car-horn, trumpet) rated as identifiable by an independent sample of participants (in 200 ms form, see Wetzel et al., 2011) were used as sound stimuli. Sounds were presented binaurally for 200 ms and were tapered-cosine windowed (10 ms rise- and 10 ms fall-time) and root mean square (RMS) matched. Loudness was set at 70.4 dB SPL for all participants. While performing the experiment, participants were asked to watch a children's movie that was played silently on a screen at ~ 60 cm distance from the participants eyes (10.3° × 18.9° visual angle). The movie (Burton & Starzak, 2015) was a clay-animated story about the adventures of a sheep, that was easy to understand without sound (as there was no speech involved) and suitable for the young age group.

6.2.3 Apparatus

Participants were seated in a dimly lit, electrically shielded, and acoustically attenuated chamber, while EEG was continuously recorded. The experiment was programmed using Psychtoolbox (version 3.0.15; Brainard, 1997) and ran on a Linux-based system using GNU Octave (version 4.0.0). Auditory stimuli were presented using Sennheiser HD-25 headphones. Visual stimuli were presented using a VIEWPixx/EEG Display (Resolution 1920(H) × 1080(V) - 23.6-in. display size). To ensure the button did not make a sound when pressed, a custom-built infra-red photoelectric button was used that was additionally padded with sound absorbing material.

6.2.4 Task and procedure

Participants sat approximately 60 cm from a screen, having their right index finger on a button. In all conditions, participants were asked to press a button every 600–1200 ms, while at the same time watch a movie. If the button was pressed too quickly (< 600 ms ISI) the movie was interrupted and a bunny would appear. If the button was pressed too slowly (> 2000 ms ISI) the movie was interrupted and a snail would appear. As soon as the bunny/snail disappeared, participants could resume the experiment with the next button press. Two distinct sound conditions (single sound, random sound) and a motor control condition were presented. In the sound conditions, a button press resulted in a sound (without delay) 85% of the time, where the remaining 15% of trials were unexpectedly omitted. Sound blocks had 220 sound trials and 40 omission trials, and motor control blocks had 100 trials. Omissions were randomly placed, under the restricting conditions that the first five trials of every block were always sound trials, and every two trials following an omission were always sound trials. In the single sound condition, the same sound was presented in all sound trials of the block. Different sounds were used as the single sound in separate blocks, where all 48 sounds were balanced across participants. In the random sound condition, sounds changed on every trial. A no-sound motor control condition was included in which no sound was presented with the button press to be able to subtract the neural activity related to the pressing of the button. Before the experiment, a few short training blocks were completed where subjects attempted to press the button every 600–1200 ms, using an intuitive feedback display. In the first training block, a speedometer was presented on the screen, where a pointer would move after every button press either in a green (correct time between button presses, middle area of the speedometer) or red (too slow/fast between button presses, left/right areas of the speedometer) area of the speedometer. This training block presented 150 trials without sound. Subsequently, three short training blocks of 20 trials were presented to familiarize participants with the motor control, single, and random sound conditions together with the movie. Training blocks were repeated when necessary (i.e., when the participant did not consistently press in the correct

rhythm yet, or when the participant wanted more practice). What followed were 8 experimental blocks (3 single sound, 3 random sound, 2 motor control). The order of the blocks was completely randomized. Blocks were approximately 3 min long. A total of 660 sound trials and 120 omission trials were performed for each sound condition, and 200 trials were performed as no-sound motor control. Total experiment time was about 45 min including breaks.

6.2.5 Data recording

EEG was recorded from a total of 31 active electrodes, placed according to the extended international 10–20 system at the following positions: FP1, Fz, F3, F7, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, Oz, P4, P8, CP6, CP2, Cz, C4, T8, FC6, FC2, F4, F8, FP2, and the left (M1) and right (M2) mastoids. Furthermore, EOG was recorded from three electrodes placed left and right of the outer canthi of the eyes and below the left eye. The reference electrode was placed on the tip of the nose. An Actichamp amplifier (BrainProducts, Gilching, Germany) was used, recording at 500 Hz using Vision Recorder software (version 1.21).

6.2.6 EEG data preprocessing

EEG data analysis was performed with MATLAB software using the EEGLAB toolbox (Delorme & Makeig, 2004). Data was filtered offline with a 0.1 Hz high-pass filter (Kaiser windowed sinc FIR filter, order = 8024, beta = 5, transition band width = 0.2 Hz) and a 48 Hz low-pass filter (Kaiser windowed sinc FIR filter, order = 402, beta = 5, transition band width = 4 Hz). Data was segmented into epochs starting 200 ms before and ending 500 ms after button press. All trials outside the 600–2000 ms button-press time limit were excluded. Noisy channels were removed from the data, which were defined as having a robust z-score of the robust standard deviation larger than 3 (Bigdely-Shamlo et al., 2015). These channels were removed from analysis and interpolated after ICA. Epochs exceeding a 500 µV signal-change per epoch threshold were removed. ICA was performed to correct for artefacts. This was done on raw data that was 1 Hz high-pass filtered (Kaiser, order = 1604, beta = 5, transition band width = 1 Hz) and 48 Hz low-pass filtered (same as above), as 1–2 Hz high-pass filters improve ICA performance (Klug & Gramann, 2020; Winkler et al., 2015). After ICA, data was segmented − 200 to 500 ms around the button press. The same channels and trials were removed as was done in the previous step. The obtained demixing matrix was subsequently applied to the 0.1–48 Hz filtered data. Artefact ICs were detected with support of the IClabel plugin (Pion-Tonachini et al., 2019). Two independent raters judged components, aiming to remove all heart-, eye- and muscle-related components. Selected components were then discussed to come to a final judgement of components to be removed. For children, on average 11 components were rejected (median = 11, min/max = 8/16, SD = 2), while for adults on average 10 components were rejected (median = 9, min/max = 6/15, SD = 2). Each epoch was baseline corrected by subtracting the mean amplitude of the − 150 to − 50 ms window preceding stimulus onset. Finally, the first five trials of each block, the two trials following an omission, and trials that exceeded 125 µV signal-change per epoch were excluded from analysis. Individual ERPs were computed for each condition and every subject.

6.2.7 Behavioral data

Behavioral data were analyzed to determine if there were systematic differences between age groups in the number of trials pressed outside the appropriate time window and in the rhythm that the button was pressed. This rhythm was determined based on the behavioral data from which any too early/late button presses were removed. Trials were defined as too early when time between button presses was less than 600 ms, and as too late when time between button presses exceeded more than 2000

ms (the same time window that would result in an interruption of the experiment in case of violation, see section 6.2.4).

6.2.8 PCA

Temporal PCA was used to analyze ERPs. This method aims to statistically decompose ERP waveforms into their constituent building blocks (see Dien, 2012 for a tutorial). PCA is particularly suited for the investigation of ERPs in developmental populations reducing problems due to the enhanced noise level (Dien, 2012). Given the typically different component structure and latencies in the child and adult groups, PCAs were performed separately for the adult and child group and for the sound and omission conditions (see Barry et al., 2016 for a demonstration that this approach is superior with systematic component latency differences). The number of retained components was determined using Horn's parallel test. An R implementation of the Component loss rotation (Jennrich, 2004a; Jennrich, 2004b; Jennrich, 2006) method with Kaiser normalization was applied to the initial PCA solution as described by Scharf and Nestler (2019). Component loss rotation is substantially less prone to conflating components with strong temporal and spatial overlap than other rotation methods. This property made component loss rotation especially appropriate since we were specifically interested in a good decomposition of components in the N1 time range. Two separate PCAs were computed on both age groups, one on the individual average ERP responses to sound omissions (plus motor-control) and one on the individual average ERP responses to sounds (plus motor-control). The PCA of omission responses (plus motor-control) focused on the analysis of the oN1, which was recognized on the basis of its typical temporal and topographical characteristics (as described, e.g., by Dercksen et al., 2020). This PCA was computed on the individual averages of the motor control, single sound omissions, and random sound omissions. The ROI for statistical testing of the oN1 was based on the topography reported in previous studies (SanMiguel et al., 2013a, c; Dercksen et al., 2020), using electrodes T7 and T8 (which were the only electrodes that were present in all three aforementioned studies). The PCA of sound responses (plus motor-control) focused on analysis of the sound ERP. This PCA was computed on the individual averages of the motor control, single sounds, and random sounds. ROIs for the components were based on the topography of activations. For children, frontal P1: F3, Fz, F4, FC1, FC2 (frontal/central); T7, T8 (temporal). Centro-lateral P1: FC5, FC1, FC2, FC6; T7, T8. N1c/P2: FC1, FC2, Cz; T7, T8. For adults, P1: F3, Fz, F4, FC1, FC2; T7, T8. N1b: C3, Cz, C4; T7, T8. N1c: F3, Fz, F4, FC1, FC2; T7, T8. P2: FC1, FC2, Cz; T7, T8. The results of the PCAs of sound-related ERPs were only analyzed within groups.

Because separate PCAs for omission responses were performed for the adult and child group, analyzing the differences between the two groups could not be performed on the level of the factor scores and required further consideration. First, we determined the oN1 components as described above separately for each group. Then, we reconstructed the omission PCA component time courses in µV-units reflecting the appropriately scaled contribution of each component to the observed ERP (as previously applied for example by Bonmassar et al., 2020) per component, participant, electrode location, and condition, by multiplying the component score by the peak amplitude of the PCA component loading times the standard deviation (per time point). This conversion of component loadings to real world units (µV) was demonstrated by Dien (1998, Appendix for a formal proof; 2012 for an accessible explanation). The resulting time course reflects the portion of the recorded waveform accounted for by each component scaled to µV, allowing a statistical comparison between the adult and child groups. An amplitude measure for the oN1 components was obtained by the peak amplitude for the single and random condition, respectively, in each group. Before the amplitudes were subjected

to comparisons between age groups, the motor-control waveform was subtracted from the motor-auditory waveform to correct for the contribution of motor activity to the ERP.

6.2.9 Statistical analyses

Behavioral data was tested for differences between groups regarding the number of trials pressed outside the appropriate time window and the time asynchrony between button presses. Both measures were tested using frequentist and Bayesian independent *t*-tests.

The early and late subcomponents of the oN1 were tested for differences between conditions using separate paired samples *t*-tests (single omission vs. motor control, random omission vs. motor control, single omission vs. random omission) within each age group. As previous literature provides clear hypotheses about the expected effects, *t*-tests were performed one-sided. Equivalent comparisons were tested using Bayesian paired samples *t*-tests (single omission vs. motor control, random omission vs. motor control, single omission vs. random).

Differences between groups were tested using a mixed model ANOVA on the omission minus motor control difference amplitudes testing for elicitation of the components (*intercept*; within subject), for condition differences within groups (*condition*: single vs. random condition; within subject), and for amplitude differences between groups (*age group*: children vs. adults; between subject). A significant interaction effect of *condition* × *age group* would indicate between group differences for the condition effects. All mixed model ANOVA main and interaction effects including the intercept term (reflecting component elicitation) were tested with the corresponding Bayesian *t*-tests. This analysis strategy provided optimal correspondence between frequentist and Bayesian tests for evaluating the support provided by the data for the alternative and null hypotheses. Effect size was reported using the generalized η^2 (η_g^2; Bakeman, 2005).

Bayesian paired samples *t*-tests corresponding to the mixed model ANOVA main effects and interactions were performed in R using the BayesFactor package (Morey & Rouder, 2018). The null hypothesis corresponded to a standardized effect size $\delta = 0$, while the alternative hypothesis was defined as a Cauchy prior distribution centered around 0 with a scaling factor of $r = 0.707$ (the default "medium" effect size prior scaling). Resulting Bayes Factors (BF_{10}) were interpreted following Lee and Wagenmakers (2013), who give the labels anecdotal (0.33–3), moderate (3–10 or 0.33–0.1), strong (10–30 or 0.1–0.033), and very strong (> 30 or < 0.033) for specific ranges of the Bayes Factor. We replaced the label "anecdotal" with "weak" and "very strong" with "decisive" to aid interpretation. Analyses were conducted using R 3.6.1 (R Core Team, 2014).

Sound evoked components were tested for differences between conditions using separate paired samples *t*-tests (single omission vs. motor control, random omission vs. motor control, single omission vs. random omission) within each age group. These *t*-tests were performed two-sided. Equivalent comparisons were tested using Bayesian paired samples *t*-tests (single omission vs. motor control, random omission vs. motor control, single omission vs. random).

6.3 Results

In general, both adults and children were able to press the button within the appropriate time window, although children made more mistakes than adults. The average number of trials pressed outside the time window in the child group was 42 (median=34, min/max=3/145, SD=38) and in the adult group 3 (median=1, min/max=1/15, SD=3). The observed data provides decisive evidence for a difference

between groups (BF_{10}=3.88×10^4, d=− 1.46 [95% CI: − 2.02 − 0.90], t(60)=− 5.757, p<.001). Mean inter-press interval in the child group was 941 ± 123 (SD) and in the adult group 960 ± 130 (SD). The observed data provides moderate evidence against a difference between groups (BF_{10}=0.30, d=− 0.15 [95% CI: − 0.65 0.35], t(60)=− 0.584, p=0.561).

The PCA of omission responses extracted a total of 13 components in the children group, and 15 components in the adult group. The PCA of sound responses extracted a total of 10 components in the children group and 13 components in the adult group (Figure 16).

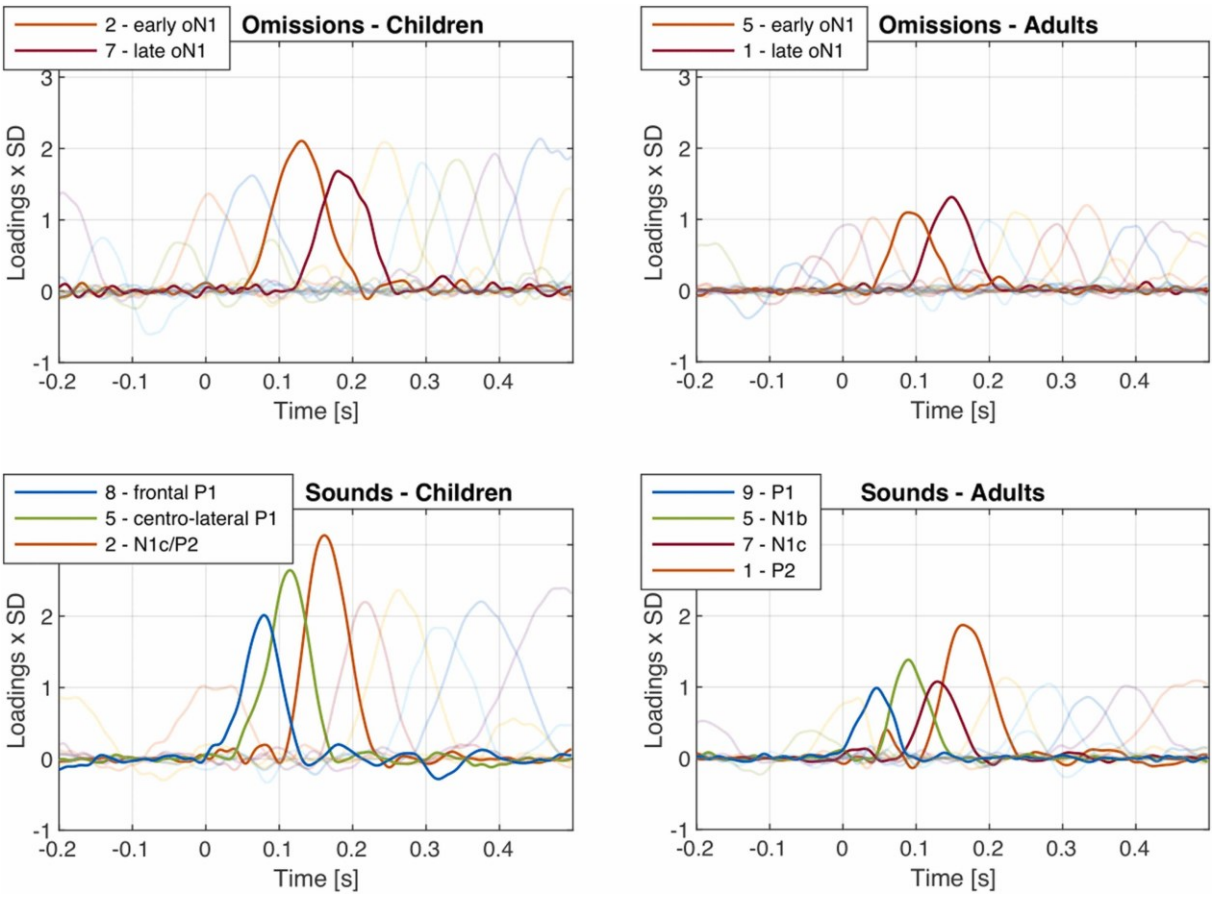

Figure 16: Overview of component loadings for omissions and sounds in children and adults. Components identified as oN1 and sound-related components of interest are shown in opaque.

6.3.1 Early oN1

PCA extracted two components in the oN1 time range, an early and a late component, in both age groups (see Table 5 for mean amplitudes). In the child group, PCA component 2 presumably reflected the early oN1 component, explaining 11.7% of variance. It peaked at 130 ms and was maximal over temporal leads (see Figure 16 for overview of component loadings, Figure 17 for component details). In the adult group, PCA component 5 presumably reflected the early oN1 component, explaining 8.9% of variance. In adults, the early oN1 component peaked at 90 ms and was maximal over temporal leads (see Figure 16 for overview of component loadings, Figure 17 for component details).

Table 5: Motor corrected early and late oN1 amplitudes in the single (SO-M) and random sound conditions (RO-M) in µV units incl. [95% CI] in children and adults.

		Adults	Children	Mean
Early oN1	SO-M	− 0.55 [− 0.77 − 0.33]	− 1.60 [− 2.21 − 1.00]	− 1.08 [− 1.42 − 0.73]
	RO-M	− 0.27 [− 0.44 − 0.09]	− 0.92 [− 1.48 − 0.36]	− 0.59 [− 0.89 − 0.29]
	Mean	− 0.41 [− 0.55 − 0.27]	− 1.26 [− 1.77 − 0.75]	
Late oN1	SO-M	− 0.67 [− 0.93 − 0.40]	− 1.22 [− 1.78 − 0.66]	− 0.94 [− 1.25 − 0.63]
	RO-M	− 0.50 [− 0.80 − 0.19]	− 0.74 [− 1.34 − 0.13]	− 0.62 [− 0.94 − 0.29]
	Mean	− 0.58 [− 0.81 − 0.35]	− 0.98 [− 1.47 − 0.49]	

The early oN1 component was elicited with comparable topography (maximal at temporal leads) across age groups (see Figure 17). Early oN1 amplitude was larger in children compared to adults and larger in the single compared to the random sound condition. The observed data provide strong evidence for the elicitation of the early oN1 component (*intercept* term: BF_{10}=6.56×10^5, *d*=0.82 [95% CI: 0.53 1.11], $F_{(1,60)}$=41.78, *p*<.001, η_g^2=0.336). Furthermore, the data provide strong evidence for higher early oN1 amplitudes in children compared to adults (main effect *age group*: BF_{10}=20.54, *d*=0.84 [95% CI: 0.29 1.37], $F_{(1,60)}$=10.89, *p*=0.002, η_g^2=0.117) and moderate to strong evidence for higher early oN1 amplitudes in the single sound compared to the random sound condition (main effect *condition*: BF_{10}=9.17, *d*=0.39 [95% CI: 0.13 0.65], $F_{(1,60)}$=9.37, *p*=0.003, η_g^2=0.041). The data indicated that the amplitude difference between single and random sound conditions is similar rather than different between the age groups, however, the evidence was not conclusive. If the condition effect is modulated by age group the interaction effect is expected to be small (interaction effect of *condition* × *age group*: BF_{10}=0.52, *d*=0.33 [95% CI: − 0.18 0.83], $F_{(1,60)}$=1.66, *p*=0.203, η_g^2=0.007).

6.3.2 Late oN1

In the child group, PCA component 7 presumably reflected the late oN1 component, explaining 8.7% of variance (see Table 5 for mean amplitudes). In children, the late oN1 component peaked at 180 ms and was maximal over temporal leads (see Figure 16 for overview of component loadings, Figure 17 for component details). In the adult group, PCA component 1 presumably reflected the late oN1 component, explaining 11.4% of variance. In adults, the late oN1 component peaked at 148 ms and was maximal over temporal leads (see Figure 16 for overview of component loadings, Figure 17 for component details).

A late oN1 component was elicited with comparable topography (maximal at temporal leads) across age groups (see Figure 17). Late oN1 had similar amplitudes in children compared to adults and in the single compared to the random sound condition. The observed data provide strong evidence for the elicitation of the late oN1 component (*intercept* term: BF_{10}=8.56×10^4, *d*=0.75 [95% CI: 0.47 1.03], $F_{(1,60)}$=34.94, *p*<.001, η_g^2=0.287). The data suggest that late oN1 amplitudes were similar rather than different between children and adults (main effect *age group*: BF_{10}=0.67, *d*=0.38 [95% CI: − 0.13 0.89], $F_{(1,60)}$=2.27, *p*=0.137, η_g^2=0.026) and also between single sound and random sound conditions (main

effect *condition*: BF_{10}=0.69, *d*=0.24 [95% CI: − 0.02 0.49], $F_{(1,60)}$=3.43, *p*=0.069, η_g^2=0.017) but the evidence was not conclusive. Potential age and condition effects are expected to be small if any. The data provide weak evidence that the amplitude difference between single and random sound conditions is similar rather than different between the age groups (interaction effect of *condition* × *age group*: BF_{10}=0.359, *d*=0.22 [95% CI: − 0.28 0.72], $F_{(1,60)}$=0.77, *p*=0.383, η_g^2=0.004).

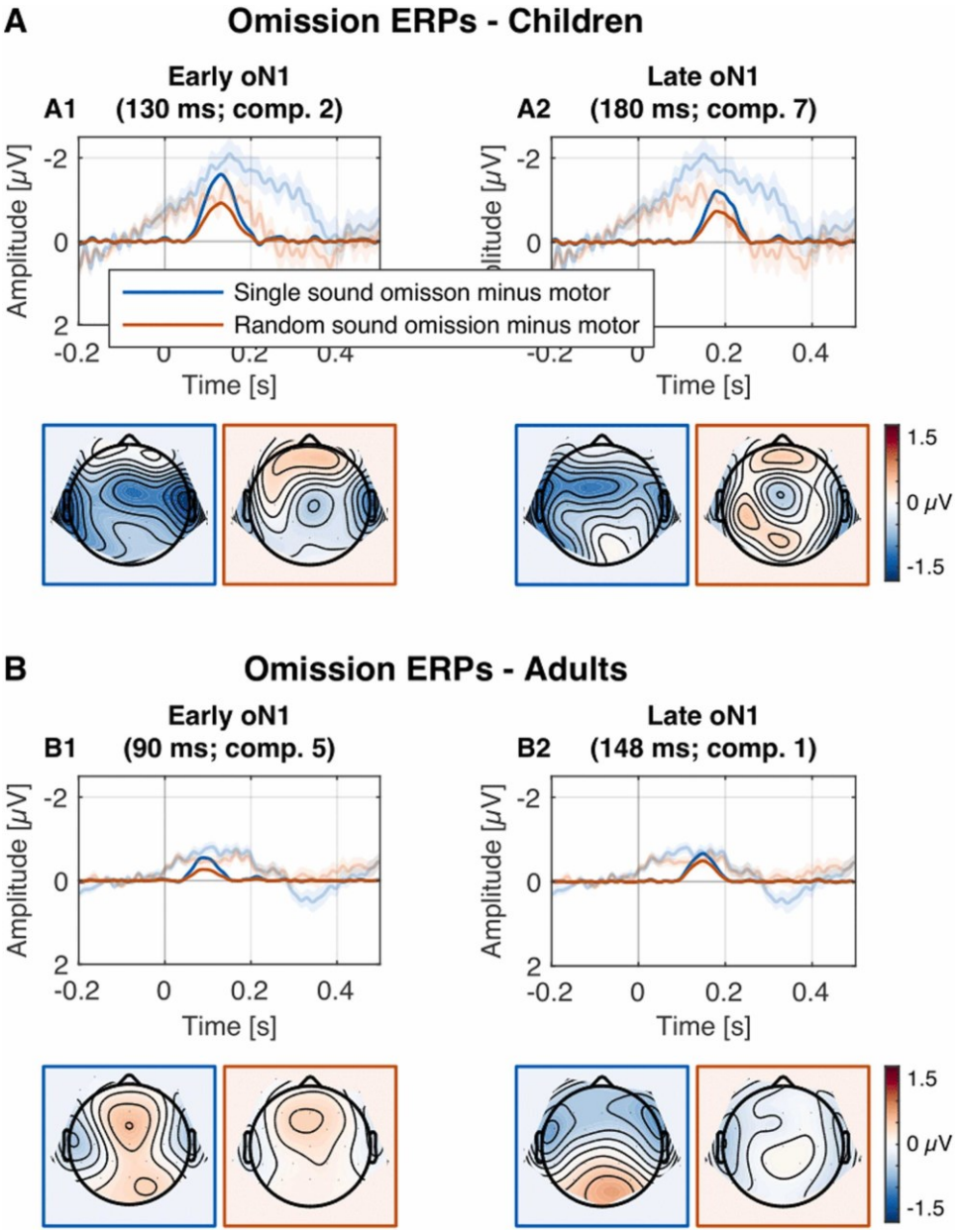

Figure 17: Early and late oN1 components in children and adults. Panel A: Reconstructed PCA component difference waveforms (opaque) and grand-average difference waves plus 95% CIs (transparent) for single (blue) and random (red) sound conditions for electrodes T7 & T8. Panel B: Omission minus motor control difference component topographies at component peak latencies (as reported in panel A) in the single (left column) and random sound conditions (right column). The omission response can be seen over temporal areas.

6.3.3 Sound-related ERPs

The morphology and amplitude of the ERPs evoked by sounds differed substantially between age groups. In adults – after motor correction – the standard P1-N1-P2-N2 morphology was observed. Here, PCA extracted two N1 components (Figure 18 panel B2/B3) presumably reflecting a vertex N1b (90 ms) and a temporal N1c (128 ms). In children, in the same time range, a large positive wave is observed, which PCA subdivides in three separate components (Figure 18 panel A): a frontal positive wave at 80 ms (termed frontal P1), a centro-lateral positive wave at 114 ms (termed centro-lateral P1), and a central positive wave at 162 ms (termed P2). At temporal leads, these components resemble parts of the T-complex (Wolpaw & Penry, 1975): the frontal P1 component inverts polarity at temporal leads and resembles the Na or N1a, the centro-lateral P1 resembles the positive Ta component, and the P2 inverts polarity resembling the Tb or N1c. None of children's components reflected characteristics of the vertex N1b observed in adults. See Table 6 for statistics.

Table 6: Statistical results for two-sided frequentist and Bayesian t-tests comparing sound vs. motor component scores evaluating the elicitation of the respective components at frontal and/or central (Frontal P1: F3, Fz, F4; Centro-lateral P1: FC5, FC1, FC2, FC6; N1c/P2: Cz, FC1, FC2; P1: F3, F4, Fz, FC1, FC2; N1b: C3, C4, Cz) and temporal ROIs (electrodes T7 and T8). Significant effects are printed bold.

	Frontal/central ROIs				**Temporal ROI**			
	d	***BF*$_{10}$**	***t* (30)**	***p***	***d***	***BF*$_{10}$**	***t* (30)**	***p***
Children								
Frontal P1	**0.85**	**496.68**	**4.74**	**< .001**	**-0.84**	**435.69**	**-4.69**	**< .001**
Centro-lateral P1	**1.23**	**1.09×10^5**	**6.83**	**< .001**	**0.76**	**141.05**	**4.24**	**< .001**
N1c/P2	**1.66**	**3.80×10^7**	**9.24**	**< .001**	**-1.01**	**4854.06**	**-5.62**	**< .001**
Adults								
P1	**0.64**	**28.18**	**3.58**	**.001**	0.02	0.19	0.10	.918
N1b	**-0.64**	**27.99**	**-3.58**	**.001**	**-0.93**	**1700.11**	**-5.22**	**< .001**
N1c	**-0.59**	**14.06**	**-3.28**	**.003**	**-1.39**	**1.10×10^6**	**-7.75**	**< .001**
P2	**1.50**	**4.66×10^6**	**8.34**	**< .001**	**0.38**	**1.35**	**2.12**	**.042**

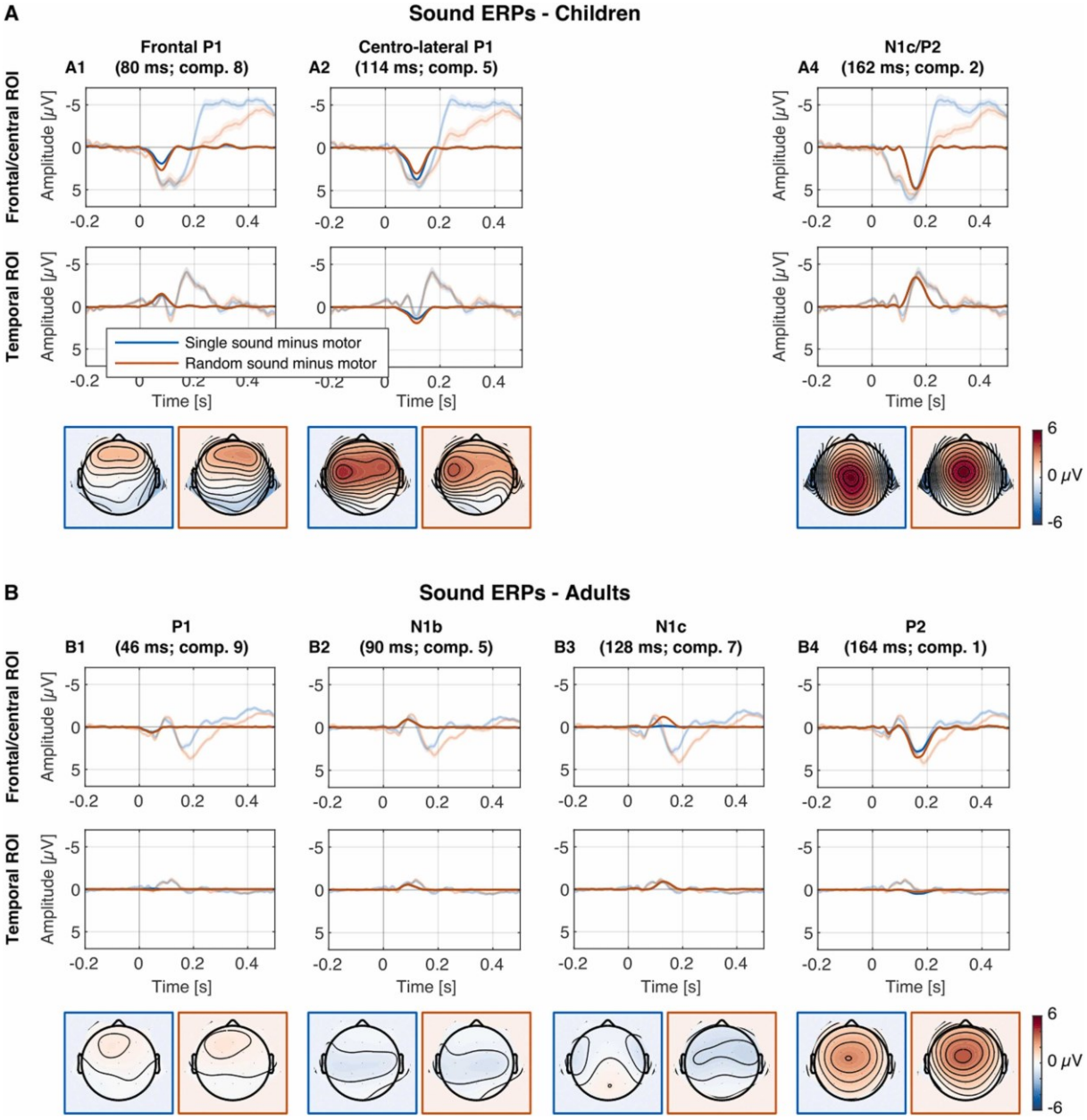

Figure 18: Reconstructed PCA component difference waveforms (opaque) and grand-average difference waves plus 95% CIs (transparent) for single (S-M; blue) and random (R-M; red) sound conditions in children and adults. Panel A: Sound evoked components of interest in children. Three positive components were observed (A1, A2, A4) at frontal (Frontal P1: F3, Fz, F4), centro-lateral (Centro-lateral P1: FC5, FC1, FC2, FC6), or fronto-central ROIs (N1c/P2: Cz, FC1, FC2) and are shown in the top row. Frontal P1 and P2 showed negative potentials over temporal ROIs (T7, T8; second row). N1c and P2 components were presumably conflated in the PCA solution in children due to temporal overlap. Bottom row shows component topographies at peak latencies. Panel B: Sound evoked components of interest in adults. Typical P1, N1b, N1c, and P2 sound components were observed. Components (B1–B4) are shown for frontal (P1: F3, F4, Fz, FC1, FC2), central (N1b: C3, C4, Cz), or fronto-central ROIs (N1c/P2: Cz, FC1, FC2) in top row and temporal ROI (T7, T8) in second row. Bottom row shows component topographies at peak latencies.

6.4 Discussion

The current study aimed to establish an understanding of how prediction related psychophysiological processes develop in the context of action-effect couplings. We developed a child-friendly version of a motor-auditory omission paradigm and recorded an electrophysiological omission response in 6–8 year old children and an adult control group. Participants repeatedly pressed a button triggering a sound which was rarely omitted while watching a silent video. ERP responses were measured in two conditions: a single sound condition where always the same sound was triggered–allowing specific predictions about the identity of the expected sound–and a random sound condition where a random sound was triggered–only allowing unspecific sound predictions. Results show similar omission responses in both age groups. The earliest observed omission response was larger in children than in adults and larger in response to identity-specific predictions compared to identity-unspecific predictions. The pattern of sound-related brain responses in the same time range notably differed between children and adults.

In the following we will discuss (1) the omission response and its subcomponents in children and adults (2) the dissociation of specific and unspecific predictions (3) early oN1 amplitude differences between groups (4) the role of the task-related attentional focus, (5) the development of sound-related brain responses in the N1 range and (6) the role of motor related activity.

6.4.1 Omission-related brain responses

In line with previous studies in adults using versions of the motor-sound omission paradigm, an oN1 in response to unexpected omission of sounds was observed in both age groups (Figure 17). The oN1 is thought to reflect a cortical sensory prediction error resulting from the comparison between predictions, provided by higher cortical levels, and actual sensory input (Dercksen et al., 2020; SanMiguel et al., 2013a, c; Van Laarhoven et al., 2017). Specifically, important higher cortical levels involved in motor-sensory prediction seem to be the (supplementary) motor area (Jo et al., 2019; Lima et al., 2016; Pazen et al., 2020; Reznik et al., 2015; Schneider & Mooney, 2018) and the cerebellum (Baumann et al., 2015; Kilteni & Ehrsson, 2020; Knolle et al., 2013a; Pazen et al., 2020). These areas, either through direct cortical (motor cortex) or indirect subcortical (cerebellum) connections, influence activity in the auditory cortex, presumably based on a predicted model of the planned movement. The observed results suggest that the above-described pathways of motor-sensory prediction are functional in 6–8 year old children.

PCA extracted two components in the time range of the oN1 over temporal electrode sites in both age groups (Figure 17). The early oN1 peaked at 90 ms in adults and 130 ms in children and the late oN1 peaked at 148 ms in adults and 180 ms in children. In Dercksen et al. (2020) only a single oN1 component was extracted. However, the late oN1 and strong oN2 (which is elicited in a similar time-window but at frontal electrodes) might have been conflated in this study because of their close temporal proximity. In the absence of an oN2, the temporal early and late oN1 omission components have been observed by Korka et al. (2020), who used two buttons and only two different tones for the unpredictable condition (in our study termed random condition). In the current study, the oN2 was also absent or severely reduced because of diverted attention. Furthermore, the use of component loss rotation (Scharf & Nestler, 2019) possibly aided in revealing the late oN1, as it is substantially less prone to conflating components with strong temporal and spatial overlap than other rotation methods.

6.4.2 Dissociation of specific and unspecific predictions

The present study dissociates psychophysiological mechanisms underlying specific (single condition) and unspecific (random condition) auditory predictions. Very similar patterns between age groups were observed regarding the differences between these conditions. The amplitude of the early oN1 was larger in the single sound compared to the random sound condition in both age groups, while the late oN1 had similar amplitudes between conditions in both age groups (Figure 17). The higher amplitude early oN1 in the single condition compared to the random condition is in line with the findings of SanMiguel et al. (2013a) and Dercksen et al. (2020). This was discussed to reflect specific and unspecific predictions along the sound processing hierarchy, where precision weighting might influence the strength of prediction error (Dercksen et al., 2020). The observed similar responses between age groups suggests that–like adults–children can implement predictions flexibly, both using specific predictions resulting in prediction errors that are attributed a high weight, and more general predictions resulting in prediction errors that are attributed a low weight. These findings contribute to the idea that prediction errors play an important role in learning processes. Learning and sensory prediction error are closely connected in models of motor control (Shadmehr et al., 2010; Imamizu, 2010) and speech production (Hickok & Poeppel, 2007; Pickering & Garrod, 2013). In these models, sensory prediction errors calibrate action in the face of various sources of noise by adapting the internal model that produces both the action and the sensory representation of its consequences. The current study contributes to these ideas by revealing a neuroscientific demonstration of such action-effect prediction errors, arguably in its purest form (using omission), to be present in children. Additionally, we find these prediction error responses to be relatively mature (as compared with sound processing responses) and sophisticated as they distinguish between specific and unspecific violations. Such findings fit well to theoretical accounts that consider prediction (Emberson, 2017; Gredebäck et al., 2018; Köster et al., 2020; Stahl & Feigenson, 2015; Stahl & Feigenson, 2017; Trainor, 2012) as well as action (Copete et al., 2016; Hunnius & Bekkering, 2014; Koziol et al., 2012; Koziol & Lutz, 2013) not to be consequences, but rather drivers of cognitive development.

6.4.3 Early oN1 amplitude difference between groups

In contrast to the similar effects between conditions, a larger absolute amplitude of the early oN1 was observed in children compared to adults. One explanation for this could be that children had to allocate more attention to the experimental task of pressing the button in a fixed rhythm. Behavioral results indicate that the child group had more difficulties compared to adults, pressing the button too soon/early more often. Increased attention or mental effort devoted to the task, and therefore to sounds vs. the movie possibly increased the early oN1 response, similar to effects of task-related attention on the sound evoked N1 (Lange, 2013). On the other hand, children were perhaps more drawn to the movie as it was suited for a young age group, making it difficult to determine the exact effect of attention in this paradigm. However, participants were constantly monitored by the experimenter, who controlled that at least overt attention was focused on the screen. An alternative explanation of the higher oN1 amplitudes in children is that many ERP amplitudes are generally higher in children, and decrease into adulthood possibly due to, e.g., a decrease in grey matter (synaptic pruning; Itier & Taylor, 2004; Segalowitz et al., 2010). Lastly, a number of studies in adults have hypothesized a shift in weighting from sensory input to the predictive model as age increases (Moran et al., 2014; Chan et al., 2017; Wolpe et al., 2016). This shift is thought to be influenced by the deteriorating sensory precision because of aging, but also by an increased precision of the predictive model as a consequence of experience. Given the latter, the higher amplitude omission responses in

children could be explained as a consequence of a still imprecise predictive model, where high weight is assigned to sensory input in order to update the model. A similar interpretation of the oN1 has recently been proposed by Van Laarhoven et al. (2020) in the context of autism, where people suffering from autism demonstrated to assign a uniform, inflexibly high weight to prediction errors (Van de Cruys et al., 2014). However, whether this hypothesis can be transferred to sensory predictions in children has to be addressed in future studies.

6.4.4 Attentional focus

An interesting consequence of the adapted experimental paradigm is the potential effect of attentional focus on the elicitation of prediction error. Several changes had to be implemented to make the experiment suitable for children compared to the study of Dercksen et al. (2020). For example, the experiment had fewer trials, a slightly higher proportion of omissions, and lower sound volume. However, the most notable change was the addition of a silent video during the experiment, which diverted attention to the visual modality. Given that the other changes were small (omission ratio 15% instead of 12%, 10.1 dB lower sound volume as compared to Dercksen et al., 2020), we assume that this diverted attention was the main driver of the observed differences between the current study and similar omission studies with adults. Compared to similar studies (e.g., Dercksen et al., 2020; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017) the oN1 amplitude was slightly reduced (although no statistical tests were performed). A diminished response would be in line with the conclusions of Chennu et al. (2016): although not specifically focused on the oN1, they used dynamic causal modelling to infer that attention modulates the strength and precision of downward predictions (and thus, theoretically, of the resulting omission response). The current study adds to these findings by demonstrating that directed attention is not required to elicit the oN1, but that diverted attention might result in a diminished amplitude of the component. The dampening effect as a presumed consequence of diverted attention was even more pronounced in the subsequent ERP components that normally follow the oN1 as observed in previous studies (e.g., oN2 and oP3; Dercksen et al., 2020; SanMiguel et al., 2013a).

6.4.5 Age differences in sound-related brain responses

Of special interest was the presumed relation of the sound-related N1 with the oN1 (SanMiguel et al., 2013c). It has been assumed that the generation of predictions induces a pattern of activity that involves shared sources and similar time courses like those of the predicted stimulus (Bastos et al., 2012; SanMiguel et al., 2013c). The current study indicates a largely developed function of cortical sensory prediction error underlying the oN1 component in children aged 6–8 years. In contrast, sound evoked N1 subcomponents in children were either absent or significantly different from adults. Instead of an N1b, children ERPs were dominated by a large amplitude, triple-peaked positive component between ~ 80 and 170 ms, followed by a negative peak N2 between ~ 200 and 250 ms, which is typical for the age group (Bruneau & Gomot, 1998; Čeponien et al., 1998; Čeponien et al., 2002; Ponton et al., 2000; Silva et al., 2017; Wunderlich & Cone-Wesson, 2006). The three extracted subcomponents of the positivity around 80–170 ms in children presumably reflect a frontal P1 at 80 ms, a centro-lateral P1 at 114 ms, and a P2 at 162 ms (Figure 18). In contrast, adults showed the standard P1-N1-P2-N2 morphology at central electrodes.

The frontal distribution of the P1 component–that is associated with stimulus encoding processes (Liegeois-Chauvel et al., 1994)–and their observed latencies in the respective age groups are in line with existing literature (Wunderlich & Cone-Wesson, 2006). It has been discussed that the polarity

inversion at temporal electrodes, that we also observed in the present study, could partly reflect the Na of the T-complex, even if a different developmental time course of P1 and Na in early childhood suggests some independence of the sources underlying P1 and Na (Shafer et al., 2015). While a bifurcation of the P1 component over fronto-central leads in children has been interpreted as the first sign of N1b (vertex N1) development in previous studies (Gilley et al., 2005; Sussman et al., 2008), PCA did not extract a N1b component. This suggests an absence of the N1b in children, which is in line with the protracted development of the N1b observed in other children studies, particularly when relatively short interstimulus intervals (lower than around 1 s) were used (Čeponien et al., 1998; Eggermont & Ponton, 2003; Wetzel & Schröger, 2007). The lack of the vertex N1 and the existence of the oN1 in children indicates a clear dissociation of mechanisms underlying both components. Based on visual inspection of the topographies displayed in Figure 18, it could be speculated that the centro-lateral P1 extracted by PCA (Figure 18) resembles the topography of the adult N1b with inverted polarity. Whether both components reflect partly overlapping mechanisms of sound processing might be an interesting question that can be addressed in further developmental studies.

In adults, the vertex N1 was temporally followed by another subcomponent of the N1 family, the bilateral temporal N1c (Figure 18 panel B3). The N1c emerges in early childhood at temporal leads with increased amplitudes and latencies compared to adults. In 4–8 year olds, the N1c peaks 170 ms after stimulus onset in response to sounds (Bruneau et al., 1997). In the current study, the N1c was probably conflated with the P2 due to strong temporal overlap, peaking around 160 ms (Figure 18 panel A4). The prominent P2 component can be observed early in childhood, can be reliably identified in the auditory ERP of children, and most studies report a similar latency and topography in primary school age children and adults (Wunderlich & Cone-Wesson, 2006). In contrast to children, adults do not show a polarity inversion at temporal leads in the time range of the P2 component (Figure 18, panels A1/A4 & B1/B4). This supports the assumption that the temporal negative pattern in the P2 range reflects the N1c in children. The topography of the sound evoked N1c of both groups with a maximum over temporal leads resembles the topography of the oN1, which might indicate at least partly similar sources of activation in the auditory cortex. The finding that both the N1c and the oN1 are strongly elicited in children can be considered additional evidence to support such a link. Taken together, a largely matured response to the unexpected omission of an expected sound is elicited in both age groups while sound-related brain responses show significant developmental differences, demonstrating that the prediction error differs from obligatory sound processing.

6.4.6 The role of motor related activity

An assumption of the current paradigm is that by subtracting the motor control condition from the single and random conditions, these latter conditions only reflect sound and omission related brain activity. This way, potential differences in motor activity between adults and children in this study should not influence the conclusions regarding sound and omission responses. Given the typical sound responses obtained in both age groups after motor subtraction, the assumption that single and random conditions only reflect sound and omission related activity seems valid. Nevertheless, little is known about how the interaction between motor and sensory activity develops as the brain matures, especially in the framework of prediction. Motor activity related to voluntary movement has been shown to differ in comparison with adults in terms of latency, amplitude, polarity and oscillatory power, where large differences have been observed until at least 10 years of age (Cheyne et al., 2014; Huo et al., 2011; Johnson et al., 2019; Trevarrow et al., 2019). How such differences influence the

interaction between motor and sensory activity is an important subject that could be addressed in future studies.

6.5 Conclusions

Both an early and late oN1 component were observed in children and adults. Children's basic oN1 morphologies and topographies were similar to adults, which is especially interesting given the pronounced differences in sound-related ERPs between groups. Children also show sophisticated processing of identity-specific and identity-unspecific stimuli, demonstrating that they implement specific, higher-weight predictions and more general, lower-weight predictions as efficient as adults. The mature manifestation of action-effect omission responses in children can be considered psychophysiological evidence supporting the important role ascribed to prediction and action as drivers of cognitive development. Furthermore, PCA revealed three distinct subcomponents of the positive peak in the auditory ERP of children, an absence of the N1b, and a presence of the temporal N1c. The early maturation of both the oN1 and the N1c, as well as similar topographies, suggests similar sources. Apart from the developmental perspective, the study shows elicitation of the oN1 in the absence of directed attention, making omission a suitable tool to study prediction in children and patients. However, absence of attention did seem to have a dampening effect on the component amplitudes, especially the components following the oN1. Finally, omission results seem congruent with earlier omission findings that apply motor-auditory couplings.

6.6 Acknowledgements

We thank all families and parents who enabled the conduction of this study. We thank Dunja Kunke, Gabriele Schöps, Celine Jakel, Lisa Pitschmann and Luisa Kocherscheid for support in data acquisition.

6.7 Funding

This work was supported by the Center for Behavioral Brain Sciences Magdeburg financed by the European Regional Development Fund (ZS/2016/04/78120) and Leibniz Association (P58/2017).

Chapter 7: General discussion

Over the past decades, the field of neuroscience has increasingly depicted the brain as a proactive organ. Rather than merely receiving input, the brain seems to employ internal models of the world to predict sensory input and refine these models through prediction errors when predictions are proven incorrect (Clark, 2013; Friston, 2005; Mumford, 1992; Rao & Ballard, 1999). This process of prediction appears to be inherent to brain function and may play a fundamental role in shaping the brain during development (Emberson, 2017; Köster et al., 2020; Trainor, 2012). Previous studies on prediction have often relied on comparing brain responses to predicted and unpredicted (surprising) stimuli. Despite the valuable insights that arose from such studies, these stimulus responses likely represent a mixture of prediction error and other, confounding activity related to stimulus presentation. A promising alternative approach is the study of unexpected stimulus omissions, which minimizes the role of stimulus-related confounds and allows for a more precise investigation of the neural mechanisms that underlie prediction. In this thesis, the study of prediction through omission responses was systematically explored in four studies. Findings expanded knowledge of prediction processes in both adults and children, and substantially deepened understanding of omission responses in various ways.

In this final chapter, I will first examine how the main findings corroborate the two key positions introduced in Chapter 1:

1. *The omission response is an appropriate, reliable, and sensitive tool to study prediction;*

2. *An omission approach is especially suitable for studying prediction processes in the developing brain.*

I will treat these positions sequentially, answering the research questions posed in Chapter 1 on the basis of the four studies presented in Chapters 3 to 6. Subsequently, I will embed the new insights regarding prediction and the omission response in the broader context of deviance detection studies, identifying parallels between phenomena and exploring possible underlying neural mechanisms. This is followed by a discussion of limitations, in which I point out some notable caveats of the work presented in this thesis. I will then outline some promising directions for future work and finalize this thesis with a summary of the general conclusions.

7.1 The omission response is an appropriate, reliable, and sensitive tool to study prediction

In this section, I will present the argument that the omission response is an appropriate, reliable, and sensitive tool to study prediction. The definitions of *appropriate*, *reliable*, and *sensitive* have been introduced in Chapter 1 but will be briefly reiterated. The appropriateness of the omission response is primarily a theoretical consideration, referring to the extent to which the omission response is suitable to study prediction-related processing, specifically in light of other markers of prediction. This concept will shortly be revisited in the context of the presented studies. The reliability of the omission response was defined in terms of replicability, not only in the context of previous studies but also in the context of different methods (EEG and pupillometry) and different sensory modalities (auditory and somatosensory systems). This will be discussed in depth with reference to **Study 1**, **Study 2**, and **Study**

3. The sensitivity of the omission response was defined as its ability to detect subtle prediction effects, and will mainly be discussed in the context of **Study 1**.

7.1.1 Appropriateness of the omission response

In Chapter 1, I discussed the problems that arise when studying prediction through the comparison of stimulus responses, and how an omission approach bypasses these problems. One important issue in this context was the adaptation hypothesis, as adaptation processes might be able to explain a host of ERP phenomena previously assumed to be manifestations of predictive coding (May & Tiitinen, 2010). For example, the MMN, a "prime specimen" of predictive coding (May, 2021), can be explained in terms of adaptation as the result of comparing activity from neural populations that are inhibited by the standard stimulus to neural populations that are not. The most sophisticated adaptation models (May, 2021; May et al., 2015; May & Tiitinen, 2010, 2013) explain a host of phenomena that were previously thought not to be explainable by adaptation processes, such as the MMN in response to sound repetitions or to breaking abstract rules. Given the extensive literature on stimulus-specific adaptation (SSA) in animals (Parras et al., 2017; see Carbajal & Malmierca, 2018 for a review), adaptation processes almost certainly play a key role in perception. However, I think that any explanation of the omission responses observed in **Studies 1** to **4** must involve some notion of prediction. These omission responses cannot be explained by the interpretation of omission responses provided by the adaptation model. That is, as interacting excitatory and inhibitory neural populations that are dynamically equivalent to driven oscillators with damping (May, 2021). Adaptation models thus explain the omission MMN as a type of reverberation of previous stimulus patterns, like a sound creating an echo in a cave. This fails to explain the omission response in this thesis, as the self-paced button presses introduce substantial variability in the time between stimuli. This variability had a standard deviation often exceeding 100 ms in **Studies 1** to **4**, making it highly implausible that low-level neural oscillation mechanisms would cause the observed omission response independent from higher-level influences. Instead, the more plausible interpretation of the omission response is that higher-level areas generate predictions in lower-level sensory areas, which are compared to actual input at the moment that the button is pressed. As neuroscience develops, specific assumptions underlying predictive coding may turn out to be incorrect. This, however, does not change the core observation in this thesis of the omission response as a partly sensory (**Study 1**, **Study 2**), endogenous response to the absence of a stimulus that is only elicited when the stimulus is predicted. With the knowledge currently available, I believe this is best interpreted as prediction error, making the omission response as presented in this thesis an appropriate tool to study prediction.

7.1.2 Reliability of the omission response

In Chapter 1, I described a number of recurring problems in the sparse history of the omission response. For example, the omission MMN is often only elicited when time between stimuli is limited, and may show broad, unspecific activations that are difficult to interpret. Such factors may have contributed to what could be considered a bad reputation of the omission response, possibly explaining why research regarding this phenomenon is scarce. Indeed, for the omission response to be useful for understanding prediction, results should be reliably observed. As discussed in Chapter 1, the lack of a time-locking cue may have contributed to the variable results in previous omission studies. In this thesis the press of a button fulfilled this role, indicating the precise moment that a stimulus should have occurred and thus potentially increasing the reliability of the response.

As a first step in determining the reliability of the omission response in this paradigm, in **Study 1**, the motor-auditory study of SanMiguel et al. (2013a) was replicated. **Study 1** presented a single condition where an identity-specific prediction of a sound was present, a random condition where an identity-unspecific prediction of a sound was present, and a motor control condition. The original study only observed an omission response when an identity-specific condition was present, consisting of a temporal oN1, frontal oN2, and central oP3. These components were thought to represent sensory prediction error (oN1) followed by higher-level prediction error processing (oN2, oP3). Sub-question **Q1a** addressed the replication of these components in the omission response:

Q1a Can the different components of the omission response in the specific condition be replicated?

To determine if these components were replicated, the Replication Bayes Factor and Effect Size Bayes Factor (Verhagen & Wagenmakers, 2014) were used, taking into account results from both the original study as well as **Study 1**. Answering **Q1a**, results convincingly indicated successful replication, showing overwhelming evidence for the presence of the oN1, oN2, and oP3 components for omissions in the identity-specific condition (single sound condition). Components in the ERP were corroborated by a data-driven PCA approach. PCA revealed distinct components for the temporal oN1 and frontal oN2, and divided the large oP3 positivity into several subcomponents over frontal and central areas, possibly analogous to subprocesses observed in the stimulus-evoked P300 response.

In the context of omission components following motor-auditory omissions, it may be useful to temporary leap towards **Study 4**. Similar to **Study 1**, **Study 4** presented an adapted version of the motor-auditory paradigm using the same conditions (specific, unspecific, motor) in children and adult groups. In this study, instead of a single oN1 component, PCA revealed two oN1 components: the early and late oN1. The oN1 component observed in **Study 1** probably represents the early oN1. The late oN1 was probably present in **Study 1** as well, but was conflated with the oN2 component because they were likely elicited too close in time to be separated by PCA (see the temporal activation in the oN2 component of Figure 5). In **Study 4**, the oN2 presented atypically as a possible result of diverted attention (directed towards a video), which is probably why PCA revealed both the early and late oN1 as separate components. This is similar to Korka et al. (2020), who also used PCA to study omissions using motor-auditory couplings. Korka et al. (2020) did not observe an oN2, possibly also as a result of diverted attention, revealing both an early and late oN1 response. Despite the lack of an oN2 response, Korka et al. (2020) did observe oP3 responses consisting of multiple components. The detailed analysis of brain responses following motor-auditory omission in **Study 1** and **Study 4** thus suggests the following structure of the omission response: an initial early and late oN1 response elicited at temporal electrodes, followed by an oN2 at frontal electrodes, concluded by a series of oP3 components at frontal and central electrodes. This structure is broadly in line with ERP patterns observed in earlier studies, although these did not perform a detailed analysis of the underlying components (SanMiguel et al., 2013a; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017).

The oN1 is thought to represent the prediction error that results from comparing a prediction of a stimulus in sensory areas to the absence of sensory input. This is explained by one of the key notions of predictive coding that states that higher-level predictions flow down to lower, sensory levels, where they are compared to actual input. Additionally, predictive coding proposes that these prediction errors should be elicited in the same areas of the cortex that are responsible for stimulus processing (Bastos et al., 2012; Jiang & Rao, 2021; Shipp, 2016). If this is indeed the case, an analogous pattern of

responses should be observed when this paradigm is performed in another modality. Sub-question **Q2a** addressed the assumed sensory origin of the initial prediction error reflected by the oN1:

Q2a Is initial prediction error in the omission response elicited from sensory areas?

Furthermore, earlier omission studies interpret the oN2 and oP3 as higher-level error processing. However, it was unknown whether these components still reflect auditory processing or rather reflect modality-unspecific processing. If the latter is the case, oN2 and oP3 should be comparable across modalities, resulting in sub-question **Q2b**:

Q2b Is later prediction error processing modality-specific or modality-unspecific?

These two questions were answered in **Study 2**, which used motor-somatosensory couplings to study somatosensory omission responses. In this study, button presses with the right hand resulted in a tactile stimulus on the left hand. If the interpretation of the oN1 as a sensory prediction error response is correct, the oN1 should be elicited on the right hemisphere of stimulation (as somatosensory stimuli of the hand are processed in the somatosensory cortex on the contralateral hemisphere). **Study 2** presented three conditions: an 88%-condition, a 50%-condition, and a motor control condition. An omission response was only expected in the 88%-condition, as this condition presented a somatosensory stimulus with the button press in the majority of cases, building a stimulus prediction. In contrast, in the 50%-condition no prediction could be established regarding the coupling between button press and stimulus, as at this chance level the occurrence of a stimulus was random and therefore unpredictable. Therefore, both in the 50%-condition and in the motor control condition, no omission responses were expected.

Results fit remarkably well to the interpretations derived from auditory studies. Omissions in the 88%-condition resulted in an early and late oN1, where the early oN1 was clearly elicited on the contralateral side of stimulation and around the same latency as the auditory early oN1. The omission response following motor-somatosensory couplings has not been researched before, but offers a unique insight into the components of the omission response. An interesting comparison in this context is the resemblance of the early oN1 to stimulus-evoked components. Following predictive coding, areas responsible for stimulus processing should be the same areas that elicit prediction error (Bastos et al., 2012; Jiang & Rao, 2021; Shipp, 2016). A resemblance between early oN1 and stimulus-evoked components would support this notion, and could indicate in which areas prediction error is elicited. In the stimulus-evoked ERP, one component indeed seemed to resemble the oN1: the N80 component elicited by tactile stimuli showed similarities with the topography and latency of the early oN1 component elicited by tactile omissions. This would suggest that the early oN1 is elicited in posterior parietal cortex (PPC) or secondary somatosensory cortex (SII), as these areas have been associated with the stimulus-evoked N80 (Forss et al., 1994a, b, 1995; Hoshiyama et al., 1997). In contrast, no omission equivalent was observed for the stimulus-evoked P45, which is thought to be generated in area 3b in SI (Allison et al., 1992; Kakigi et al., 1995; Xiang et al., 1997). Elicitation of the oN1 in secondary areas is congruent with **Study 1** and **Study 4**, where the oN1 resembles the topography of the temporally elicited N1a and N1c, which are thought to originate from secondary auditory cortex or belt regions (Bruneau et al., 1999; Eggermont et al., 2002; Näätänen & Picton, 1987; Ponton et al., 2002; Woods, 1995). Answering **Q2a**, the similarities between omission- and stimulus-evoked components together with the topography over the right hemisphere strongly suggest a sensory origin of the oN1. This finding possibly has interesting consequences regarding deviance

detection, discussed in more detail in section 7.3. However, it is important to note that this interpretation of the oN1 is based on assumptions that need further support: although there are similarities between stimulus- and omission-evoked responses, these are not always convincing (e.g., in **Study 1**). An important question for future research is therefore to determine to what extent oN1 responses reflect stimulus-evoked responses (see section 7.5).

From the omission components that followed the oN1 in **Study 2**, some showed strong similarities to the oN2 and oP3 omission components observed in the auditory omission response of **Study 1**. Like in **Study 1**, the oN2 in **Study 2** showed a frontal activation and was elicited around 170 ms. This supports the idea that the oN2 is a modality-unspecific component reflecting higher-level prediction error processing. In **Study 1**, it was argued that the oN2 component might best be interpreted as an omission MMN considering its latency and polarity reversal at mastoid electrodes. The fact that a similar component was elicited in **Study 2** would suggest that the oN2 might reflect the modality-unspecific, frontal generator of the MMN. Furthermore, PCA of the oP3 in **Study 2** resulted in five subcomponents, from which three showed evident similarities to the oP3 subcomponents observed in **Study 1**. The elicitation of these components across modalities is in line with its interpretation as a response similar to the P300. The P300, often elicited by surprising stimuli, is thought to reflect higher-order processes related to attention reorienting and knowledge updating (Barry et al., 2016; Escera et al., 1998; Polich, 2007). Interestingly, the two additional oP3 components in **Study 2** showed a topography contralateral to the stimulus. Together with the additional oN3 component observed in **Study 2**, these components suggest that higher-level prediction error processing is both modality-unspecific as well as modality-specific, answering **Q2b**.

As a final step in determining its reliability, the omission response was measured using pupillometry in both the auditory and somatosensory modalities. Sub-question **Q3a** addressed the issue of whether pupil omission responses could be measured using the action-effect paradigm:

Q3a Can action-effect couplings be used to measure omission responses in the pupil?

Furthermore, this study allowed for a direct comparison between auditory and somatosensory modalities, resulting in **Q3b**:

Q3b Do auditory and somatosensory omission responses in the pupil elicit similar or different responses?

These research questions were answered in **Study 3**, which used the same action-effect paradigm as **Study 2**, presenting three conditions in the auditory and somatosensory modality: an 88%-condition, a 50%-condition, and a motor control condition. Answering **Q3a**, results show a larger omission pupil dilation response (PDR) in the 88%-condition compared to the motor control condition for both modalities, showing that the omission response can be effectively measured using pupillometry. The same results were observed in the 88%-condition compared to the 50%-condition, but only when the number of experimental blocks were matched. That is, a post-hoc analysis revealed that pupil responses severely diminished over the presented blocks in a condition, which masked the omission effect compared to the 50%-condition. These are important lessons for future work where pupillometry may serve as a more convenient alternative to EEG, offering practical advantages such as shorter preparation time and high SNR, making experiments shorter and therefore more suitable for clinical or developmental populations. Moreover, pupil dilation likely reflects subcortical activity, specifically the locus coeruleus norepinephrine (LC-NE) system and the superior colliculus (Aston-Jones

& Cohen, 2005; Joshi et al., 2016, 2020; Murphy et al., 2011, 2014; Wang & Munoz, 2021). In the context of **Study 1** and **Study 2**, this subcortical activity is likely coupled with the oP3 given the relation between subcortical activity and the stimulus-evoked P300. Specifically, salient stimuli are thought to cause phasic activity from the locus coeruleus, resulting in norepinephrine release in the cortex that enhances the gain of neurons that produce the P300 (Nieuwenhuis et al., 2005; Vazey et al., 2018).

Answering **Q3b**, the direct comparison between the auditory and somatosensory PDR showed similar activation between modalities. This is in line with the similar oP3 responses observed between **Study 1** and **Study 2**, supporting the notion of partly modality-unspecific activation of these brain circuits.

Taken together, the answers provided by **Study 1**, **Study 2**, and **Study 3** make a strong case for the reliability of the omission response in the context of the action-effect omission paradigm. The omission response was not only replicated, but was replicated in different modalities and using different measurement methods. Moreover, these studies provided a novel understanding of the structure of prediction error generation, offering detailed insights regarding the function and possible neural origins of the different components of the omission response.

7.1.3 Sensitivity of the omission response

The studies of SanMiguel et al. (2013a) and Van Laarhoven et al. (2017) both only showed omission responses when a specific prediction of an upcoming sound was present. Two possible conclusions could be derived from this. On the one hand, omission responses might lack sensitivity to detect the violation of unspecific predictions, either due to insufficient SNR or because they are encoded differently in the brain. On the other hand, it could be that the brain can only use predictions when exact foreknowledge about the upcoming stimulus is present. This latter option would signify a rather rigid model of prediction, incongruent with predictive coding (Feldman & Friston, 2010) and non-omission studies (Bäß et al., 2008; Bednark et al., 2015; Knolle et al., 2013b, 2019). Additionally, exact foreknowledge of stimuli is scarce in everyday life, severely limiting the generalizability of conclusions to outside the lab. Although both SanMiguel et al. (2013a) and Van Laarhoven et al. (2017) concluded an absence of omission effects in the unspecific condition, trends seemed present in both studies. Increased power could therefore discern whether the omission response is sensitive also to unspecific predictions, which was addressed in sub-question **Q1b**:

Q1b Are unspecific sound predictions reflected in the omission response?

In **Study 1**, increased power was realized by measuring double the amount of participants (n=30) compared to the study of SanMiguel et al. (2013a), and using sophisticated preprocessing such as ICA to maximize the SNR per participant. Answering **Q1b**, PCA convincingly showed oN1 as well as oP3 components also when the specific identity of the upcoming sound could not be predicted (random sound condition). Moreover, Bayesian analyses showed that this effect was not necessarily absent in the original study, and that there is strong evidence in favor of these effects when considering both studies. The oN1 in response to unspecific predictions is an important finding, as it indicates that sensory predictions can be flexibly applied, and omissions can be used to study the resulting prediction errors. The oN1 as well as oP3 responses were considerably smaller in the unspecific condition compared to the specific condition. This is congruent with the concept of precision weighting, where the gain of prediction error units is adapted based on their expected precision (Feldman & Friston, 2010). As the unspecific condition only allowed broad, imprecise predictions, the gain on the respective prediction error units would be diminished, resulting in a diminished prediction error response.

Alternatively, the neural populations that are part of the prediction template might differ between conditions. In the specific condition, the prediction template might contain both broadly and narrowly tuned neural populations, whereas in the unspecific condition only broadly tuned neural populations might be part of the prediction template. In the unspecific condition, no oN2 component was elicited. The lack of a higher-order prediction regarding sound identity in this condition might explain the absence of the oN2. Finally, **Study 4** further supports the conclusions regarding unspecific sound predictions, replicating the oN1 in the unspecific condition, as well as the diminished amplitude compared to the specific condition (for the early oN1).

7.1.4 Summary of first position

The answers to the sub-questions can be used to answer the main research questions **Q1**, **Q2**, and **Q3**, summarizing the main conclusions of **Study 1**, **Study 2**, and **Study 3**. The first main research question was:

Q1 To what extent can specific and unspecific omission findings in the motor-auditory paradigm be replicated?

Study 1 demonstrated convincing evidence that omission responses in the specific condition could be replicated, showing a fixed pattern of components with distinct and replicable elicitation patterns. Additionally, attenuated omission responses were observed in the unspecific condition, demonstrating that the omission response is sensitive to more subtle types of prediction.

The second main research question was:

Q2 How do motor-sensory omission responses transfer to the somatosensory modality?

Study 2 showed the hypothesized pattern of a unilateral oN1 over the right hemisphere following left hand tactile omission, congruent with the oN1 reflecting sensory prediction error. Furthermore, a partly similar elicitation of the oN2 and oP3 components was observed, suggesting that these are common processes across modalities. However, other higher-level processes seemed to be modality-specific.

The third main research question was:

Q3 How are omission responses using motor-auditory and motor-somatosensory couplings reflected in pupillary activity?

Study 3 showed an increased PDR following omission both when using motor-auditory as well as motor-somatosensory couplings. Evidence against a difference between modalities was observed, suggesting similar subcortical activation, congruent with similar oP3 responses across modalities as observed in **Study 1** and **Study 2**.

In summary, this section asserts that the omission response is an appropriate, reliable, and sensitive tool to study prediction. The omission response isolates prediction-related activity, making it appropriate, shows replicable and converging results, making it reliable, and can distinguish between different types of predictions, making it sensitive. This is a considerable update to existing knowledge and opens up exciting new possibilities for the future (see section 7.5).

7.2 An omission approach is especially suitable for studying prediction processes in the developing brain

A lot of cognitive functions, such as attention, memory, and stimulus processing, undergo large changes over the course of development (Sprondel et al., 2011; Wetzel et al., 2006; Wunderlich & Cone-Wesson, 2006). The interconnectedness of these functions make it challenging to study one of these in particular. The omission response, as an endogenous response to the absence of a stimulus, minimizes the influence of factors unrelated to prediction. This makes it particularly useful to study prediction-related processes during development. Still, only very few omission studies exist in the developmental literature, which is a missed opportunity given the central role of these processes during development. Indeed, the perpetual cycle of prediction and prediction error that infants and children seem to engage in is deemed a crucial, driving element of cognitive development (Emberson, 2017; Gredebäck et al., 2018; Köster et al., 2020; Trainor, 2012; Stahl & Feigenson, 2015, 2017). That is why in **Study 4** I set out to provide a first demonstration of the motor-auditory omission paradigm in 6–8 year old children, and compare these results with those from adults. This age range ensured that children on the one hand were able to perform the task, but on the other hand still demonstrated an immature brain response to sounds. **Study 4** used the same paradigm as **Study 1**, presenting specific and unspecific conditions, but was adapted to children by making it shorter and including a video. An additional benefit of the motor-auditory paradigm is that it tests the specific predictions that accompany an action. The interplay of action and prediction is especially relevant during development, for example in the context of play behavior (Perez & Feigenson, 2022; Sim & Xu, 2019; Stahl & Feigenson, 2015). Considering the scarcity of omission studies in children, it was unknown whether this paradigm would elicit an omission response and how this response would present, resulting in sub-question **Q4a**:

Q4a How do sensory prediction errors manifest in children compared to adults?

Additionally, it was unknown whether children already showed a similar response pattern to specific and unspecific conditions as adults. That is, whether violations of specific predictions result in a larger prediction error response than violations of unspecific predictions, which was addressed in sub-question **Q4b**:

Q4b Do specific and unspecific sound predictions have similar effects on omission responses in children compared to adults?

Answering **Q4a**, both early and late oN1 responses were observed in the children group of **Study 4**, suggesting that also in children, actions are accompanied by sensory predictions. The topography of the oN1 responses was similar between children and adults, where children also showed peak activations over temporal electrodes. This was surprising given the auditory ERPs in response to actual sounds, where children showed a large P1 followed by an N2 (typical for the age group), and adults showed the standard P1-N1-P2-N2 morphology. The differences between auditory-evoked responses and similarities of omission-evoked responses between groups underlines the importance of separating these processes when studying prediction. Interestingly, the temporal components of the auditory-evoked response in children (N1a, N1c) were relatively mature, and resembled the topography of the oN1. The relative maturity of both the auditory-evoked components and oN1 over temporal electrodes in children supports the notion that these may resemble similar activations. Apart

from similarities, children also showed some differences regarding oN1 elicitation compared to adults, in terms of both latency and amplitude.

Answering **Q4b**, the oN1 was elicited in both specific and unspecific conditions, showing that like adults, children can flexibly apply predictions. In line with **Study 1**, children demonstrated a significant but attenuated (early) oN1 response in the unspecific condition. That in children the strength or precision of a prediction can be observed in the oN1 opens up interesting directions for future developmental research (see section 7.5). In the adult group, an early and late oN1 was observed as well for the specific and unspecific condition, also showing larger amplitudes for the early oN1 in response to specific omissions.

The subsequent oN2 and oP3 components were not analyzed further in this study. Although oN2 and oP3 were partly present also in children, these were likely influenced by the diverted attention to the video. For valid conclusions to be drawn about the development of these later components, attention thus has to be selectively manipulated in future studies.

The answers to sub-questions **Q4a** and **Q4b** help answer the fourth main research question:

Q4 Are omission responses elicited in children, and how do these responses compare between children and adults?

Study 4 shows that omission responses in 6–8 year old children are elicited, and are remarkably similar to adults. Like adults, children seem to be able to implement specific and unspecific sound predictions flexibly, indicating largely mature prediction error elicitation despite immature sound processing.

In conclusion, **Study 4** supports the position that an omission approach is especially suitable for studying prediction processes in the developing brain. Despite immature sound processing, early omission responses were largely similar, in line with the increasingly supported notion that prediction-related processes play a driving role in development. Specifically, movement or action in the world seems to be accompanied by sophisticated predictions, providing a potential source for learning in the form of prediction errors.

7.3 The omission response in the broader context of deviance detection

Prediction error, or more broadly deviance detection, is typically studied by analyzing responses to exogenous stimuli in various paradigms. In Chapter 1, I discussed the MMN, RS, IR, and self-generation effects as commonly studied markers of prediction error. I also identified some important problems with the interpretation of these effects in terms of prediction, mainly in the context of stimulus-related confounds such as the influence of adaptation or attention. In the EEG studies presented in this thesis, PCA assisted in establishing the omission response as a consistent pattern of components, similar to the stimulus-evoked responses that are normally elicited to study prediction. This facilitates a discussion of the individual omission components in the broader context of the MMN, RS, IR, and self-generation studies, in which I will explore potential parallels that might aid future work on deviance detection in the brain. In this section, the emphasis is on exploration. In other words, I did not restrict myself by some obvious limitations – such as differences between the human and animal perceptual systems (e.g., King et al., 2015) – in order to allow for an open discussion of the literature.

7.3.1 Mismatch negativity and repetition suppression

As discussed in Chapter 1, the MMN is likely a combination of adaptation and "genuine" prediction effects. It must be noted that some may consider this a misleading dichotomy, as adaptation effects can also be interpreted as local, low-level predictions in the context of predictive coding (Garrido et al., 2009c). Nevertheless, May and Tiitinen (2010) rightfully invoke Occam's razor to suggest that prediction should only be included in the theory if it is necessary to explain the MMN. Thus, going forward, the distinction between adaptation and prediction processes will be maintained.

Detailed study of the MMN has revealed both temporal and frontal generators (Opitz et al., 2002; Paavilainen et al., 2003). Classically, temporal sources in the auditory cortex were thought to encode acoustic regularities in sensory memory, while frontal sources in the prefrontal cortex assessed behavioral relevance, potentially switching attention towards a change (Doeller et al., 2003; Giard et al., 1990; Näätänen et al., 2007; Näätänen & Alho, 1995). More recent models inspired by predictive coding propose a hierarchical relation between the auditory and prefrontal cortex. First, bottom-up information arrives in the auditory cortex, where spectral properties of the stimulus are predominantly encoded by adaptation processes. This is well supported by the strong RS and SSA effects observed in the auditory cortex in both humans and animals (Auksztulewicz & Friston, 2016; Carbajal & Malmierca, 2018; Garrido et al., 2009b; Todorovic et al., 2011; Todorovic & de Lange, 2012; Ulanovski et al., 2004). Subsequently, additional prediction errors are forwarded to higher levels, where in the prefrontal cortex, they are explained in terms of higher-order, complex representations (Garrido et al., 2008, 2009a). Auditory cortex would thus represent low-level prediction errors, while prefrontal cortex represents more abstract, higher-level prediction errors.

Although more research is needed before clear lines can be drawn between MMN and omission responses, some obvious parallels should be discussed. Starting with the more obvious component, the frontally elicited oN2 resembles some important characteristics of the MMN elicited in frontal areas. In **Study 1**, the oN2 was only elicited when a more abstract, higher-level concept of the sound was available in the specific condition, congruent with the frontal MMN as a marker of higher-level prediction error. **Study 2** showed that the oN2 is similarly elicited in response to somatosensory omissions, consistent with a generator in the prefrontal cortex. Moreover, the frontal MMN is a somewhat inconsistent finding compared to the temporal MMN (Deouell, 2007), reminiscent of the absence of the oN2 in Korka et al. (2020) and Van Laarhoven et al. (2020). Lastly, in **Study 1** as well as in **Study 2**, the oN2 showed a subtle dominance to the right hemisphere, congruent with frontal MMN findings (Giard et al., 1990; Näätänen, 2018).

A recent invasive study in rats supports the hierarchical model of the MMN (Casado-Román et al., 2020), showing initial mismatch responses in the auditory cortex (presumably temporal MMN) followed by frontal areas (presumably frontal MMN). Comparing this with omission responses, the oN1 seems to share the same hierarchical position as the temporal MMN, since it precedes the oN2 and **Study 2** further supports that it is elicited from modality-specific areas. However, the oN1 does not seem to be identical to the temporal MMN, as Casado-Román et al. (2020) show that the temporal MMN is mostly driven by adaptation. This is incongruent with the oN1, as it represents an endogenous response to omission, which cannot be explained by adaptation differences. In **Study 1**, it was therefore discussed that the oN1 may be elicited from nonlemniscal sensory areas.

The terms lemniscal and nonlemniscal are predominantly used in animal research and are also referred to as primary or core areas and nonprimary or belt areas in the auditory cortex. The lemniscal pathway

tends to contain neurons that are sharply tuned to sound frequencies, and is often organized in a tonotopic fashion. Lemniscal neurons show a better consistency in their response to sounds than nonlemniscal areas, including shorter latencies, increased firing rates, more overall spikes per stimulus, and higher spontaneous activity. Moreover, lemniscal areas mostly receive input from other downward lemniscal areas (Malmierca, 2015). These characteristics make the lemniscal pathway highly suitable for accurately relaying sensory input, while largely disregarding context or abstract relations between stimuli. In contrast, the nonlemniscal pathway seems more sensitive to context, showing broader frequency-response areas and longer response latencies. Nonlemniscal areas are wrapped around the lemniscal areas that they receive input from and connect to nonlemniscal structures in other areas. This is why nonlemniscal areas are a prime candidate to host the top-down flow of predictions and bottom-up transmission of prediction errors (Carbajal & Malmierca, 2018). This role of the nonlemniscal pathway is supported by a recent study of Parras et al. (2021), also using a rat model. In this study, single-unit recordings were measured from distinct lemniscal and nonlemniscal auditory areas while oddball experiments were presented. The oddball paradigms controlled for stimulus adaptation by using the many-standards and cascade sequences. The many-standards sequence (as discussed in Chapter 1) is supposed to control for stimulus adaptation by comparing the deviant sound to a standard sound of the same frequency that is taken from a condition where many different sounds are randomly presented (Schröger & Wolff, 1996). The cascade sequence is a variant of the many-standards that also controls for the fact that in the many-standards paradigm a regularity is presented in one condition, while random sounds are presented in the other (Ruhnau et al., 2012). The only area of the auditory cortex showing significant activity in response to deviants compared to these control conditions was the nonlemniscal posterior auditory field. This area thus seems to reflect what is understood as prediction error in the prediction versus adaptation dichotomy. The oN1, given its independence from adaptation and responsivity to prediction, could therefore be hypothesized to originate primarily from nonlemniscal areas.

In this context, some additional inferences may be explored if we presume that the oN1 reflects the sound-evoked N1a or N1c components in auditory studies and the tactile-evoked N80 component in somatosensory studies. For example, in **Study 2**, the P45 evoked by tactile stimuli is thought to be elicited in primary or lemniscal areas (Allison et al., 1992; Kakigi et al., 1995; Xiang et al., 1997), whereas the N80 is associated with the secondary or nonlemniscal areas (Forss et al., 1994a, b, 1995; Hoshiyama et al., 1997). The sensitivity of nonlemniscal areas to prediction error could explain why only the N80 and not the P45 is reflected in the omission response. Additionally, **Study 2** shows that the P45 does reflect adaptation effects. Again, this is in line with Parras et al. (2021), who show strong adaptation of stimulus-evoked responses also in primary areas but only “genuine” prediction effects in nonlemniscal areas. In auditory **Study 1** and **Study 4**, the same principle applies, as the oN1 shows similarities to the stimulus-evoked N1a and N1c components, which are thought to be elicited in nonlemniscal areas (Bruneau et al., 1999; Näätänen & Picton, 1987; Ponton et al., 2002; Woods, 1995). However, the similarity between the topographies of stimulus- and omission-evoked components is not entirely compelling. This may be explained by the largely different response patterns to deviant versus standard stimuli of nonlemniscal areas as seen in Parras et al. (2021), possibly resulting in a similar topography pattern but different reflections of that pattern in omissions.

The MMN in oddball studies is often followed by a positivity referred to as the P3 or P300 (Horváth et al., 2008; Polich, 2003). The MMN and subsequent P3a are often interpreted as the first two stages in the three-stage model of auditory distraction (Escera et al., 1998, 2000; Schröger et al., 2000; Wetzel

& Schröger, 2014). This model describes how stimuli are selected for further attentive processing considering the limited resources of the attentive system. In the first stage, sensory prediction violations are detected by the continuous unconscious prediction processes as described by predictive coding. In oddball studies, these prediction violations are thought to be signaled by the MMN. Subsequently, when the prediction violation is of sufficient saliency, stage two is triggered in which attention is directed towards the violating stimulus. This stage is thought to be reflected by the P3a, a fronto-central peak in the ERP elicited by rare stimuli irrespective of their task relevance (Friedman et al., 2001; Kok, 2001; Ranganath & Rainer, 2003). When stimuli are task relevant, the P3a is often followed by the P3b, which is a broadly distributed positive peak over parietal areas. It is still unclear what processes are exactly reflected by the P3b, but there seems to be a strong association with memory and context updating (Polich, 2007; Rac-Lubashevsky & Kessler, 2019). The P300 wave is concluded by the novelty-P3, which presents as a frontal component after the P3b and as a reflection of stimulus novelty has a close relation to the orienting reflex (Barry et al., 2016).

The oP3 positivity observed in response to omissions had only been broadly interpreted as some reflection of the P300 (SanMiguel et al., 2013a; Stekelenburg & Vroomen, 2015; Van Laarhoven et al., 2017). The subsequent **Studies 1** to **3** in this thesis have each led to an increasingly comprehensive understanding of this response. In **Study 1**, PCA was able to successfully separate the large oP3 in three different subcomponents. Judging by the latency and topography of these subcomponents, these seemed to resemble the P3a, P3b and novelty-P3. PCA showed very similar components in **Study 2**, which shows that – like the stimulus-evoked P3a, P3b and novelty-P3 – these oP3 components were modality-unspecific. Moreover, additional modality-specific oP3 components were observed, congruent with P300 findings that also show modality-specific components (Dreo et al., 2017). Finally, **Study 3** showed that stimulus omission results in a response of the pupil, suggesting involvement of the same subcortical structures as elicited in stimulus-evoked P300 responses related to attention orienting and surprise (Nieuwenhuis et al., 2005, 2011a). These studies thus strongly suggest that omission responses elicit very similar responses compared to the stimulus-evoked P300. Specifically, the oP3-1, oP3-2, and oP3-3 may represent the P3a, P3b, and novelty-P3 respectively. This finding corroborates the three-stage model from a unique perspective. That is, prediction violation in the first stage can not only be reflected by N1 or MMN, but also by oN1 or oN2 components. These markers of sensory prediction error result in a similar elicitation of stage two, showing a P3a-like component that would indicate attention-switching. Apart from that, it seems that the absence of a stimulus can also elicit components analogous to P3b and novelty-P3. An important implication of this is that these components do not seem related to the processing of stimulus characteristics of the deviant stimulus. Instead, what is being processed could be better explained as the entropy, surprise, or Shannon information (Shannon, 1948) related to the deviant stimulus.

7.3.2 Incongruency response

The IR is typically elicited when visual information predicts an auditory stimulus, but instead a different auditory stimulus is presented. Interestingly, the IR is elicited around the same latency as the oN1, and also shows a response towards temporal areas (Dercksen et al., 2021; Pieszek et al., 2013, 2014; Stuckenberg et al., 2019, 2021). Although it is unjustified to draw conclusions purely based on such similarities, it is an interesting topic to explore. Indeed, there is good reason to believe that a common prediction system underlies both stimulus based (e.g. visual to auditory) and motor-based predictions (Korka et al., 2022). A reasonable and interesting speculation would therefore be that the IR may also be generated in nonlemniscal areas of the auditory cortex, as discussed in the previous section.

7.3.3 Self-generation studies

In self-generation studies, a stimulus that is elicited by a motor act typically results in an attenuated response compared to a stimulus that is not (Aliu et al., 2009; Knolle et al., 2012; Martikainen et al, 2005; Timm et al., 2013; for reviews, see Horváth, 2015; Hughes et al., 2013). To what extent this attenuation involves prediction is an ongoing discussion. Part of this attenuation effect may be explained or influenced by other processes like attention (Saupe et al., 2013; Timm et al., 2013), sensory gating (Chapman & Beauchamp, 2006), or a reduced orienting response (SanMiguel et al., 2013b). Additionally, studies increasingly show a neural enhancement instead of attenuation of predicted action outcomes (Dogge et al., 2019; Guo & Song, 2019; Paraskevoudi & SanMiguel, 2021; Reznik et al., 2014, 2021; Reznik & Mukamel, 2019; Thomas et al., 2022; Yon et al., 2018, 2021, 2022). Such results may lead to serious reinterpretations of earlier data, whereas future studies should take care to clearly differentiate prediction from other processes (Press et al., 2023). The omission response as presented in this thesis is particularly suitable to only analyze the predictions that accompany an action. As suggested in **Study 2**, these likely involve secondary (nonlemniscal) areas, congruent with fMRI studies of self-generation effects (Arikan et al., 2021; Blakemore et al., 1998, 2000; Kilteni & Ehrsson, 2020; Shergill et al., 2013). In auditory self-generation studies both the N1a/N1c as well as the N1b are suppressed when coupled with an action (Horváth, 2015). However, in the omission response the N1b is not reflected (i.e., no central negativity resembling the N1b is elicited in the omission response). Two possible explanations could be given for the discrepancy that the N1b is supposedly attenuated by sensory predictions but absent in the omission response. One possibility is that the N1b attenuation does not reflect prediction but rather other processes, such as attention, sensory gating, or a reduced orienting response (see Horváth, 2015 for more examples of other processes that may play a role). In the context of the lemniscal versus nonlemniscal distinction, this would make sense: the N1b is thought to predominantly reflect activity in the primary auditory cortex (Näätänen & Picton, 1987; Ponton et al., 2000; Woods, 1995), which as a lemniscal area is supposedly less responsive to prediction (Carbajal & Malmierca, 2018). Alternatively, predictions regarding the N1b might simply not result in prediction errors following stimulus omission, but for example only have a modulating influence on stimulus processing (see limitations in section 7.4).

7.3.4 Towards an updated model of the omission response

Concluding the above discussion of the omission response in the broader context of deviance detection, I will formulate an updated model of prediction and omission in the brain as introduced in Chapter 1 (Figure 2, which was based on Arnal & Giroud, 2012; Korka et al., 2022; SanMiguel et al., 2013b; Schröger et al., 2015). Note that this updated model is highly speculative as it heavily leans on assumptions that are not at all clear from the findings in this thesis. It is therefore intended as a summary of the possible mechanisms discussed in this section and a possible starting point for future research.

The updated model of prediction and omission in the brain is presented below in Figure 19. Compared to the previous model (Figure 2), this model acknowledges two main concepts: the contribution of adaptation (or local prediction, as proposed by Garrido et al., 2009c), and the distinction between lemniscal (or primary) and nonlemniscal (or secondary) areas. As previously discussed, predictable stimuli can be reflected by both higher-level predictions (for example in the case of motor-sensory associations) as well as adaptation (repeated stimulation resulting in local inhibition). Based on animal studies, lemniscal areas are predominantly sensitive to adaptation, while nonlemniscal areas seem

more sensitive to higher-level predictions (discussed in section 7.3.1). In the case of a correctly predicted stimulus, both mechanisms result in an absence of prediction error and thus a diminished neural response to the stimulus (Figure 19, left side). However, in the case of a mispredicted stimulus, for example in an oddball paradigm, the two mechanisms diverge (Figure 19, middle). On the one hand, neurons influenced by a higher-level prediction template (assumed to be mainly located in nonlemniscal areas) signal prediction error in response to the unpredicted deviant stimulus (shown in red in Figure 19) as well as to the predicted stimulus that is absent (shown in grey in Figure 19). On the other hand, neurons influenced by local adaptation do not elicit what is understood as "genuine" prediction error (Schröger & Wolff, 1996), but prediction error is rather signaled by the non-inhibited neurons associated with the deviant stimulus (shown in red in Figure 19). Finally, in the case of omission, the same mechanisms would result in observations that may explain the omission findings in this thesis (Figure 19, right side). That is, neurons influenced by a higher-level prediction template signal prediction error as the sensory template of a stimulus is compared to an absence of actual input. As these neurons are thought to be mainly located in nonlemniscal areas, this might explain why omission responses only seem to resemble stimulus responses elicited in such areas. In contrast, in neurons inhibited by local adaptation, the absence of a stimulus does not elicit prediction error responses. As no other deviant response is present, these neurons, thought to be predominantly located in lemniscal areas, remain unresponsive.

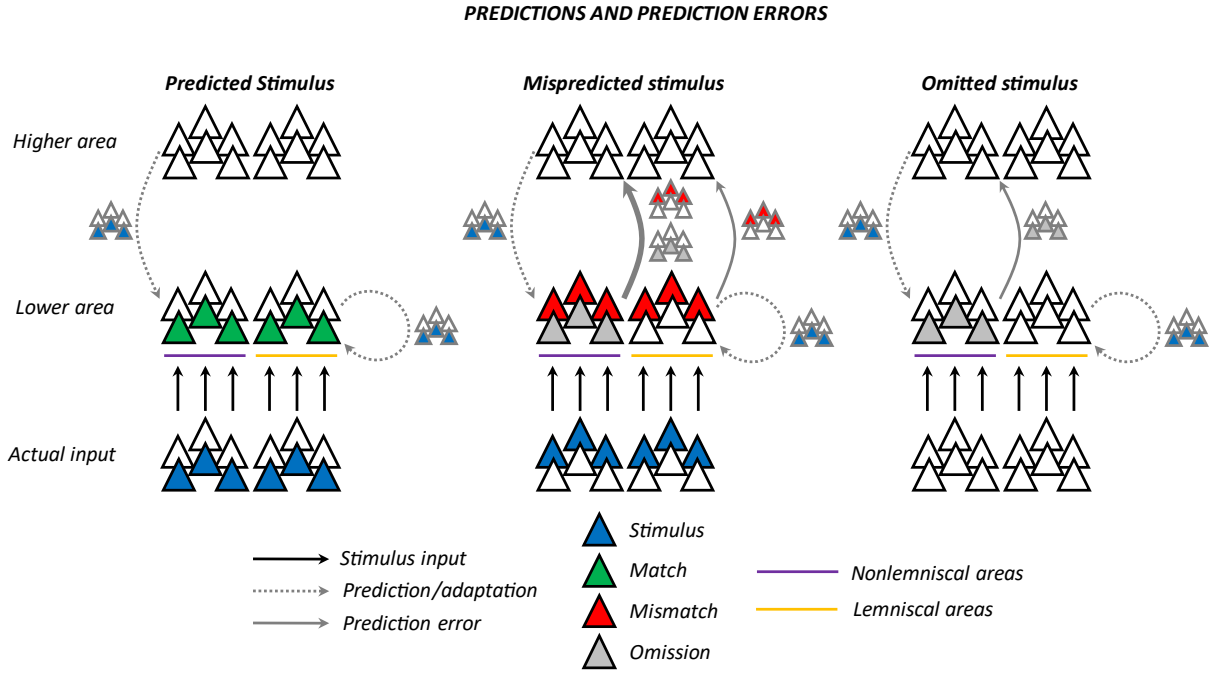

Figure 19: A possible updated model of prediction and prediction error in the brain. Higher areas primarily influence nonlemniscal areas (arrows from higher to lower levels), while lemniscal areas are predominantly sensitive to adaptation (circle arrows, reflecting local inhibition processes). When a stimulus is correctly predicted (left), both mechanisms result in a diminished neural response reflecting an absence of prediction error. When a stimulus is mispredicted (middle), the two areas show different response profiles. Nonlemniscal areas signal prediction error to both the absence of the predicted stimulus as well as the presence of the unpredicted stimulus. Lemniscal areas only respond to the latter, signaling prediction error in the form of a non-adapted response to the unpredicted stimulus. Consequently, when a stimulus is predicted but omitted (right), main prediction error responses are elicited from nonlemniscal areas. Figure adapted from Schröger et al. (2015, p. 647) and Korka et al. (2022, p. 331).

7.4 Limitations

In this thesis, I have advocated for the use of omission responses as a means of investigating prediction, thereby surpassing the inherent constraints of stimulus-based approaches. However, it is important to

acknowledge that the omission approach also carries its own set of limitations, and that some discrepancies remain unresolved. Hence, in the subsequent critical evaluation of this paradigm, I will address the most notable limitations, serving to guide future work.

Throughout this thesis, an important limitation has repeatedly come up: the extent to which the oN1 reflects stimulus-related components is largely unknown. Although there may be topographical similarities between omission and stimulus ERP components, these similarities are an inadequate indicator of truly similar neural sources. Therefore, any conclusions based on the assumption that omission activity is elicited by the same areas responsible for stimulus processing should be regarded as speculative. The sparse research on this topic shows variable results. For example, Fonken et al. (2019) used intracranial electrode measurements from epileptic patients to study omission responses to speech sounds. Their results suggest partly distinct pathways of omission and stimulus activity, with some electrodes on the superior temporal gyrus exclusively responding to omissions. However, Auksztulewicz et al. (2022) demonstrate that the vast majority of areas that respond to omissions also respond to sounds, revealing that only a small percentage of channels from their microelectrodes in rat auditory cortex exclusively respond to omissions. Consequently, definitive conclusions regarding this aspect of the omission response cannot be drawn until the relationship between omission and stimulus components has been mapped out more precisely.

Omission responses observed in this thesis exhibit a remarkable degree of consistency with previous studies on the topic. However, one noteworthy exception is the omission study conducted by Bendixen et al. (2009), which revealed an initial positivity instead of the typical negativity that has been observed in this thesis and elsewhere. Given that the paradigm employed in Bendixen et al. (2009) only allowed for a limited analysis of the omission response (first 50 ms), the precise discrepancy with typical omission responses remains unknown. This discrepancy, however, points to a larger limitation in our current understanding of omission responses. For example, the initial positivity observed in Bendixen et al. (2009) may be influenced by the rapid stimulus presentation rate (150 ms ISI) employed in their paradigm. The impact of contextual factors such as ISI, stimulus type (e.g., environmental sound versus simple frequency), or stimulus intensity (e.g., sound volume) on the elicitation of the omission response is not well understood. Although these factors have been shown to significantly influence stimulus responses (Borgmann et al., 2001; Pereira et al., 2014; Woods, 1995), they have not been systematically investigated in the context of omission. Therefore, while omission responses appear to exhibit a consistent pattern across studies, this may be due to its limited investigation under alternative conditions.

In this thesis, the brain's response to omission has been interpreted as prediction error, in accordance with the principles of predictive coding and the model of omission advanced by Schröger et al. (2015; see Figure 2). However, in some models of perception, the interpretation of the omission response changes. For example, in the model proposed by Wacongne et al. (2012), inhibitory pulses are used to subtract predictions from sensory input, which poses a challenge for omissions to straightforwardly result in prediction error. In this model, omission responses are therefore hypothesized to represent pure prediction signals. This issue touches upon a more fundamental problem, namely that it is unknown what exactly the omission response reflects. To solve this problem, more detailed empirical research is needed. For example, Auksztulewicz et al. (2022) recently employed invasive recordings to investigate omission responses in rats. They detected significant activity in response to omissions using local field potentials, but surprisingly, this was not accompanied by significant spike activity. The

potential presence of neural membrane potentials but absence of spiking activity in response to omissions allows for interesting new interpretations. Combining such empirical work with computational modeling may eventually clarify what the omission response truly reflects: prediction or prediction error (or, of course, something else entirely). Until then, the lacking knowledge at the microscopic level limits a comprehensive understanding of omission responses.

One of the underlying assumptions of the predictive coding framework is that any (sufficiently weighted) unfulfilled predictions lead to prediction error. Consequently, the omission response should reflect all predictions associated with a particular event. However, it is possible to think of alternative models where this assumption may not hold. For example, predictive influences could potentially adjust only the gain of bottom-up processing without resulting in prediction error in response to omissions. This is similar to how low-level adaptation is thought to function in the brain (Carbajal & Malmierca, 2018; see Figure 19), and it is possible that higher-level influences could have analogous effects. It is therefore important to acknowledge that although the omission response is a strong marker of prediction compared to other phenomena, it may have its own blind spots. To properly build theories and test hypotheses about prediction in the brain, it is therefore essential to employ multiple paradigms, where the true strength of evidence lies not in any one paradigm, but rather in their diversity.

Finally, an important nuance regarding the role of motor activity in this thesis should be made clear. As previously noted, both stimulus-based and motor-based predictions produce comparable patterns of omission components. While intriguing, this finding may also indicate the superficial nature of the coupling. To conduct the experiments in this thesis, actions were temporarily coupled to arbitrary stimuli, where omission results showed that these couplings were learned quickly. However, such couplings likely do not capture the tightly coupled body-sensory interactions that are traditionally understood under the notion of efference copy (Dogge et al., 2019). Indeed, Schneider et al. (2018) conducted a study on mice which demonstrated how sustained, consistent coupling of movement to sounds results in slow, gradual changes in auditory cortex activity over the course of several days. Hence, it is crucial to differentiate between such long-term, intrinsic couplings and the short-term, arbitrary couplings used in the experiments of this thesis. This is not to say that one type of coupling is more important than the other. Taking cognitive development as an example, play behavior in children consists of many temporary and arbitrary couplings between actions and stimuli, and is therefore arguably well modeled by the action-effect couplings as presented in this thesis. In contrast, this is likely not the case for slower processes, such as how babies learn the tactile consequences of their own actions over the course of many months (Bremner & Spence, 2017). Although short-term couplings may influence these long-term processes, the specifics of this connection are still unknown, and researchers must exercise caution when extending findings from these experiments beyond their scope.

7.5 Future perspectives

Having established the omission response as a suitable tool to study prediction in the brain, in this section I will identify some promising directions to apply this tool in future research. Two main directions will be explored: fundamental research on the omission response and application of the omission response to study prediction in development.

7.5.1 Fundamental research on the omission response

The research presented in this thesis converges to a few core questions regarding the omission response that remain unanswered but are crucial for a comprehensive understanding. Perhaps the most prominent open issue is the relation between brain activity evoked by stimuli and omissions. As discussed in section 7.4, the topographical similarities between stimulus- and omission-evoked components in the ERPs of **Study 1**, **Study 2**, and **Study 4** are a poor indicator of truly similar underlying neural sources. Resolving to what extend these responses overlap not only aids our comprehension of the omission response, but could substantially influence models of prediction in the brain. Of particular interest is the similarity between the oN1 and stimulus-evoked components in light of predictive coding models that postulate that stimulus processing and prediction error are elicited in different layers of the same cortical column (Bastos et al., 2012; Jiang & Rao, 2021; Shipp, 2016). Furthermore, it is worth considering the comparison between omission components and stimulus-evoked mismatch responses (MMN, IR). As mentioned in Chapter 1, these mismatch responses likely reflect two different signals: one related to input that was encountered but not predicted, and one related to input that was predicted but was absent (Schröger et al., 2015; Figure 2). If this distinction holds true, it is likely that partly overlapping brain regions are activated across these phenomena, and a detailed comparison of omission- and stimulus-based deviance responses could assist in distinguishing these signals.

To gain a comprehensive understanding of the relation between stimulus- and omission-evoked activity, a multidisciplinary approach applying both non-invasive and invasive methods may prove most effective. Some non-invasive imaging methods possess the ability to reveal large-scale activity with high-spatial precision. Specifically, MEG offers both high spatial as well as temporal precision, making it one of the most promising methods to isolate specific omission components in time and to compare their spatial activation in the cortex to stimulus-evoked components. To convincingly test the dependence of omission-related activity on stimulus-related activity, ideally a correspondence should be demonstrated between a changing stimulus and changing omission activity. The tonotopically organized nature of sounds, for example, allows MEG to distinguish between high and low sounds already in the M100 (the magnetic counterpart of the N1) of the auditory evoked potential (Langner et al., 1997; Pantev & Lütkenhöner, 2000). If the omission response indeed reflects activity from similar areas as stimuli, the activation pattern of stimulus and omission responses should change in similar ways to pitch changes. An analogous approach would be feasible in tactile studies, for example by changing the stimulated limb.

Contrary to MEG, fMRI lacks detailed temporal resolution, but can instead provide high dimensional cortical as well as subcortical spatial resolution of brain activity. Some fMRI studies have shown general activation of stimulus-specific activity when a stimulus was unexpectedly omitted (Berlot et al., 2018; Den Ouden et al., 2009; Kok et al., 2014; Kühn et al., 2010; Kühn & Brass, 2010). These studies could be extended in interesting ways in the future, as recent advancements in fMRI have made it possible to conduct layer-specific analyses of cortical activity (Finn et al., 2021; Haarsma et al., 2022; Stephan et al., 2019). Theoretically, this enables detailed analyses regarding the specific proposal of predictive coding that distinct cortical layers encode prediction and prediction error (Bastos et al., 2012; Jiang & Rao, 2021; Shipp, 2016). However, it is still an open question to what extend fMRI can live up to this potential considering its limited temporal resolution. Regarding the omission response, it is difficult to differentiate oN1 activity from later activity, and this temporal order has substantial implications for how to interpret omission activity. One possibility that could be explored to overcome this limitation

is the use of paradigms that elicit only specific omission components. For example, in MMN research, Wacongne et al. (2011) and Chennu et al. (2016) use series of five tones, with the final tone being either a local or global deviant. Whereas local deviants only trigger early, sensory prediction error (MMN), global deviants trigger later, higher-level prediction error (P300). The same may apply for omissions, where an expected omission might only trigger oN1 and oN2 responses (local deviant), but an unexpected omission might additionally trigger later responses (global deviant; but note that it is uncertain whether the same applies for omissions, see omission control conditions of Wacongne et al., 2011 and Chennu et al., 2016). In future research, experimental designs inspired by such studies might enable detailed, layer-specific source localization of omission responses using fMRI.

As has already become apparent in this chapter, invasive studies in animals can be highly informative in elucidating non-invasive human findings. Although these fields have traditionally operated largely independent from each other, the recent study of Parras et al. (2021), as discussed in section 7.3, shows the potential knowledge gains that could be achieved through close collaboration. Regarding basic research on the omission response, at least two interesting directions could be explored. The first direction is the possible distinction between lemniscal and nonlemniscal areas in the elicitation of the omission response. The research in this thesis suggests that motor-sensory couplings primarily elicit omission responses in nonlemniscal areas (see Figure 19). By employing both single-unit recordings and local field potentials (see Auksztulewicz et al., 2022, for an explanation regarding why both should be used for omission responses), one could convincingly test this hypothesis using a methodological setup similar to that used by Parras et al. (2021). A second direction for invasive future research is the distinction between stimulus- and omission-specific neurons. So far, the evidence is conflicting whether stimulus-responsive neurons also elicit omission responses (Auksztulewicz et al., 2022), or that instead omission responses are elicited by partly separate populations (Fonken et al., 2019). Further investigation at the neuronal level in this direction will be crucial to develop comprehensive models of the omission response and, consequently, prediction in the brain.

Finally, research is yet to fill an important gap regarding predictive coding in the brain. That is, although many markers of prediction error have been identified (e.g. MMN, IR, oN1), very little observations are reported regarding the propagation of predictions themselves. One of the few convincing studies on this topic was published by Dürschmid et al. (2019), who used human intracranial recordings in an auditory experiment. In this study, participants listened to an oddball sequence, where in one condition the deviant was completely predictable (every fifth tone) and in the other condition the deviant was unpredictable. Dürschmid et al. (2019) showed that shortly preceding the predictable deviant, high frequency activity measured from frontal areas decreased. Moreover, pre-stimulus high frequency activity correlated with the post-stimulus response to deviants. Contrary to markers of prediction error, these results seem to provide direct evidence for prediction in the cortex. It would be highly interesting to couple this marker of prediction to omission responses. Using such an approach could convincingly demonstrate the causal relationship between these supposed markers of prediction (high frequency activity) and prediction error (oN1, oN2) at different levels of the cortical hierarchy.

7.5.2 Application of the omission response to study prediction in development

In the developmental literature, a leading question over the past years is how prediction shapes cognitive development. As argued in this thesis, the omission response is particularly well-suited to reveal the neural processes associated with prediction during development, opening up many new directions for future research. Arguably one of the primary objectives of developmental research is to

outline how experiences in the world shape the maturing brain through learning processes. This not only requires a thorough understanding of the learning process itself, but also of other cognitive processes that modulate learning such as attention and top-down control. Understanding the role of prediction in these processes may be the key towards a more profound understanding of brain development.

As discussed in section 1.5, a perpetual cycle of prediction and prediction error appears to be instrumental for infants and children in order to learn about the world. However, the precise neural mechanisms underlying learning from prediction error remain unclear. Recent studies suggest that explicit prediction before receiving the answer can enhance learning, especially when the response contradicts the prediction (Brod, 2021; Brod et al., 2018, 2022; Brod & Breitwieser, 2019). For example, if participants were asked which of two countries had more inhabitants, formulating a prediction just before the answer was presented resulted in a surprise response when the answer defied the expectation and facilitated learning (Brod et al., 2018). Brod (2021) explains this as a sequential process, where incorrect predictions trigger surprise, surprise triggers enhanced attention, and enhanced attention strengthens encoding. This aligns closely with electrophysiological studies, where initial prediction error (MMN, IR, oN1) is succeeded by later attention-related processes (P300, oP3), which may facilitate learning by norepinephrine release that upregulates cortical sensitivity to the relevant sensory input (Aston-Jones & Cohen, 2005; Mather et al., 2016; Sakaki et al., 2019). From a functional brain imaging perspective, this sensory prediction error followed by attentional processing thus seems to capture vital aspects of learning (see also Quent et al., 2021). However, a link to structural brain changes associated with learning is yet to be established. That is, to characterize the complete learning process, it should be clarified how prediction error processing leads to structural adaptations in the brain that reflect the newly acquired knowledge.

As a first step, a compelling structural brain marker of learning should be defined. A possible candidate would be dendritic spines, as changes in dendritic spines have been shown to play a causal role in learning (Hayashi-Takagi et al., 2015; Moda-Sava et al., 2019). For example, in rodent fear conditioning studies, if a foot shock is presented together with a sound, merely the presentation of the sound results in freezing behavior. The learning of this coupling results in increasing spine densities in specific brain areas that can occur within minutes (Segal, 2005). Interestingly, if subsequently only the sound is repeatedly presented without the shock (in essence a type of omission response design), dendritic spine density is restored to pre-fear levels (Heinrichs et al., 2013). A major challenge for future research would be to couple the brain activity related to prediction error processing to such types of structural changes in the brain related to learning. An in-depth understanding of this process could be crucial in gaining insights into the structural brain changes associated with cognitive development (Anderson, 2003; Johnson, 2001; Runge et al., 2020). Using omission responses, one could theoretically isolate the effects of prediction error processing to properly study the impact of prediction error on structural brain changes.

The studies of Brod and colleagues (Brod, 2021; Brod et al., 2018, 2022; Brod & Breitwieser, 2019) provide convincing evidence that attention plays an important role in learning. In children, the ability to voluntarily direct attention and disregard distractors is limited and progressively improves during development (Gomes et al., 2000; Lane & Pearson, 1982; Wetzel et al., 2019). Moreover, Wetzel et al. (2006, 2015) demonstrated that the direction of voluntary attention may in some cases be necessary for prediction error to be elicited in developmental populations. Specifically, they observed that a

MMN was present only when 6–8 year old children attended to the sounds, but not when they directed their attention away from the sounds. Omission responses allow for a detailed analysis of the impact of attention on prediction without the interfering influence of bottom-up processing. Indeed, **Study 4** already indicated considerable effects of attention on the omission response. Future investigations in this direction could facilitate a deeper understanding of attention and its role in the development process.

Apart from attention, another important factor that impacts learning and developmental processes is top-down control. Infants and children show substantial difficulties in a number of tasks related to top-down control, such as switching from one rule to another (Cepeda et al., 2001; Davidson et al., 2006; Lehto et al., 2003; Treit et al., 2014). This has generally been linked to the protracted developmental pathway of the frontal cortex, which continuous to develop well into adulthood (Aron et al., 2007; Casey et al., 1997; Dempster, 1992; Diamond, 2002; Kirkham, 2003; Rubia et al., 2006). However, it is unknown how exactly immature frontal areas lead to impaired performance on top-down related tasks. One possibility is that predictions play a role. A number of studies have shown the important role of frontal areas in generating predictions (Alexander & Brown, 2018; Avenanti et al., 2018; Jakuszeit et al., 2013; see Waszak et al., 2012 for a review), specifically higher-order predictions that involve a substantial switch of the sensory template (Dürschmid et al., 2016, 2019). Therefore, an interesting direction for future research is to explore whether these predictions might be impaired as a consequence of immature frontal areas. This might explain the functional mechanism linking the immature frontal cortex to impaired top-down behavioral performance in developmental populations. An approach incorporating omission responses might be particularly useful in this setting. For example, an interesting hypothesis would be that the oN2 component of the omission response, presumably reflecting higher-order frontal prediction error, is impaired in children shortly after rule-switching.

In summary, the research in this thesis lays the foundation for a multitude of interesting directions for future research. Regarding basic research, both non-invasive as well as invasive approaches may be used to study prediction through the use of omission responses. In developmental research, especially interesting directions may involve the interaction between prediction processes and learning, attention, and top-down control.

7.6 General conclusions

This thesis demonstrates the central role of top-down prediction in the brain by investigating its response to stimulus omission. In four studies, the coupling of a button press with a stimulus consistently elicited a brain response when the stimulus was predicted but unexpectedly absent. This response demonstrated a fixed pattern of initial activity in sensory areas followed by higher-level processing, congruent with current models of prediction error generation. The fixed pattern of responses could be corroborated by data-driven methods, further establishing the omission response as a marker of deviance detection. Moreover, I could show that predictions do not have to be specific for such prediction errors to be elicited, that a similar pattern is visible across tested modalities (auditory and somatosensory), and that these processes are also reflected in the pupil. Together, these results showed that the omission response is not only an appropriate, but also a reliable and sensitive measure of prediction-related activity in the brain. This can be considered a substantial improvement compared to the situation regarding omission studies before this thesis.

Additional to this basic research, I could also demonstrate the presence of omission responses in children. The surprising similarity of these responses to adults shows the value of this approach, and is in line with emerging theoretical models that put prediction at the core of brain development. Further integration of omission studies in the developmental field may be especially beneficial in elucidating how prediction shapes development.

Concluding, the studies in this thesis together with my theoretical treatment of their potential implications contribute to the knowledge of prediction and deviance detection in the brain. I hope that these contributions will inspire future research.

References

Acunzo, D. J., Mackenzie, G., & van Rossum, M. C. (2012). Systematic biases in early ERP and ERF components as a result of high-pass filtering. *J Neurosci Methods, 209*(1), 212-218.

Adams, R. A., Shipp, S., & Friston, K. J. (2013). Predictions not commands: active inference in the motor system. *Brain Structure and Function*, *218*(3), 611-643.

Adolph, K. E., & Hoch, J. E. (2019). Motor development: Embodied, embedded, enculturated, and enabling. *Annual review of psychology*, *70*, 141-164.

Albrecht, R., Suchodoletz, W. V., & Uwer, R. (2000). The development of auditory evoked dipole source activity from childhood to adulthood. *Clinical Neurophysiology*, *111*(12), 2268-2276.

Alexander, W. H., & Brown, J. W. (2018). Frontal cortex function as derived from hierarchical predictive coding. *Scientific reports*, *8*(1), 3843.

Alho, K. (1995). Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear and hearing*, *16*(1), 38-51.

Allison, T., McCarthy, G., & Wood, C. C. (1992). The relationship between human long-latency somatosensory evoked potentials recorded from the cortical surface and from the scalp. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *84*(4), 301-314.

Andersen, L. M., & Dalal, S. S. (2021). The cerebellar clock: Predicting and timing somatosensory touch. *NeuroImage*, *238*, 118202.

Andersen, S. L. (2003). Trajectories of brain development: point of vulnerability or window of opportunity?. *Neuroscience & Biobehavioral Reviews*, *27*(1-2), 3-18.

Andersen, L. M., & Lundqvist, D. (2019). Somatosensory responses to nothing: an MEG study of expectations during omission of tactile stimulations. *NeuroImage*, *184*, 78-89.

Andreou, L. V., Griffiths, T. D., & Chait, M. (2015). Sensitivity to the temporal structure of rapid sound sequences—an MEG study. *Neuroimage*, *110*, 194-204.

Antony, J. W., Hartshorne, T. H., Pomeroy, K., Gureckis, T. M., Hasson, U., McDougle, S. D., & Norman, K. A. (2021). Behavioral, physiological, and neural signatures of surprise during naturalistic sports viewing. *Neuron*, *109*(2), 377-390.

Arikan, B. E., Voudouris, D., Voudouri-Gertz, H., Sommer, J., & Fiehler, K. (2021). Reach-relevant somatosensory signals modulate activity in the tactile suppression network. *NeuroImage*, *236*, 118000.

Arnal, L. H., & Giraud, A. L. (2012). Cortical oscillations and sensory predictions. *Trends Cogn Sci, 16*(7), 390-398.

Aron, A. R., Durston, S., Eagle, D. M., Logan, G. D., Stinear, C. M., & Stuphorn, V. (2007). Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. *Journal of Neuroscience*, *27*(44), 11860-11864.

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, *28*, 403-450.

Auksztulewicz, R., & Friston, K. (2016). Repetition suppression and its contextual determinants in predictive coding. *cortex*, *80*, 125-140.

Avenanti, A., Paracampo, R., Annella, L., Tidoni, E., & Aglioti, S. M. (2018). Boosting and decreasing action prediction abilities through excitatory and inhibitory tDCS of inferior frontal cortex. *Cerebral Cortex*, *28*(4), 1282-1296.

Bakeman, R. (2005). Recommended effect size statistics for repeated measures designs. *Behavior research methods*, *37*(3), 379-384.

Baldeweg, T. (2006). Repetition effects to sounds: evidence for predictive coding in the auditory system. *Trends in cognitive sciences*.

Baldeweg, T. (2007). ERP repetition effects and mismatch negativity generation: A predictive coding perspective. *Journal of Psychophysiology*, *21*(3-4), 204.

Barry, R. J., De Blasio, F. M., Fogarty, J. S., & Karamacoska, D. (2016). ERP Go/NoGo condition effects are better detected with separate PCAs. *International Journal of Psychophysiology*, *106*, 50-64.

Barry, R. J., Steiner, G. Z., & De Blasio, F. M. (2016). Reinstating the Novelty P3. *Sci Rep, 6*(1), 31200.

Barry, R. J., Steiner, G. Z., De Blasio, F. M., Fogarty, J. S., Karamacoska, D., & MacDonald, B. (2020). Components in the P300: Don't forget the Novelty P3!. *Psychophysiology*, *57*(7), e13371.

Basirat, A., Dehaene, S., & Dehaene-Lambertz, G. (2014). A hierarchy of cortical responses to sequence violations in three-month-old infants. *Cognition*, *132*(2), 137-150.

Bäß, P., Jacobsen, T., & Schröger, E. (2008). Suppression of the auditory N1 event-related potential component with unpredictable self-initiated tones: evidence for internal forward models with dynamic stimulation. *Int J Psychoph, 70*(2), 137-143.

Bastos, A. M., Usrey, W. M., Adams, R. A., Mangun, G. R., Fries, P., & Friston, K. J. (2012). Canonical microcircuits for predictive coding. *Neuron*, *76*(4), 695-711.

Baumann, O., Borra, R. J., Bower, J. M., Cullen, K. E., Habas, C., Ivry, R. B., ... & Sokolov, A. A. (2015). Consensus paper: the role of the cerebellum in perceptual processes. *The Cerebellum*, *14*(2), 197-220.

Bays, P. M., Flanagan, J. R., & Wolpert, D. M. (2006). Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS biology*, *4*(2), e28.

Bays, P. M., Wolpert, D. M., & Flanagan, J. R. (2005). Perception of the consequences of self-action is temporally tuned and event driven. *Current Biology*, *15*(12), 1125-1128.

Bednark, J. G., Poonian, S. K., Palghat, K., McFadyen, J., & Cunnington, R. (2015). Identity-specific predictions and implicit measures of agency. *Psychology of Consciousness: Theory, Research, and Practice*, *2*(3), 253.

Bendixen, A., Grimm, S., Deouell, L. Y., Wetzel, N., Mädebach, A., & Schröger, E. (2010). The time-course of auditory and visual distraction effects in a new crossmodal paradigm. *Neuropsychologia*, *48*(7), 2130-2139.

Bendixen, A., SanMiguel, I., & Schröger, E. (2012). Early electrophysiological indicators for predictive processing in audition: a review. *International Journal of Psychophysiology*, *83*(2), 120-131.

Bendixen, A., Scharinger, M., Strauss, A., & Obleser, J. (2014). Prediction in the service of comprehension: modulated early brain responses to omitted speech segments. *Cortex*, *53*, 9-26.

Bendixen, A., Schröger, E., & Winkler, I. (2009). I heard that coming: event-related potential evidence for stimulus-driven prediction in the auditory system. *Journal of Neuroscience*, *29*(26), 8447-8451.

Berger, A., & Posner, M. I. (2022). Beyond Infant's Looking: The Neural Basis for Infant Prediction Errors. *Perspectives on Psychological Science*, 17456916221112918.

Berlot, E., Formisano, E., & De Martino, F. (2018). Mapping frequency-specific tone predictions in the human auditory cortex at high spatial resolution. *Journal of Neuroscience*, *38*(21), 4934-4942.

Bianchi, F., Santurette, S., Wendt, D., & Dau, T. (2016). Pitch discrimination in musicians and non-musicians: Effects of harmonic resolvability and processing effort. *Journal of the Association for Research in Otolaryngology*, *17*(1), 69-79.

Bigdely-Shamlo, N., Mullen, T., Kothe, C., Su, K. M., & Robbins, K. A. (2015). The PREP pipeline: standardized preprocessing for large-scale EEG analysis. *Front Neuroinform, 9*, 16.

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nature neuroscience*, *1*(7), 635-640.

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1999). The cerebellum contributes to somatosensory cortical activity during self-produced tactile stimulation. *Neuroimage*, *10*(4), 448-459.

Blakemore, S. J., Wolpert, D., & Frith, C. (2000). Why can't you tickle yourself?. *Neuroreport*, *11*(11), R11-R16.

Boldin, A. M., Geiger, R., & Emberson, L. L. (2018). The emergence of top-down, sensory prediction during learning in infancy: A comparison of full-term and preterm infants. *Developmental psychobiology*, *60*(5), 544-556.

Bonferroni, C. (1936). Teoria statistica delle classi e calcolo delle probabilita. *Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commericiali di Firenze*, *8*, 3-62.

Bonmassar, C., Scharf, F., Widmann, A., & Wetzel, N. (2021). On the relationship of behavioral distraction and pupil dilation caused by emotional novel sounds.

Bonmassar, C., Widmann, A., & Wetzel, N. (2020). The impact of novelty and emotion on attention-related neuronal and pupil responses in children. *Developmental cognitive neuroscience*, *42*, 100766.

Borgmann, C., Roß, B., Draganova, R., & Pantev, C. (2001). Human auditory middle latency responses: influence of stimulus type and intensity. *Hearing research*, *158*(1-2), 57-64.

Braeken, J., & Van Assen, M. A. (2017). An empirical Kaiser criterion. *Psychological methods*, *22*(3), 450.

Braga, A., & Schönwiesner, M. (2022). Neural substrates and models of omission responses and predictive processes. *Frontiers in Neural Circuits*, *16*.

Brainard, D. H. (1997). The Psychophysics Toolbox. Spat Vis, 10(4), 433-436.

Bremner, A. J., & Spence, C. (2017). The development of tactile perception. *Advances in child development and behavior*, *52*, 227-268.

Brod, G. (2021). Predicting as a learning strategy. *Psychonomic Bulletin & Review*, *28*(6), 1839-1847.

Brod, G., & Breitwieser, J. (2019). Lighting the wick in the candle of learning: generating a prediction stimulates curiosity. *NPJ science of learning*, *4*(1), 17.

Brod, G., Greve, A., Jolles, D., Theobald, M., & Galeano-Keiner, E. M. (2022). Explicitly predicting outcomes enhances learning of expectancy-violating information. *Psychonomic Bulletin & Review*, 1-10.

Brod, G., Hasselhorn, M., & Bunge, S. A. (2018). When generating a prediction boosts learning: The element of surprise. *Learning and Instruction*, *55*, 22-31.

Bruneau, N., & Gomot, M. (1998). Auditory evoked potentials (N1 wave) as indices of cortical development. In *Neuroimaging in child neuropsychiatric disorders* (pp. 113-123). Springer, Berlin, Heidelberg.

Bruneau, N., Roux, S., Adrien, J. L., & Barthélémy, C. (1999). Auditory associative cortex dysfunction in children with autism: evidence from late auditory evoked potentials (N1 wave–T complex). *Clinical Neurophysiology*, *110*(11), 1927-1934.

Bruneau, N., Roux, S., Guerin, P., Barthelemy, C., & Lelord, G. (1997). Temporal prominence of auditory evoked potentials (N1 wave) in 4-8-year-old children. *Psychophysiology*, *34*(1), 32-38.

Burton, M., & Starzak, R. (2015). *Shaun the Sheep Movie* [Film]. Aardman Animations.

Butler, R. A. (1968). Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. *The Journal of the Acoustical Society of America*, *44*(4), 945-950.

Cannon, J., O'Brien, A. M., Bungert, L., & Sinha, P. (2021). Prediction in autism spectrum disorder: a systematic review of empirical evidence. *Autism research*, *14*(4), 604-630.

Carbajal, G. V., & Malmierca, M. S. (2018). The neuronal basis of predictive coding along the auditory pathway: from the subcortical roots to cortical deviance detection. *Trends in Hearing*, *22*, 2331216518784822.

Casado-Román, L., Carbajal, G. V., Pérez-González, D., & Malmierca, M. S. (2020). Prediction error signaling explains neuronal mismatch responses in the medial prefrontal cortex. *PLoS Biology*, *18*(12), e3001019.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., ... & Rapoport, J. L. (1997). A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. *Journal of cognitive neuroscience*, *9*(6), 835-847.

Cepeda, N. J., Kramer, A. F., & Gonzalez de Sather, J. (2001). Changes in executive control across the life span: examination of task-switching performance. *Developmental psychology*, *37*(5), 715.

Čeponien, R., Cheour, M., & Näätänen, R. (1998). Interstimulus interval and auditory event-related potentials in children: evidence for multiple generators. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(4), 345-354.

Čeponien, R., Rinne, T., & Näätänen, R. (2002). Maturation of cortical sound processing as indexed by event-related potentials. *Clinical Neurophysiology*, *113*(6), 870-882.

Chan, J. S., Wibral, M., Wollstadt, P., Stawowsky, C., Brandl, M., Helbling, S., ... & Kaiser, J. (2017). Predictive coding over the lifespan: Increased reliance on perceptual priors in older adults–a magnetoencephalography and dynamic causal modelling study. *bioRxiv*, 178095.

Chapman, C. E., & Beauchamp, E. (2006). Differential controls over tactile detection in humans by motor commands and peripheral reafference. *Journal of Neurophysiology*, *96*(3), 1664-1675.

Chaumon, M., Bishop, D. V., & Busch, N. A. (2015). A practical guide to the selection of independent components of the electroencephalogram for artifact correction. *Journal of neuroscience methods*, *250*, 47-63.

Chennu, S., Noreika, V., Gueorguiev, D., Shtyrov, Y., Bekinschtein, T. A., & Henson, R. (2016). Silent expectations: dynamic causal modeling of cortical prediction and attention to sounds that weren't. *Journal of Neuroscience*, *36*(32), 8305-8316.

Chouiter, L., Tzovara, A., Dieguez, S., Annoni, J. M., Magezi, D., De Lucia, M., & Spierer, L. (2015). Experience-based auditory predictions modulate brain activity to silence as do real sounds. *Journal of cognitive neuroscience*, *27*(10), 1968-1980.

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci, 36*(3), 181-204.

Clayson, P. E., Carbine, K. A., Baldwin, S. A., & Larson, M. J. (2019). Methodological reporting behavior, sample sizes, and statistical power in studies of event-related potentials: Barriers to reproducibility and replicability. *Psychophysiology*, *56*(11), e13437.

Cohen, M. X. (2017). Where does EEG come from and what does it mean?. *Trends in neurosciences*, *40*(4), 208-218.

Cooper, C. L., Ashe, J. H., & Weinberger, N. M. (1978). Effects of stimulus omission during habituation of the pupillary dilation reflex. *Physiological Psychology*, *6*(1), 1-6.

Copete, J. L., Nagai, Y., & Asada, M. (2016, September). Motor development facilitates the prediction of others' actions through sensorimotor predictive learning. In *2016 Joint IEEE International Conference on Development and Learning and Epigenetic Robotics (ICDL-EpiRob)* (pp. 223-229). IEEE.

Costa-Faidella, J., Baldeweg, T., Grimm, S., & Escera, C. (2011). Interactions between “what” and “when” in the auditory system: temporal predictability enhances repetition suppression. *Journal of Neuroscience*, *31*(50), 18590-18597.

Csifcsák, G., Balla, V. R., Dalos, V. D., Kilencz, T., Biró, E. M., Urbán, G., & Szalóki, S. (2019). Action-associated modulation of visual event-related potentials evoked by abstract and ecological stimuli. *Psychophysiology*, *56*(2), e13289.

Damsma, A., & van Rijn, H. (2017). Pupillary response indexes the metrical hierarchy of unattended rhythmic violations. *Brain and cognition*, *111*, 95-103.

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: Evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia*, *44*(11), 2037-2078.

Dawson, G.D. (1951). A summation technique for detecting small signals in an irregular background. *J Physiol (Lond)*, *115*, 2-3.

De Lange, F. P., Heilbron, M., & Kok, P. (2018). How do expectations shape perception? *Trends in cognitive sciences*, *22*(9), 764-779.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods, 134*(1), 9-21.

Demarchi, G., Sanchez, G., & Weisz, N. (2019). Automatic and feature-specific prediction-related neural activity in the human auditory system. *Nat Commun, 10*(1), 3440.

Dempster, F. N. (1992). The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. *Developmental review*, *12*(1), 45-75.

Deouell, L. Y. (2007). The frontal generator of the mismatch negativity revisited. *Journal of Psychophysiology*, *21*(3-4), 188-203.

Dercksen, T. T., Stuckenberg, M. V., Schröger, E., Wetzel, N., & Widmann, A. (2021). Cross-modal predictive processing depends on context rather than local contingencies. *Psychophysiology*, *58*(6), e13811.

Dercksen, T. T., Widmann, A., Scharf, F., & Wetzel, N. (2022b). Sound omission related brain responses in children. *Developmental Cognitive Neuroscience*, *53*, 101045.

Dercksen, T. T., Widmann, A., Schröger, E., & Wetzel, N. (2020). Omission related brain responses reflect specific and unspecific action-effect couplings. *NeuroImage*, *215*, 116840.

Dercksen, T. T., Widmann, A., & Wetzel, N. Salient omissions-pupil dilation in response to unexpected omissions of sound and touch. *Frontiers in Psychiatry*, *14*, 367.

Dercksen, T., Widmann, A., Noesselt, T. & Wetzel, N. (2022a). Somatosensory omissions reveal action-related predictive processing.

Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: Cognitive functions, anatomy, and biochemistry. *Principles of frontal lobe function*, *466*, 503.

Dien, J. (1998). Addressing misallocation of variance in principal components analysis of event-related potentials. *Brain Topogr, 11*(1), 43-55.

Dien, J. (2010). The ERP PCA Toolkit: an open source program for advanced statistical analysis of event-related potential data. *J Neurosci Methods, 187*(1), 138-145.

Dien, J. (2012). Applying principal components analysis to event-related potentials: a tutorial. *Developmental neuropsychology*, *37*(6), 497-517.

Doeller, C. F., Opitz, B., Mecklinger, A., Krick, C., Reith, W., & Schröger, E. (2003). Prefrontal cortex involvement in preattentive auditory deviance detection:: neuroimaging and electrophysiological evidence. *Neuroimage*, *20*(2), 1270-1282.

Dreo, J., Attia, D., Pirtošek, Z., & Repovš, G. (2017). The P3 cognitive ERP has at least some sensory modality-specific generators: Evidence from high-resolution EEG. *Psychophysiology*, *54*(3), 416-428.

Dürschmid, S., Edwards, E., Reichert, C., Dewar, C., Hinrichs, H., Heinze, H. J., ... & Knight, R. T. (2016). Hierarchy of prediction errors for auditory events in human temporal and frontal cortex. *Proceedings of the National Academy of Sciences*, *113*(24), 6755-6760.

Dürschmid, S., Reichert, C., Hinrichs, H., Heinze, H. J., Kirsch, H. E., Knight, R. T., & Deouell, L. Y. (2019). Direct evidence for prediction signals in frontal cortex independent of prediction error. *Cerebral Cortex*, *29*(11), 4530-4538.

Eggermont, J. J., & Ponton, C. W. (2003). Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: correlations with changes in structure and speech perception. *Acta oto-laryngologica*, *123*(2), 249-252.

Eggermont, Jos J.; Ponton, Curtis W. (2002). *The Neurophysiology of Auditory Perception: From Single Units to Evoked Potentials. Audiology and Neuro-Otology, 7(2), 71–99.* doi:10.1159/000057656

Einhäuser, W. (2017). The pupil as marker of cognitive processes. In *Computational and cognitive neuroscience of vision* (pp. 141-169). Springer, Singapore.

Elsner, B. (2007). Infants' imitation of goal-directed actions: The role of movements and action effects. *Acta psychologica*, *124*(1), 44-59.

Emberson, L. L. (2017). How does experience shape early development? Considering the role of top-down mechanisms. *Advances in child development and behavior*, *52*, 1-41.

Emberson, L. L., Richards, J. E., & Aslin, R. N. (2015). Top-down modulation in the infant brain: Learning-induced expectations rapidly affect the sensory cortex at 6 months. *Proceedings of the National Academy of Sciences*, *112*(31), 9585-9590.

Escera, C., & Malmierca, M. S. (2014). The auditory novelty system: an attempt to integrate human and animal research. *Psychophysiology*, *51*(2), 111-123.

Escera, C., Alho, K., Winkler, I., & Näätänen, R. (1998). Neural mechanisms of involuntary attention to acoustic novelty and change. *J Cogn Neurosci, 10*(5), 590-604.

Feldman, H., & Friston, K. (2010). Attention, uncertainty, and free-energy. *Frontiers in human neuroscience*, *4*, 215.

Fitzgerald, K., & Todd, J. (2020). Making sense of mismatch negativity. *Frontiers in Psychiatry*, *11*, 468.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology, 45*(1), 152-170.

Fonken, Y. M., Mukerji, A., Jimenez, R., Lin, J., Brunner, P., Schalk, G., & Knight, R. T. (2019). Unexpected sound omissions are signaled in human posterior superior temporal gyrus: an intracranial study. *bioRxiv*, 733212.

Forss, N., Hari, R., Salmelin, R., Ahonen, A., Hämäläinen, M., Kajola, M., ... & Simola, J. (1994a). Activation of the human posterior parietal cortex by median nerve stimulation. *Experimental brain research*, *99*(2), 309-315.

Forss, N., Jousmäki, V., & Hari, R. (1995). Interaction between afferent input from fingers in human somatosensory cortex. *Brain Research*, *685*(1-2), 68-76.

Forss, N., Salmelin, R., & Hari, R. (1994b). Comparison of somatosensory evoked fields to airpuff and electric stimuli. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *92*(6), 510-517.

Friedman, D., Hakerem, G., Sutton, S., & Fleiss, J. L. (1973). Effect of stimulus uncertainty on the pupillary dilation response and the vertex evoked potential. *Electroencephalography and clinical neurophysiology*, *34*(5), 475-484.

Friston, K. (2005). A theory of cortical responses. *Philosophical transactions of the Royal Society B: Biological sciences*, *360*(1456), 815-836.

Friston, K. (2009). The free-energy principle: a rough guide to the brain?. *Trends in cognitive sciences*, *13*(7), 293-301.

Friston, K. (2010). The free-energy principle: a unified brain theory?. *Nature reviews neuroscience*, *11*(2), 127-138.

Friston, K. (2018). Does predictive coding have a future?. *Nature neuroscience*, *21*(8), 1019-1021.

Friston, K., & Kiebel, S. (2009a). Cortical circuits for perceptual inference. *Neural Netw., 22*(8), 1093-1104.

Friston, K., & Kiebel, S. (2009b). Predictive coding under the free-energy principle. *Philosophical transactions of the Royal Society B: Biological sciences*, *364*(1521), 1211-1221.

Friston, K., FitzGerald, T., Rigoli, F., Schwartenbeck, P., & Pezzulo, G. (2017). Active inference: a process theory. *Neural computation*, *29*(1), 1-49.

Garrido, M. I., Friston, K. J., Kiebel, S. J., Stephan, K. E., Baldeweg, T., & Kilner, J. M. (2008). The functional anatomy of the MMN: a DCM study of the roving paradigm. *Neuroimage*, *42*(2), 936-944.

Garrido, M. I., Kilner, J. M., Kiebel, S. J., & Friston, K. J. (2009a). Dynamic causal modeling of the response to frequency deviants. *Journal of Neurophysiology*, *101*(5), 2620-2631.

Garrido, M. I., Kilner, J. M., Kiebel, S. J., Stephan, K. E., Baldeweg, T., & Friston, K. J. (2009b). Repetition suppression and plasticity in the human brain. *Neuroimage*, *48*(1), 269-279.

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009c). The mismatch negativity: a review of underlying mechanisms. *Clinical neurophysiology*, *120*(3), 453-463.

Geuter, S., Boll, S., Eippert, F., & Büchel, C. (2017). Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. *Elife*, *6*, e24770.

Giard, M. H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. *Psychophysiology*, *27*(6), 627-640.

Gilley, P. M., Sharma, A., Dorman, M., & Martin, K. (2005). Developmental changes in refractoriness of the cortical auditory evoked potential. *Clinical Neurophysiology*, *116*(3), 648-657.

Gomot, M., Giard, M. H., Roux, S., Barthélémy, C., & Bruneau, N. (2000). Maturation of frontal and temporal components of mismatch negativity (MMN) in children. *Neuroreport*, *11*(14), 3109-3112.

Gredebäck, G., Lindskog, M., Juvrud, J. C., Green, D., & Marciszko, C. (2018). Action prediction allows hypothesis testing via internal forward models at 6 months of age. *Frontiers in psychology*, *9*, 290.

Grill-Spector, K., Henson, R., & Martin, A. (2006). Repetition and the brain: neural models of stimulus-specific effects. *Trends in cognitive sciences*, *10*(1), 14-23.

Grotheer, M., & Kovács, G. (2016). Can predictive coding explain repetition suppression?. *Cortex*, *80*, 113-124.

Gusso, M. D. M., Serur, G., & Nohama, P. (2021). Pupil Reactions to Tactile Stimulation: A Systematic Review. *Frontiers in Neuroscience*, *15*, 610841.

Haenschel, C., Vernon, D. J., Dwivedi, P., Gruzelier, J. H., & Baldeweg, T. (2005). Event-related brain potential correlates of human auditory sensory memory-trace formation. *Journal of Neuroscience*, *25*(45), 10494-10501.

Hajizadeh, A., Matysiak, A., Wolfrum, M., May, P. J., & König, R. (2022). Auditory cortex modelled as a dynamical network of oscillators: understanding event-related fields and their adaptation. *Biological cybernetics*, *116*(4), 475-499.

Hayashi-Takagi, A., Yagishita, S., Nakamura, M., Shirai, F., Wu, Y. I., Loshbaugh, A. L., ... & Kasai, H. (2015). Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature*, *525*(7569), 333-338.

Heilbron, M., & Chait, M. (2018). Great expectations: is there evidence for predictive coding in auditory cortex? *Neuroscience, 389*, 54-73.

Heinrichs, S. C., Leite-Morris, K. A., Guy, M. D., Goldberg, L. R., Young, A. J., & Kaplan, G. B. (2013). Dendritic structural plasticity in the basolateral amygdala after fear conditioning and its extinction in mice. *Behavioral brain research*, *248*, 80-84.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature reviews neuroscience*, *8*(5), 393-402.

Hohwy, J., Roepstorff, A., & Friston, K. (2008). Predictive coding explains binocular rivalry: An epistemological review. *Cognition*, *108*(3), 687-701.

Horváth, J. (2015). Action-related auditory ERP attenuation: Paradigms and hypotheses. *Brain Research*, *1626*, 54-65.

Horváth, J., Müller, D., Weise, A., & Schröger, E. (2010). Omission mismatch negativity builds up late. *Neuroreport*, *21*(7), 537-541.

Horváth, J., Winkler, I., & Bendixen, A. (2008). Do N1/MMN, P3a, and RON form a strongly coupled chain reflecting the three stages of auditory distraction?. *Biological psychology*, *79*(2), 139-147.

Hoshiyama, M., Kakigi, R., Koyama, S., Watanabe, S., & Shimojo, M. (1997). Activity in posterior parietal cortex following somatosensory stimulation in man: magnetoencephalographic study using spatio-temporal source analysis. *Brain topography*, *10*(1), 23-30.

Hughes, G., & Waszak, F. (2011). ERP correlates of action effect prediction and visual sensory attenuation in voluntary action. *Neuroimage*, *56*(3), 1632-1640.

Hughes, H. C., Darcey, T. M., Barkan, H. I., Williamson, P. D., Roberts, D. W., & Aslin, C. H. (2001). Responses of human auditory association cortex to the omission of an expected acoustic event. *Neuroimage*, *13*(6), 1073-1089.

Hunnius, S., & Bekkering, H. (2014). What are you doing? How active and observational experience shape infants' action understanding. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1644), 20130490.

Hupé, J. M., Lamirel, C., & Lorenceau, J. (2009). Pupil dynamics during bistable motion perception. Journal of vision, 9(7), 10-10.

Imamizu, H. (2010). Prediction of sensorimotor feedback from the efference copy of motor commands: a review of behavioral and functional neuroimaging studies. *Japanese Psychological Research*, *52*(2), 107-120.

Ioannidis, J. P. (2005). Why most published research findings are false. *PLoS medicine*, *2*(8), e124.

Itier, R. J., & Taylor, M. J. (2004). Effects of repetition and configural changes on the development of face recognition processes. *Developmental Science*, *7*(4), 469-487.

Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. *Psychophysiology*, *51*(11), 1061-1071.

Jakuszeit, M., Kotz, S. A., & Hasting, A. S. (2013). Generating predictions: lesion evidence on the role of left inferior frontal cortex in rapid syntactic analysis. *Cortex*, *49*(10), 2861-2874.

Janata, P. (2001). Brain electrical activity evoked by mental formation of auditory expectations and images. *Brain topography*, *13*, 169-193.

JASP Team. (2021). JASP [Computer software] (Version 0.16.0). https://jasp-stats.org/download

JASP Team. (2022). JASP [Computer software] (Version 0.16.4). https://jasp-stats.org/download

Jennrich, R. I. (2004a). Derivative free gradient projection algorithms for rotation. *Psychometrika*, *69*(3), 475-480.

Jennrich, R. I. (2004b). Rotation to simple loadings using component loss functions: The orthogonal case. *Psychometrika*, *69*(2), 257-273.

Jennrich, R. I. (2006). Rotation to simple loadings using component loss functions: The oblique case. *Psychometrika*, *71*(1), 173-191.

Jiang, L. P., & Rao, R. P. (2021). Predictive Coding Theories of Cortical Function. arXiv preprint arXiv:2112.10048.

Jo, H. G., Habel, U., & Schmidt, S. (2019). Role of the supplementary motor area in auditory sensory attenuation. *Brain Structure and Function*, *224*(7), 2577-2586.

Johnson, M. H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience*, *2*(7), 475-483.

Jongsma, M. L., Quiroga, R. Q., & van Rijn, C. M. (2004). Rhythmic training decreases latency-jitter of omission evoked potentials (OEPs) in humans. *Neuroscience Letters*, *355*(3), 189-192.

Joos, K., Gilles, A., Van de Heyning, P., De Ridder, D., & Vanneste, S. (2014). From sensation to percept: the neural signature of auditory event-related potentials. *Neuroscience & Biobehavioral Reviews*, *42*, 148-156.

Joshi, S., & Gold, J. I. (2020). Pupil size as a window on neural substrates of cognition. *Trends in cognitive sciences*, *24*(6), 466-480.

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron*, *89*(1), 221-234.

Joutsiniemi, S. L., & Hari, R. (1989). Omissions of auditory stimuli may activate frontal cortex. *European Journal of Neuroscience*, *1*(5), 524-528.

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., Mckeown, M. J., Iragui, V., & Sejnowski, T. J. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology*, *37*(2), 163-178.

Kahnemann, D., & Beatty, J. (1967). Pupillary responses in a pitch-discrimination task. *Perception & Psychophysics*, *2*(3), 101-105.

Kakigi, R., Koyama, S., Hoshiyama, M., Shimojo, M., Kitamura, Y., & Watanabe, S. (1995). Topography of somatosensory evoked magnetic fields following posterior tibial nerve stimulation. *Electroencephalography and clinical neurophysiology*, *95*(2), 127-134.

Karamürsel, S., & Bullock, T. H. (2000). Human auditory fast and slow omitted stimulus potentials and steady-state responses. *International Journal of Neuroscience*, *100*(1-4), 1-20.

Kekoni, J., Hämäläinen, H., Saarinen, M., Gröhn, J., Reinikainen, K., Lehtokoski, A., & Näätänen, R. (1997). Rate effect and mismatch responses in the somatosensory system: ERP-recordings in humans. *Biological psychology*, *46*(2), 125-142.

Kida, T., Nishihira, Y., Wasaka, T., Nakata, H., & Sakamoto, M. (2004). Passive enhancement of the somatosensory P100 and N140 in an active attention task using deviant alone condition. *Clinical neurophysiology*, *115*(4), 871-879.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. *Cognitive processing*, *8*, 159-166.

Kilteni, K., & Ehrsson, H. H. (2017a). Sensorimotor predictions and tool use: Hand-held tools attenuate self-touch. *Cognition*, *165*, 1-9.

Kilteni, K., & Ehrsson, H. H. (2017b). Body ownership determines the attenuation of self-generated tactile sensations. *Proceedings of the National Academy of Sciences*, *114*(31), 8426-8431.

Kilteni, K., & Ehrsson, H. H. (2020). Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. *Journal of Neuroscience*, *40*(4), 894-906.

Kilteni, K., & Ehrsson, H. H. (2020). Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. *Journal of Neuroscience*, *40*(4), 894-906.

King, J., Insanally, M., Jin, M., Martins, A. R. O., D'amour, J. A., & Froemke, R. C. (2015). Rodent auditory perception: Critical band limitations and plasticity. *Neuroscience*, *296*, 55-65.

Kinney, L., & O'Hare, D. (2020). Responding to an unexpected in-flight event: physiological arousal, information processing, and performance. *Human factors*, *62*(5), 737-750.

Kirkham, N. Z., Cruess, L., & Diamond, A. (2003). Helping children apply their knowledge to their behavior on a dimension-switching task. *Developmental science*, *6*(5), 449-467.

Kloosterman, N. A., Meindertsma, T., van Loon, A. M., Lamme, V. A., Bonneh, Y. S., & Donner, T. H. (2015). Pupil size tracks perceptual content and surprise. *European Journal of Neuroscience*, *41*(8), 1068-1078.

Klug, M., & Gramann, K. (2021). Identifying key factors for improving ICA-based decomposition of EEG data in mobile and stationary experiments. *European Journal of Neuroscience*, *54*(12), 8406-8420.

Knolle, F., Schröger, E., & Kotz, S. A. (2013a). Cerebellar contribution to the prediction of self-initiated sounds. *Cortex*, *49*(9), 2449-2461.

Knolle, F., Schröger, E., & Kotz, S. A. (2013b). Prediction errors in self-and externally-generated deviants. *Biological Psychology*, *92*(2), 410-416.

Knolle, F., Schroger, E., Baess, P., & Kotz, S. A. (2012). The cerebellum generates motor-to-auditory predictions: ERP lesion evidence. *J Cogn Neurosci, 24*(3), 698-706.

Knolle, F., Schwartze, M., Schroger, E., & Kotz, S. A. (2019). Auditory Predictions and Prediction Errors in Response to Self-Initiated Vowels. *Front Neurosci, 13*, 1146.

Kok, P., Failing, M. F., & de Lange, F. P. (2014). Prior expectations evoke stimulus templates in the primary visual cortex. *J Cogn Neurosci, 26*(7), 1546-1554.

Kok, P., Mostert, P., & de Lange, F. P. (2017). Prior expectations induce prestimulus sensory templates. *Proc Natl Acad Sci U S A, 114*(39), 10473-10478.

Korka, B., Schröger, E., & Widmann, A. (2020). What exactly is missing here? The sensory processing of unpredictable omissions is modulated by the specificity of expected action-effects. *European Journal of Neuroscience*, *52*(12), 4667-4683.

Korka, B., Widmann, A., Waszak, F., Darriba, Á., & Schröger, E. (2022). The auditory brain in action: Intention determines predictive processing in the auditory system—A review of current paradigms and findings. *Psychonomic Bulletin & Review*.

Köster, M., Kayhan, E., Langeloh, M., & Hoehl, S. (2020). Making sense of the world: infant learning from a predictive processing perspective. *Perspectives on psychological science*, *15*(3), 562-571.

Koziol, L. F., & Lutz, J. T. (2013). From movement to thought: the development of executive function. *Applied Neuropsychology: Child*, *2*(2), 104-115.

Koziol, L. F., Budding, D. E., & Chidekel, D. (2012). From movement to thought: executive function, embodied cognition, and the cerebellum. *The Cerebellum*, *11*(2), 505-525.

Kraemer, D. J., Macrae, C. N., Green, A. E., & Kelley, W. M. (2005). Sound of silence activates auditory cortex. *Nature*, *434*(7030), 158-158.

Kret, M. E., & Sjak-Shie, E. E. (2019). Preprocessing pupil size data: Guidelines and code. *Behavior research methods*, *51*(3), 1336-1342.

Lange, K. (2013). The ups and downs of temporal orienting: a review of auditory temporal orienting studies and a model associating the heterogeneous findings on the auditory N1 with opposite effects of attention and prediction. *Frontiers in human neuroscience*, *7*, 263.

Lee, M., & Wagenmakers, E.-J. (2013). Bayesian data analysis for cognitive science: A practical course. In: New York, NY: Cambridge University Press.

Lee, T. S., & Mumford, D. (2003). Hierarchical Bayesian inference in the visual cortex. *JOSA A*, *20*(7), 1434-1448.

Lehmann, A., Arias, D. J., & Schönwiesner, M. (2016). Tracing the neural basis of auditory entrainment. *Neuroscience*, *337*, 306-314.

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British journal of developmental psychology*, *21*(1), 59-80.

Leonard, M. K., Baud, M. O., Sjerps, M. J., & Chang, E. F. (2016). Perceptual restoration of masked speech in human cortex. *Nat Commun, 7*(1), 13619.

Liao, H. I., Kidani, S., Yoneya, M., Kashino, M., & Furukawa, S. (2016). Correspondences among pupillary dilation response, subjective salience of sounds, and loudness. *Psychonomic bulletin & review*, *23*(2), 412-425.

Liebenthal, E., Ellingson, M. L., Spanaki, M. V., Prieto, T. E., Ropella, K. M., & Binder, J. R. (2003). Simultaneous ERP and fMRI of the auditory cortex in a passive oddball paradigm. *Neuroimage*, *19*(4), 1395-1404.

Liegeois-Chauvel, C., Musolino, A., Badier, J. M., Marquis, P., & Chauvel, P. (1994). Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *92*(3), 204-214.

Lima, C. F., Krishnan, S., & Scott, S. K. (2016). Roles of supplementary motor areas in auditory processing and auditory imagery. *Trends in neurosciences*, *39*(8), 527-542.

Liss, M., Saulnier, C., Fein, D., & Kinsbourne, M. (2006). Sensory and attention abnormalities in autistic spectrum disorders. *Autism*, *10*(2), 155-172.

Liu, Y., Rodenkirch, C., Moskowitz, N., Schriver, B., & Wang, Q. (2017). Dynamic lateralization of pupil dilation evoked by locus coeruleus activation results from sympathetic, not parasympathetic, contributions. *Cell reports*, *20*(13), 3099-3112.

Loewenfeld, I. E. (1958). *Mechanisms of reflex dilatation of the pupil. , 12(1), 185–448.* doi:10.1007/bf00913471

Mahajan, Y., & McArthur, G. (2013). Maturation of the auditory t-complex brain response across adolescence. *International Journal of Developmental Neuroscience*, *31*(1), 1-10.

Makeig, S., Westerfield, M., Jung, T. P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science*, *295*(5555), 690-694.

Mäkelä, A. M., Alku, P., Mäkinen, V., Valtonen, J., May, P., & Tiitinen, H. (2002). Human cortical dynamics determined by speech fundamental frequency. *Neuroimage*, *17*(3), 1300-1305.

Malmierca, M. S. (2015). Auditory system. In *The rat nervous system* (pp. 865-946). Academic Press.

Malmierca, M. S., Sanchez-Vives, M. V., Escera, C., & Bendixen, A. (2014). Neuronal adaptation, novelty detection and regularity encoding in audition. *Frontiers in systems neuroscience*, *8*, 111.

Maslow, Abraham Harold (1966). The Psychology of Science: A Reconnaissance. Harper & Row. ISBN 978-0-8092-6130-7.

Mathôt, S. (2018). Pupillometry: Psychology, physiology, and function. *Journal of Cognition*, *1*(1).

May, P. J. (2021). The adaptation model offers a challenge for the predictive coding account of mismatch negativity. *Frontiers in Human Neuroscience*, *15*, 721574.

May, P. J., & Tiitinen, H. (2010). Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology*, *47*(1), 66-122.

May, P. J., & Tiitinen, H. (2013). Temporal binding of sound emerges out of anatomical structure and synaptic dynamics of auditory cortex. *Frontiers in Computational Neuroscience*, *7*, 152.

May, P. J., Westö, J., & Tiitinen, H. (2015). Computational modelling suggests that temporal integration results from synaptic adaptation in auditory cortex. *European Journal of Neuroscience*, *41*(5), 615-630.

May, P., & Tiitinen, H. (2001). Human cortical processing of auditory events over time. *NeuroReport*, *12*(3), 573-577.

Merritt, S. L., Keegan, A. P., & Mercer, P. W. (1994). Artifact management in pupillometry. *Nursing research*, *43*(1), 56-59.

Moda-Sava, R. N., Murdock, M. H., Parekh, P. K., Fetcho, R. N., Huang, B. S., Huynh, T. N., ... & Liston, C. (2019). Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*, *364*(6436), eaat8078.

Moerel, M., De Martino, F., Santoro, R., Ugurbil, K., Goebel, R., Yacoub, E., & Formisano, E. (2013). Processing of natural sounds: characterization of multipeak spectral tuning in human auditory cortex. *J Neurosci, 33*(29), 11888-11898.

Montoya, P., & Sitges, C. (2006). Affective modulation of somatosensory-evoked potentials elicited by tactile stimulation. *Brain research*, *1068*(1), 205-212.

Moran, R. J., Symmonds, M., Dolan, R. J., & Friston, K. J. (2014). The brain ages optimally to model its environment: evidence from sensory learning over the adult lifespan. *PLoS Comput Biol*, *10*(1), e1003422.

Motz, B. A., Erickson, M. A., & Hetrick, W. P. (2013). To the beat of your own drum: Cortical regularization of non-integer ratio rhythms toward metrical patterns. *Brain and cognition*, *81*(3), 329-336.

Mumford, D. (1992). On the computational architecture of the neocortex. *Biological cybernetics*, *66*(3), 241-251.

Murphy, P. R., O'connell, R. G., O'sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human brain mapping*, *35*(8), 4140-4154.

Murphy, P. R., Robertson, I. H., Balsters, J. H., & O'connell, R. G. (2011). Pupillometry and P3 index the locus coeruleus–noradrenergic arousal function in humans. *Psychophysiology*, *48*(11), 1532-1543.

Näätänen, R. (2009). Somatosensory mismatch negativity: a new clinical tool for developmental neurological research?. *Developmental medicine and child neurology*, *51*(12), 930.

Näätänen, R. (2018). *Attention and brain function*. Routledge.

Näätänen, R., & Alho, K. (1995). Mismatch negativity-a unique measure of sensory processing in audition. *International Journal of Neuroscience*, *80*(1-4), 317-337.

Näätänen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology*, *24*(4), 375-425.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta psychologica*, *42*(4), 313-329.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical neurophysiology*, *118*(12), 2544-2590.

Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., & Winkler, I. (2001). 'Primitive intelligence'in the auditory cortex. *Trends in neurosciences*, *24*(5), 283-288.

Naeije, G., Vaulet, T., Wens, V., Marty, B., Goldman, S., & De Tiège, X. (2018). Neural basis of early somatosensory change detection: a magnetoencephalography study. *Brain topography*, *31*(2), 242-256.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus--norepinephrine system. *Psychological bulletin*, *131*(4), 510.

Nieuwenhuis, S., De Geus, E. J., & Aston-Jones, G. (2011a). The anatomical and functional relationship between the P3 and autonomic components of the orienting response. *Psychophysiology*, *48*(2), 162-175.

Nieuwenhuis, S., Forstmann, B. U., & Wagenmakers, E. J. (2011b). Erroneous analyses of interactions in neuroscience: a problem of significance. *Nature neuroscience*, *14*(9), 1105-1107.

Obleser, J., Elbert, T., Lahiri, A., & Eulitz, C. (2003). Cortical representation of vowels reflects acoustic dissimilarity determined by formant frequencies. *Cognitive Brain Research*, *15*(3), 207-213.

Oceák, A., Winkler, I., Sussman, E., & Alho, K. (2006). Loudness summation and the mismatch negativity event-related brain potential in humans. *Psychophysiology*, *43*(1), 13-20.

Ody, E., Straube, B., He, Y., & Kircher, T. (2022). Perception of self-and externally-generated visual stimuli: Evidence from EEG and behavior. *bioRxiv*, 2022-05.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Oliva, M., & Anikin, A. (2018). Pupil dilation reflects the time course of emotion recognition in human vocalizations. *Scientific reports*, *8*(1), 1-10.

Oostenveld, R., & Oostendorp, T. F. (2002). Validating the boundary element method for forward and inverse EEG computations in the presence of a hole in the skull. *Human brain mapping*, *17*(3), 179-192.

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational intelligence and neuroscience*, *2011*.

Opitz, B., Rinne, T., Mecklinger, A., Von Cramon, D. Y., & Schröger, E. (2002). Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. *Neuroimage*, *15*(1), 167-174.

Ouyang, G., Sommer, W., & Zhou, C. (2016). Reconstructing ERP amplitude effects after compensating for trial-to-trial latency jitter: A solution based on a novel application of residue iteration decomposition. *Int J Psychophysiol, 109*, 9-20.

Paavilainen, P., Mikkonen, M., Kilpeläinen, M., Lehtinen, R., Saarela, M., & Tapola, L. (2003). Evidence for the different additivity of the temporal and frontal generators of mismatch negativity: a human auditory event-related potential study. *Neuroscience letters*, *349*(2), 79-82.

Parras, G. G., Casado-Román, L., Schröger, E., & Malmierca, M. S. (2021). The posterior auditory field is the chief generator of prediction error signals in the auditory cortex. *NeuroImage*, *242*, 118446.

Parras, G. G., Nieto-Diego, J., Carbajal, G. V., Valdés-Baizabal, C., Escera, C., & Malmierca, M. S. (2017). Neurons along the auditory pathway exhibit a hierarchical organization of prediction error. *Nature communications, 8*(1), 1-17.

Patel, S. H., & Azzam, P. N. (2005). Characterization of N200 and P300: selected studies of the Event-Related Potential. *Int J Med Sci, 2*(4), 147-154.

Paulus, M., Hunnius, S., Van Elk, M., & Bekkering, H. (2012). How learning to shake a rattle affects 8-month-old infants' perception of the rattle's sound: Electrophysiological evidence for action-effect binding in infancy. *Developmental Cognitive Neuroscience*, *2*(1), 90-96.

Pavlov, I. P. (1927). *Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex.* Oxford Univ. Press.

Pavlov, Y. G., Adamian, N., Appelhoff, S., Arvaneh, M., Benwell, C. S., Beste, C., ... & Mushtaq, F. (2021). # EEGManyLabs: Investigating the replicability of influential EEG experiments. *cortex*, *144*, 213-229.

Pazen, M., Uhlmann, L., van Kemenade, B. M., Steinsträter, O., Straube, B., & Kircher, T. (2020). Predictive perception of self-generated movements: commonalities and differences in the neural processing of tool and hand actions. *NeuroImage*, *206*, 116309.

Pazo-Alvarez, P., Cadaveira, F., & Amenedo, E. (2003). MMN in the visual modality: a review. *Biological psychology*, *63*(3), 199-236.

Pereira, D. R., Cardoso, S., Ferreira-Santos, F., Fernandes, C., Cunha-Reis, C., Paiva, T. O., ... & Marques-Teixeira, J. (2014). Effects of inter-stimulus interval (ISI) duration on the N1 and P2 components of the auditory event-related potential. *International journal of psychophysiology*, *94*(3), 311-318.

Pickering, M. J., & Garrod, S. (2013). An integrated theory of language production and comprehension. *Behavioral and brain sciences*, *36*(04), 329-347.

Picton, T. W., Alain, C., Woods, D. L., John, M. S., Scherg, M., Valdes-Sosa, P., ... & Trujillo, N. J. (1999). Intracerebral sources of human auditory-evoked potentials. *Audiology and Neurotology, 4*(2), 64-79.

Picton, T. W., Woods, D. L., Baribeau-Braun, J., & Healey, T. M. (1977). Evoked potential audiometry. *J Otolaryngol*, *6*(2), 90-119.

Pieszek, M., Widmann, A., Gruber, T., & Schröger, E. (2013). The human brain maintains contradictory and redundant auditory sensory predictions. *PLoS One*, *8*(1), e53634.

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*, *198*, 181-197.

Polich, J. (1989). Habituation of P300 from auditory stimuli. *Psychobiology*, *17*(1), 19-28.

Polich, J. (2003). Theoretical overview of P3a and P3b. *Detection of change: Event-related potential and fMRI findings*, 83-98.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol, 118*(10), 2128-2148.

Ponton, C. W., Eggermont, J. J., Kwong, B., & Don, M. (2000). Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clinical neurophysiology*, *111*(2), 220-236.

Ponton, C., Eggermont, J. J., Khosla, D., Kwong, B., & Don, M. (2002). Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modeling. *Clinical Neurophysiology*, *113*(3), 407-420.

Preuschoff, K., ’t Hart, B. M., & Einhäuser, W. (2011). Pupil dilation signals surprise: Evidence for noradrenaline’s role in decision making. *Frontiers in neuroscience*, *5*, 115.

Qiyuan, J., Richer, F., Wagoner, B. L., & Beatty, J. (1985). The pupil and stimulus probability. *Psychophysiology*, *22*(5), 530-534.

Quent, J. A., Henson, R. N., & Greve, A. (2021). A predictive account of how novelty influences declarative memory. *Neurobiology of Learning and Memory*, *179*, 107382.

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Rac-Lubashevsky, R., & Kessler, Y. (2019). Revisiting the relationship between the P3b and working memory updating. *Biological psychology*, *148*, 107769.

Raij, T., McEvoy, L., Mäkelä, J. P., & Hari, R. (1997). Human auditory cortex is activated by omissions of auditory stimuli. *Brain research*, *745*(1-2), 134-143.

Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci, 2*(1), 79-87.

Rapin, I., Schimmel, H., Tourk, L. M., Krasnegor, N. A., & Pollak, C. (1966). Evoked responses to clicks and tones of varying intensity in waking adults. *Electroencephalography and clinical neurophysiology*, *21*(4), 335-344.

Read, H. L., & Reyes, A. D. (2018). Sensing Sound Through Thalamocortical afferent architecture and cortical microcircuits. *The Mammalian Auditory Pathways: Synaptic Organization and Microcircuits*, 169-198.

Recasens, M., & Uhlhaas, P. J. (2017). Test–retest reliability of the magnetic mismatch negativity response to sound duration and omission deviants. *Neuroimage*, *157*, 184-195.

Reznik, D., Ossmy, O., & Mukamel, R. (2015). Enhanced auditory evoked activity to self-generated sounds is mediated by primary and supplementary motor cortices. *Journal of Neuroscience*, *35*(5), 2173-2180.

Richer, F., & Beatty, J. (1985). Pupillary dilations in movement preparation and execution. *Psychophysiology*, *22*(2), 204-207.

Rinker, T., Shafer, V. L., Kiefer, M., Vidal, N., & Yu, Y. H. (2017). T-complex measures in bilingual Spanish-English and Turkish-German children and monolingual peers. *PloS one*, *12*(3), e0171992.

Roberts, T. P., & Poeppel, D. (1996). Latency of auditory evoked M100 as a function of tone frequency. *Neuroreport*, *7*(6), 1138-1140.

Rogers, R. L., Papanicolaou, A. C., Baumann, S. B., & Eisenberg, H. M. (1992). Late magnetic fields and positive evoked potentials following infrequent and unpredictable omissions of visual stimuli. *Electroencephalography and clinical Neurophysiology*, *83*(2), 146-152.

Rouder, J. N., Morey, R. D., Verhagen, J., Swagman, A. R., & Wagenmakers, E. J. (2017). Bayesian analysis of factorial designs. *Psychological Methods*, *22*(2), 304.

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychonomic bulletin & review*, *16*(2), 225-237.

Roussel, C., Hughes, G., & Waszak, F. (2013). A preactivation account of sensory attenuation. *Neuropsychologia*, *51*(5), 922-929.

Roussel, C., Hughes, G., & Waszak, F. (2014). Action prediction modulates both neurophysiological and psychophysical indices of sensory attenuation. *Frontiers in human neuroscience*, *8*, 115.

Rubia, K., Smith, A. B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., & Brammer, M. (2006). Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Human brain mapping*, *27*(12), 973-993.

Ruhnau, P., Herrmann, B., & Schröger, E. (2012). Finding the right control: the mismatch negativity under investigation. *Clinical Neurophysiology*, *123*(3), 507-512.

Rummell, B. P., Klee, J. L., & Sigurdsson, T. (2016). Attenuation of responses to self-generated sounds in auditory cortical neurons. *Journal of Neuroscience*, *36*(47), 12010-12026.

Saarinen, J., Paavilainen, P., Schöger, E., Tervaniemi, M., & Näätänen, R. (1992). Representation of abstract attributes of auditory stimuli in the human brain. *NeuroReport*, *3*(12), 1149-1151.

Salisbury, D. F. (2012). Finding the missing stimulus mismatch negativity (MMN): emitted MMN to violations of an auditory gestalt. *Psychophysiology*, *49*(4), 544-548.

SanMiguel, I., Saupe, K., & Schröger, E. (2013a). I know what is missing here: electrophysiological prediction error signals elicited by omissions of predicted" what" but not" when". *Front Neurosci, 7*, 407.

Sanmiguel, I., Todd, J., & Schröger, E. (2013b). Sensory suppression effects to self-initiated sounds reflect the attenuation of the unspecific N 1 component of the auditory ERP. *Psychophysiology*, *50*(4), 334-343.

SanMiguel, I., Widmann, A., Bendixen, A., Trujillo-Barreto, N., & Schroger, E. (2013c). Hearing silences: human auditory processing relies on preactivation of sound-specific brain activity patterns. J *Neurosci, 33*(20), 8633-8639.

Saupe, K., Widmann, A., Trujillo-Barreto, N. J., & Schröger, E. (2013). Sensorial suppression of self-generated sounds and its dependence on attention. *International Journal of Psychophysiology*, *90*(3), 300-310.

Scharf, F., & Nestler, S. (2018). Principles behind variance misallocation in temporal exploratory factor analysis for ERP data: Insights from an inter-factor covariance decomposition. *International Journal of Psychophysiology*, *128*, 119-136.

Scharf, F., & Nestler, S. (2019). A comparison of simple structure rotation criteria in temporal exploratory factor analysis for event-related potential data. *Methodology*.

Scharf, F., Widmann, A., Bonmassar, C., & Wetzel, N. (2022). A tutorial on the use of temporal principal component analysis in developmental ERP research–opportunities and challenges. *Developmental Cognitive Neuroscience*, 101072.

Schlemmer, K. B., Kulke, F., Kuchinke, L., & Van Der Meer, E. (2005). Absolute pitch and pupillary response: Effects of timbre and key color. *Psychophysiology*, *42*(4), 465-472.

Schlögl, A., Keinrath, C., Zimmermann, D., Scherer, R., Leeb, R., & Pfurtscheller, G. (2007). A fully automated correction method of EOG artifacts in EEG recordings. *Clin Neurophysiol, 118*(1), 98-104.

Schneider, D. M., & Mooney, R. (2018). How movement modulates hearing. *Annual Review of Neuroscience*, *41*, 553-572.

Schneider, D. M., Sundararajan, J., & Mooney, R. (2018). A cortical filter that learns to suppress the acoustic consequences of movement. *Nature*, *561*(7723), 391-395.

Schröger, E. (1996). A neural mechanism for involuntary attention shifts to changes in auditory stimulation. *Journal of cognitive neuroscience*, *8*(6), 527-539.

Schröger, E., & Wolff, C. (1996). Mismatch response of the human brain to changes in sound location. *Neuroreport*, *7*(18), 3005-3008.

Schröger, E., Marzecová, A., & SanMiguel, I. (2015). Attention and prediction in human audition: a lesson from cognitive psychophysiology. *European Journal of Neuroscience*, *41*(5), 641-664.

Schubert, R., Ritter, P., Wüstenberg, T., Preuschhof, C., Curio, G., Sommer, W., & Villringer, A. (2008). Spatial attention related SEP amplitude modulations covary with BOLD signal in S1—a simultaneous EEG—fMRI study. *Cerebral cortex*, *18*(11), 2686-2700.

Segal, M. (2005). Dendritic spines and long-term plasticity. *Nature Reviews Neuroscience*, *6*(4), 277-284.

Segalowitz, S. J., Santesso, D. L., & Jetha, M. K. (2010). Electrophysiological changes during adolescence: a review. *Brain and cognition*, *72*(1), 86-100.

Severens, M., Farquhar, J., Desain, P., Duysens, J., & Gielen, C. C. A. M. (2010). Transient and steady-state responses to mechanical stimulation of different fingers reveal interactions based on lateral inhibition. *Clinical Neurophysiology*, *121*(12), 2090-2096.

Shadmehr, R., Smith, M. A., & Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Annual review of neuroscience*, *33*, 89-108.

Shafer, V. L., Yan, H. Y., & Wagner, M. (2015). Maturation of cortical auditory evoked potentials (CAEPs) to speech recorded from frontocentral and temporal sites: three months to eight years of age. *International Journal of Psychophysiology*, *95*(2), 77-93.

Shannon, C. E. A mathematical theory of communication. *Bell Syst. Tech. J.* **27**, 379–423 (1948).

Shergill, S. S., White, T. P., Joyce, D. W., Bays, P. M., Wolpert, D. M., & Frith, C. D. (2013). Modulation of somatosensory processing by action. *Neuroimage*, *70*, 356-362.

Shin, Y. K., Proctor, R. W., & Capaldi, E. J. (2010). A review of contemporary ideomotor theory. *Psychological bulletin*, *136*(6), 943.

Shinozaki, N., Yabe, H., Sutoh, T., Hiruma, T., & Kaneko, S. (1998). Somatosensory automatic responses to deviant stimuli. *Cognitive Brain Research*, *7*(2), 165-171.

Shipp, S. (2016). Neural elements for predictive coding. *Frontiers in psychology*, *7*, 1792.

Silva, L. A. F., Magliaro, F. C. L., Carvalho, A. C. M., & Matas, C. G. (2017). Maturation of long latency auditory evoked potentials in hearing children: systematic review. In *CoDAS* (*Vol. 29*, No. 3, p. e20160107).

Sokolov, E. N. (1963). Perception and the Conditioned Reflex. Oxford: Pergamon Press.

Southwell, R., & Chait, M. (2018). Enhanced deviant responses in patterned relative to random sound sequences. *Cortex, 109*, 92-103.

Spackman, L. A., Towell, A., & Boyd, S. G. (2010). Somatosensory discrimination: an intracranial event-related potential study of children with refractory epilepsy. *Brain research*, *1310*, 68-76.

Sperry, R. W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of comparative and physiological psychology*, *43*(6), 482.

Sprondel, V., Kipp, K. H., & Mecklinger, A. (2011). Developmental changes in item and source memory: Evidence from an ERP recognition memory study with children, adolescents, and adults. *Child Development*, *82*(6), 1638-1953.

Squires, N. K., Squires, K. C., & Hillyard, S. A. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography and clinical neurophysiology*, *38*(4), 387-401.

Stahl, A. E., & Feigenson, L. (2015). Observing the unexpected enhances infants' learning and exploration. *Science, 348*(6230), 91-94.

Stahl, A. E., & Feigenson, L. (2017). Expectancy violations promote learning in young children. *Cognition*, *163*, 1-14.

Stahl, A. E., & Feigenson, L. (2019). Violations of core knowledge shape early learning. *Topics in cognitive science*, *11*(1), 136-153.

Steinhauer, S. R., Bradley, M. M., Siegle, G. J., Roecklein, K. A., & Dix, A. (2022). Publication guidelines and recommendations for pupillary measurement in psychophysiological studies. *Psychophysiology*, *59*(4), e14035.

Stekelenburg, J. J., & Vroomen, J. (2015). Predictive coding of visual–auditory and motor-auditory events: An electrophysiological study. *Brain Res, 1626*, 88-96.

Stemerding, L. E., van Ast, V. A., Gerlicher, A. M., & Kindt, M. (2022). Pupil dilation and skin conductance as measures of prediction error in aversive learning. *Behavior Research and Therapy*, *157*, 104164.

Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., ... & Corlett, P. R. (2018). The predictive coding account of psychosis. *Biological psychiatry*, *84*(9), 634-643.

Strauch, C., Wang, C. A., Einhäuser, W., Van der Stigchel, S., & Naber, M. (2022). Pupillometry as an integrated readout of distinct attentional networks. *Trends in Neurosciences*.

Summerfield, C., Trittschuh, E. H., Monti, J. M., Mesulam, M. M., & Egner, T. (2008). Neural repetition suppression reflects fulfilled perceptual expectations. *Nature neuroscience*, *11*(9), 1004-1006.

Sussman, E. S., Chen, S., Sussman-Fort, J., & Dinces, E. (2014). The five myths of MMN: redefining how to use MMN in basic and clinical research. *Brain Topogr, 27*(4), 553-564.

Sussman, E., Steinschneider, M., Gumenyuk, V., Grushko, J., & Lawson, K. (2008). The maturation of human evoked brain potentials to sounds presented at different stimulus rates. *Hearing research, 236*(1-2), 61-79.

Szucs, D., & Ioannidis, J. P. (2017). Empirical assessment of published effect sizes and power in the recent cognitive neuroscience and psychology literature. *PLoS biology*, *15*(3), e2000797.

Tanner, D., Morgan-Short, K., & Luck, S. J. (2015). How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. *Psychophysiology, 52*(8), 997-1009.

Tarkka, I. M., Micheloyannis, S., & Stokić, D. S. (1996). Generators for human P300 elicited by somatosensory stimuli using multiple dipole source analysis. *Neuroscience*, *75*(1), 275-287.

Tervaniemi, M., Maury, S., & Näätänen, R. (1994a). Neural representations of abstract stimulus features in the human brain as reflected by the mismatch negativity. *Neuroreport*, *5*(7), 844-846.

Tervaniemi, M., Saarinen, J., Paavilainen, P., Danilova, N., & Näätänen, R. (1994b). Temporal integration of auditory information in sensory memory as reflected by the mismatch negativity. *Biological psychology*, *38*(2-3), 157-167.

Tesche, C. D., & Karhu, J. J. (2000). Anticipatory cerebellar responses during somatosensory omission in man. *Human brain mapping*, *9*(3), 119-142.

Tiitinen, H., Mäkelä, A. M., Mäkinen, V., May, P. J., & Alku, P. (2005). Disentangling the effects of phonation and articulation: Hemispheric asymmetries in the auditory N1m response of the human brain. *BMC neuroscience*, *6*(1), 1-9.

Timm, J., SanMiguel, I., Saupe, K., & Schröger, E. (2013). The N1-suppression effect for self-initiated sounds is independent of attention. *BMC neuroscience*, *14*(1), 1-11.

Todorovic, A., & de Lange, F. P. (2012). Repetition suppression and expectation suppression are dissociable in time in early auditory evoked fields. *Journal of Neuroscience*, *32*(39), 13389-13395.

Todorovic, A., van Ede, F., Maris, E., & de Lange, F. P. (2011). Prior expectation mediates neural adaptation to repeated sounds in the auditory cortex: an MEG study. *Journal of Neuroscience*, *31*(25), 9118-9123.

Tonnquist-Uhlen, I., Ponton, C. W., Eggermont, J. J., Kwong, B., & Don, M. (2003). Maturation of human central auditory system activity: the T-complex. *Clinical Neurophysiology, 114*(4), 685-701.

Trainor, L. J. (2012). Predictive information processing is a fundamental learning mechanism present in early development: Evidence from infants. *International Journal of Psychophysiology*, *83*(2), 256-258.

Treit, S., Chen, Z., Rasmussen, C., & Beaulieu, C. (2014). White matter correlates of cognitive inhibition during development: a diffusion tensor imaging study. *Neuroscience*, *276*, 87-97.

Tremblay, K., Kraus, N., & McGee, T. (1998). The time course of auditory perceptual learning: neurophysiological changes during speech-sound training. *Neuroreport*, *9*(16), 3557-3560.

Ulanovsky, N., Las, L., & Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. *Nature neuroscience*, *6*(4), 391-398.

Ulanovsky, N., Las, L., Farkas, D., & Nelken, I. (2004). Multiple time scales of adaptation in auditory cortex neurons. *Journal of Neuroscience*, *24*(46), 10440-10453.

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., De-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism. *Psychological review*, *121*(4), 649.

Van de Wassenberg, W., Van der Hoeven, J., Leenders, K., & Maurits, N. (2008). Multichannel recording of median nerve somatosensory evoked potentials. *Neurophysiologie Clinique/Clinical Neurophysiology*, *38*(1), 9-21.

van Hooijdonk, R., Mathôt, S., Schat, E., Spencer, H., van der Stigchel, S., & Dijkerman, H. C. (2019). Touch-induced pupil size reflects stimulus intensity, not subjective pleasantness. *Experimental brain research*, *237*(1), 201-210.

Van Laarhoven, T., Stekelenburg, J. J., & Vroomen, J. (2017). Temporal and identity prediction in visual-auditory events: Electrophysiological evidence from stimulus omissions. *Brain Res, 1661*, 79-87.

Van Laarhoven, T., Stekelenburg, J. J., Eussen, M. L., & Vroomen, J. (2020). Atypical visual-auditory predictive coding in autism spectrum disorder: Electrophysiological evidence from stimulus omissions. *Autism*, *24*(7), 1849-1859.

VanRullen, R. (2011). Four common conceptual fallacies in mapping the time course of recognition. *Frontiers in psychology*, *2*, 365.

Vazey, E. M., Moorman, D. E., & Aston-Jones, G. (2018). Phasic locus coeruleus activity regulates cortical encoding of salience information. *Proceedings of the National Academy of Sciences*, *115*(40), E9439-E9448.

Verhagen, J., & Wagenmakers, E. J. (2014). Bayesian tests to quantify the result of a replication attempt. *Journal of Experimental Psychology: General*, *143*(4), 1457.

von Holst, E., & Mittelstaedt, H. (1950). Das reafferenzprinzip. *Naturwissenschaften*, *37*(20), 464-476.

Vroomen, J., & Stekelenburg, J. J. (2010). Visual anticipatory information modulates multisensory interactions of artificial audiovisual stimuli. *Journal of cognitive neuroscience*, *22*(7), 1583-1596.

Wacongne, C., Labyt, E., Van Wassenhove, V., Bekinschtein, T., Naccache, L., & Dehaene, S. (2011). Evidence for a hierarchy of predictions and prediction errors in human cortex. *Proceedings of the National Academy of Sciences*, *108*(51), 20754-20759.

Wagenmakers, E. J. (2007). A practical solution to the pervasive problems of p values. *Psychonomic bulletin & review*, *14*(5), 779-804.

Wagenmakers, E. J., Grünwald, P., & Steyvers, M. (2006). Accumulative prediction error and the selection of time series models. *Journal of Mathematical Psychology*, *50*(2), 149-166.

Wagenmakers, E. J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Love, J., ... & Morey, R. D. (2018). Bayesian inference for psychology. Part I: Theoretical advantages and practical ramifications. *Psychonomic bulletin & review*, *25*, 35-57.

Walsh, L. D., Taylor, J. L., & Gandevia, S. C. (2011). Overestimation of force during matching of externally generated forces. *The Journal of physiology*, *589*(3), 547-557.

Wang, C. A., & Munoz, D. P. (2015). A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. *Current opinion in neurobiology*, *33*, 134-140.

Wang, C. A., & Munoz, D. P. (2021). Coordination of pupil and saccade responses by the superior colliculus. *Journal of cognitive neuroscience*, *33*(5), 919-932.

Wang, C. A., Boehnke, S. E., White, B. J., & Munoz, D. P. (2012). Microstimulation of the monkey superior colliculus induces pupil dilation without evoking saccades. *Journal of Neuroscience*, *32*(11), 3629-3636.

Waszak, F., Cardoso-Leite, P., & Hughes, G. (2012). Action effect anticipation: neurophysiological basis and functional consequences. *Neuroscience & Biobehavioral Reviews*, *36*(2), 943-959.

Wei, J.-H., Chan, T.-C., & Luo, Y.-J. (2002). A modified oddball paradigm "cross-modal delayed response" and the research on mismatch negativity. *Brain research bulletin, 57*(2), 221-230.

Wetzel, N. (2015). Effects of the short-term learned significance of task-irrelevant sounds on involuntary attention in children and adults. *International journal of psychophysiology*, *98*(1), 17-26.

Wetzel, N., & Schröger, E. (2007). Modulation of involuntary attention by the duration of novel and pitch deviant sounds in children and adolescents. *Biological Psychology*, *75*(1), 24-31.

Wetzel, N., Buttelmann, D., Schieler, A., & Widmann, A. (2016). Infant and adult pupil dilation in response to unexpected sounds. *Developmental psychobiology*, *58*(3), 382-392.

Wetzel, N., Scharf, F., & Widmann, A. (2019). Can't ignore—Distraction by task-irrelevant sounds in early and middle childhood. *Child development*, *90*(6), e819-e830.

Wetzel, N., Widmann, A., & Schroger, E. (2011). Processing of novel identifiability and duration in children and adults. *Biol Psychol, 86*(1), 39-49.

Wetzel, N., Widmann, A., Berti, S., & Schröger, E. (2006). The development of involuntary and voluntary attention from childhood to adulthood: a combined behavioral and event-related potential study. *Clinical Neurophysiology*, *117*(10), 2191-2203.

Widmann, A., & Schröger, E. (2012). Filter effects and filter artifacts in the analysis of electrophysiological data. *Frontiers in psychology*, *3*, 233.

Widmann, A., Schröger, E., & Maess, B. (2015). Digital filter design for electrophysiological data–a practical approach. *Journal of neuroscience methods*, *250*, 34-46.

Widmann, A., Schröger, E., & Wetzel, N. (2018). Emotion lies in the eye of the listener: Emotional arousal to novel sounds is reflected in the sympathetic contribution to the pupil dilation response and the P3. *Biological psychology*, *133*, 10-17.

Wilson, Edward O (1998). Consilience: the unity of knowledge. New York: Knopf. ISBN 978-0-679-45077-1. OCLC 36528112

Winkler, I., Debener, S., Müller, K. R., & Tangermann, M. (2015). On the influence of high-pass filtering on ICA-based artifact reduction in EEG-ERP. In *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 4101-4105). IEEE.

Winkler, I., Háden, G. P., Ladinig, O., Sziller, I., & Honing, H. (2009). Newborn infants detect the beat in music. *Proceedings of the National Academy of Sciences*, *106*(7), 2468-2471.

Winkler, I., Haufe, S., & Tangermann, M. (2011). Automatic classification of artifactual ICA-components for artifact removal in EEG signals. Behavioral and brain functions, 7(1), 1-15.

Wolpaw, J. R., & Penry, J. K. (1975). A temporal component of the auditory evoked response. *Electroencephalography and clinical neurophysiology*, *39*(6), 609-620.

Wolpe, N., Ingram, J. N., Tsvetanov, K. A., Geerligs, L., Kievit, R. A., Henson, R. N., ... & Rowe, J. B. (2016). Ageing increases reliance on sensorimotor prediction through structural and functional differences in frontostriatal circuits. *Nature communications*, *7*(1), 1-11.

Woods, D. L. (1995). The component structure of the N 1 wave of the human auditory evoked potential. *Electroencephalography and Clinical Neurophysiology-Supplements Only*, *44*, 102-109.

Wunderlich, J. L., & Cone-Wesson, B. K. (2006). Maturation of CAEP in infants and children: a review. *Hearing research, 212*(1-2), 212-223.

Xiang, J., Hoshiyama, M., Koyama, S., Kaneoke, Y., Suzuki, H., Watanabe, S., ... & Kakigi, R. (1997). Somatosensory evoked magnetic fields following passive finger movement. *Cognitive brain research*, *6*(2), 73-82.

Yabe, H., Tervaniemi, M., Reinikainen, K., & Näätänen, R. (1997). Temporal window of integration revealed by MMN to sound omission. *Neuroreport*, *8*(8), 1971-1974.

Yabe, H., Tervaniemi, M., Sinkkonen, J., Huotilainen, M., Ilmoniemi, R. J., & Näätänen, R. (1998). Temporal window of integration of auditory information in the human brain. *Psychophysiology*, *35*(5), 615-619.

Yates, A. (1987). *Multivariate exploratory data analysis: A perspective on exploratory factor analysis*. Suny Press.

Zekveld, A. A., Koelewijn, T., & Kramer, S. E. (2018). The pupil dilation response to auditory stimuli: Current state of knowledge. *Trends in hearing*, *22*, 2331216518777174.

Zhang, F., Jaffe-Dax, S., Wilson, R. C., & Emberson, L. L. (2019). Prediction in infants and adults: A pupillometry study. *Developmental science*, *22*(4), e12780.

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