School of Population Health

Sensory Gating of Conscious Perception: The Influence of Stimuli Intensities, Timing, and Predictability

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This thesis is presented for the Degree of

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics (For projects involving human participants/tissue, etc) The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number HRE2018-0257

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Article 3: The effect of temporal predictability on sensory gating: Cortical responses inform Perception

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GENERAL ABSTRACT

Sensory gating is an integral set of processes responsible for the filtering of incoming sensory information. In the psychology and neuroscience literature, the brain's ability to limit one stimulus while permitting the further processing of another is typically studied using startle prepulse inhibition (PPI). Startle PPI is a phenomenon where the physiological response (startle or blink reflex) to an intense stimulus is reduced when it is preceded by a weaker stimulus. While startle PPI has provided a wealth of clinical and mechanistic insights, there is a growing debate about its applicability to understanding higher-level and everyday experiences of sensory gating (e.g., how does sensory gating influence conscious perception, and how is sensory gating consciously perceived?).

Alternative phenomena that have the potential to investigate such higher-level processes and questions more directly exist but are far less researched. One such phenomenon is prepulse inhibition of perceived stimulus intensity (PPIPSI). Related to startle PPI, PPIPSI is the reduction in the perceived intensity of a stronger stimulus when it is preceded by a weaker stimulus. Although the PPIPSI literature is limited, its focus on the gating of perceived intensity (a higher-level process) suggests it may offer a more direct method of studying and understanding the gating of conscious perception. Initial accounts of PPIPSI interpreted it as a downstream effect of startle PPI mechanisms. Considering that the observation of PPIPSI requires an active experimental procedure and longer stimulus onset asynchronies (SOAs), more recent theories suggest that PPIPSI shares lower-level mechanisms with startle PPI but diverges as PPIPSI also recruits higher-level (likely attentional) processes. However, except for key parametric studies by Swerdlow et al. (2005), little to no research has directly investigated the processes that influence PPIPSI or the stimulus parameters that elicit PPIPSI.

Better understanding the neural mechanisms of PPIPSI is important for a more comprehensive knowledge of sensory gating. For example, PPIPSI may be used to provide insights into how sensory gating is consciously perceived and which higher-level processes contribute to the gating of conscious perception. Furthermore, understanding the processes central to sensory gating may later be studied in clinical populations characterised by reduced sensory gating, where targeting these processes may improve symptoms. Consequently, in this thesis, I examine the stimulus parameters and processes that influence

PPIPSI to provide a better understanding of the mechanisms underlying the gating of conscious perception.

In chapter two, optimal SOA and prepulse intensity parameters for electrotactile PPIPSI elicitation were investigated. Our analysis revealed that across the tested SOAs (no gap, 40, 80, 120, 160, and 200 ms), as SOA increases, so too does the proportion of PPIPSI trials observed. However, PPIPSI does not rise significantly above chance level until SOAs of ≥160 ms. In a second experiment, we tested whether even longer SOAs (200 – 600 ms) produced greater PPIPSI. This experiment revealed that all tested SOAs produce above chance levels of PPIPSI, with no significant difference in elicitation among SOAs observed. Lastly, our analysis of the effects of prepulse intensity identified that of the three prepulse intensities tested (1x, 2x, and 3x perceptual threshold), the 2x condition produced the greatest proportion of PPIPSI trials. Cumulatively, the data from these experiments demonstrate that the optimal parameters for electrotactile PPIPSI are a 2x perceptual threshold prepulse with an SOA of 200 ms. We propose that the emergence of greater PPIPSI at longer SOAs (≥160 ms) indicates that the time gap allows greater activation of attentional and self-monitoring processes, which are required for PPIPSI, but not startle PPI.

In chapter three, the relationship between PPIPSI and cortical PPI (N1-P2 gating) in both electrotactile and acoustic modalities was examined. The influence of attentional load on acoustic PPIPSI and cortical PPI was also investigated. We observed that in both modalities, the greater the prepulse suppression of the N1-P2 ERPs to the pulse, the higher the probability that participants perceive the 'with prepulse' condition as less intense (i.e., PPIPSI). Further analysis revealed that attentional load affects PPIPSI but did not detect a significant change in cortical PPI. Under higher attentional load, the observation of PPIPSI was significantly reduced; we interpret this as further support for propositions that the gating of perception involves attentional processes (Swerdlow et al., 2005). The finding that attentional load does not influence cortical PPI suggests that these processes (largely the N1 component) are independent of attentional mechanisms, and likely represent stimulus features or traces, which at a later stage attentional processes access to form a conscious percept (Näätänen and Winkler, 1999). In other words, we suggest that what initially reaches the cortex (N1-P2 timeframe) is largely independent of attentional processes, but to consciously perceive that gating has occurred requires directing attention to the processes

or channels associated with these cortical readouts. We propose that one reason PPIPSI emerges at longer SOAs than startle PPI is because, even if driven indirectly by the prepulse, allocating attention to the relevant cortical channels requires more time.

Finally, chapter four examined the influence of temporal predictability on the SOA at which PPIPSI is observed, and whether it affects the previously identified relationship between PPIPSI and cortical PPI. By increasing the temporal predictability of when the pulse stimulus was presented, we increased the observation of PPIPSI at both a longer (150 ms) and shorter (90 ms) SOAs. Moreover, the relationship between PPIPSI and cortical PPI was maintained. As seen in other paradigms (Alegria, 1975; Herbst & Obleser, 2019; McInnes et al., 2021; van Ede et al., 2018), we suggest that in PPIPSI, temporal predictability facilitates the allocation of finite attentional resources that are used to perceive the inhibitory effects of the prepulse. Temporal predictability's enhancement of PPIPSI also suggests that the pulse information that reaches conscious perception has already undergone gating. If PPIPSI were merely a perceptual level error, temporal predictability would be expected to minimise it, as is seen in similar studies (Gresch et al., 2021; Herbst & Obleser, 2019; Jones, 1976; Jones et al., 2006; McInnes et al., 2021; van Ede et al., 2018). We propose a model in which the inhibitory processes activated by the prepulse are predominantly acting at lower-level, subcortical mechanisms (likely shared with startle PPI and cortical PPI). However, these inhibited signals can be brought to conscious perception (resulting in PPIPSI) when attention is sufficiently allocated towards relevant processing channels.

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LIST OF ABBREVIATIONS

AB	Attentional Blink
ADHD	Attention Deficit Hyperactive Disorder
ANT	Attention Network Task
ASE	Accessory Stimulus Effect
CMS	Common Mode Sense
CN	Cochlear Nucleus
CRNs	Cochlear Root Neurons
CSPS	Cortico-Striatal-Pallido-Thalamic Circuit
CSD	Current Source Density
DRL	Driven Right Leg
EEG	Electroencephalogram
ERP	Event Related Potential
GLMM	Generalised Linear Mixed Model
IC	Inferior Colliculus
ICs	Independent Components
LMM	Linear Mixed Model
LC	Locus Coeruleus
MN	Motor Neurons
mPFC	Medial Prefrontal Cortex
N1	Negative 100 Event Related Potential
OCD	Obsessive Compulsive Disorder
P2	Positive 200 Event Related Potential
PD	Panic Disorder
PFC	Prefrontal Cortex
PnC	Caudal Pontine Reticular Neurones
PPF	Prepulse Facilitation
PPI	Prepulse Inhibition

PPIPSI	Prepulse Inhibition of Perceived Stimulus Intensity
PTTg	Pedunculopontine Tegmental Nucleus
RT	Reaction Time
S1	Stimulus 1 (first stimulus)
S2	Stimulus 2 (second stimulus)
SC	Superior Colliculus
SOA	Stimulus Onset Asynchrony
TP	Temporal Predictability
VAS	Visual Analogue Scale
VNTB	Ventral Nucleus of the Trapezoid Body

CHAPTER ONE: GENERAL INTRODUCTION

This chapter provides an overview of sensory gating, starting with an exploration of Startle PPI, including its mechanisms and pathways in both rodents and humans. It then delves into Prepulse Inhibition of Perceived Stimulus Intensity (PPIPSI), highlighting its differences from PPI and the role of the prepulse. Additionally, the chapter discusses cortical PPI, the unknown relationship between cortical PPI and PPIPSI, and the potential influence of attention and predictability on these phenomena.

1.0 Introduction (Sensory Gating)

Every day our brains are tasked with navigating a dynamic and intricate environment. An environment filled with sensory information - whether driving to work or catching a friend for coffee in a busy café. To successfully function within this environment requires attending to key information while tuning out less relevant information. One facet that plays a pivotal role in the management of incoming information is sensory gating. Sensory gating is not a singular process, but rather a term for the multiple processes responsible for either permitting or inhibiting the further processing of incoming sensory information. It may be thought of as a filter or sift, which catches some information while allowing other information to flow through to conscious awareness. While for most individuals this process seems automatic and effortless, impaired sensory gating (weakening of the filter) is characteristic of numerous clinical presentations, including, but not limited to Schizophrenia, PTSD, anxiety, OCD and ADHD (Geyer, 2006). For these clinical populations reduced sensory gating is implicated in symptoms such as sensory overload, thought flooding, and inattentiveness, which can severely affect individuals' daily functioning and quality of life (Blumenthal, 2015; Geyer, 2006; Naegeli et al., 2018). The aetiology and mechanism(s) of sensory gating are complex and many aspects unknown. Much of our understanding about sensory gating mechanisms is inferred from a phenomenon known as startle prepulse inhibition (PPI) - an operational measure of sensorimotor gating denoted by the reduction in the startle response or blink reflex to an intense stimulus when it is preceded at a short latency by a weaker stimulus (known as the *prepulse*; Graham, 1975). As will be discussed below, growing research suggests that startle PPIs' utility to provide inferences and further understanding about the higher-level (conscious perception) aspects of sensory gating may be limited by its reliance on a reflexive motor response. To elaborate, startle PPI involves measuring a physical response (sensorimotor gating), whilst sensory gating is concerned with information processing. Thus, while sensorimotor and sensory gating may be related, they differ both conceptually and in how they are measured. For example, an associated phenomenon known as prepulse inhibition of perceived stimulus intensity (PPIPSI) exists which focusses on the sensory processing aspect of PPI. PPIPSI is defined as the reduction in perceived intensity of the strong stimulus when preceded by a less intense stimulus (Swerdlow et al., 2005). However, apart from a few core works

(Swerdlow et al., 2005; Swerdlow et al., 2007) PPIPSI remains largely under researched, despite its potential to provide novel insights into sensory gating processes. Consequently, the current thesis focusses on broadening our understanding of PPIPSI and the effects of the processes contributing to gating on conscious perception.

1.1 Startle PPI

Historically and most prominently, gating has been researched in the context of lower-level stimulus processing via a phenomenon known as startle prepulse inhibition (PPI). First identified by Graham (1975), PPI denotes the startle or blink reflex to a startling stimulus being dampened by the presentation of a weaker stimulus (prepulse) delivered immediately prior to the startling stimulus (30 – 500ms; Blumenthal, 2015). Graham (1975) proposed two hypotheses for the existence of PPI, those being the protection and interruption hypotheses. The protection hypothesis posits that the prepulse activates two processes, one of processing the prepulse stimulus, and a gating mechanism which aids this processing by inhibiting the physiological response to and information received about the following more intense stimulus. Such a gating mechanism exists to prevent processing of the more intense stimulus from *interrupting* that of the preceding weaker stimulus. The interruption hypothesis also posits that the startle response interferes with any processes and behaviours that are ongoing when the response occurs, including processing of the pulse or startle stimulus. This is due to the startle's rapid onset, often occurring within 15 to 40 milliseconds post-stimulus (Blumenthal, 2015). This rapid response indicates that sensory processing, particularly at higher levels of the brain, is likely unfinished by the time the startle response is elicited, allowing it to potentially interrupt processing of the pulse stimulus itself (Blumenthal, 2015; Graham, 1975). The protection and interruption hypotheses will be returned to throughout the chapter where I review more recent advances in their testing.

To quantify PPI, researchers compare the amplitude of the startle response (or blink reflex) in two types of trials: those with the pulse alone (control trials) and those where a prepulse precedes the pulse ('with prepulse' trials). Startle PPI is observed using within-modality (e.g. electrical prepulse - electrical pulse and acoustic prepulse – acoustic pulse; Blumenthal, 2015) and multi-modal stimuli, such as tactile-acoustic (Elden & Flaten, 2002;

Hill & Blumenthal, 2005), visual-acoustic (Oranje et al., 2006; Rossi et al., 1995) and electro-acoustic (Hab et al., 2017). However, the elicitation of PPI with different stimulus setups varies as a function of different prepulse durations, intensities, and times between prepulse onset and pulse onset settings (referred to as stimulus onset asynchrony; SOA). For example, using within-modality acoustic stimuli, PPI emerges at SOAs of 15 - 30ms, peaking at around 60 – 240ms SOAs (Blumenthal et al., 1999; Graham, 1975; Graham & Murray, 1977; Swerdlow et al., 2005). Whereas SOAs of 120 – 400 ms are required for visual prepulses and acoustic pulses (Aitken et al., 1999), and 100 – 800ms for vibrotactile prepulse and acoustic pulses (Norris & Blumenthal, 1996). With regards to prepulse intensity and duration settings, PPI increases with prepulse intensity and duration to an asymptote, after which further intensity increases result in a decline in PPI (Blumenthal, 1995; Franklin et al., 2007). Notably, the most prevalent setup is within modality acoustic stimuli, with considerably less research into PPI using non-acoustic pulses (Blumenthal, 2015).

The blink reflex is elicited at very short latencies post-stimulus onset (9 - 25 ms; Blumenthal et al., 2005), and the SOAs required to observe startle PPI are also very brief (15 - 300 ms, depending on experimental parameters). The short latencies at which startle PPI occurs make it unlikely that higher-level processes have sufficient time to be activated and contribute to the gating effect. Due to this, the underlying mechanisms of startle PPI are believed to be sub-cortical, automatic, and pre-attentive (Blumenthal, 2015; Bohmelt et al., 1999; Swerdlow et al., 2005). That is, at the physiological level of sensory gating, attentional and higher-order processes are less likely involved, as the processes occur at too rapid a pace to engage higher-level areas of the brain and attentional mechanisms. This conceptualisation is consistent with neurological pathway studies (discussed in more detail below) and evidence that PPI is present in infants (Graham et al., 1981), sleeping adults (Silverstein et al., 1980) and decorticated rats (Ison et al., 1991). PPI experiments are typically passive in their design; the participants are not required to engage with the task for the prepulse to inhibit the blink reflex. That said, active designs can also influence PPI. For example, instructing participants to direct their attention to the prepulse has been found to enhance PPI above non-directed trials (Ashare et al., 2007). However, it has been extensively shown that this enhancement only influences startle PPI using continuous

prepulses (prepulses which end at or after the pulse onset) and SOAs ≥ 120 ms. Attention to prepulse studies using short-duration prepulses which end prior to the pulse onset (referred to as discrete stimuli) and SOAs shorter than 120 ms produce inconsistent results (Ashare et al., 2007; Dawson et al., 1993; Elden & Flaten, 2002; Filion & Poje, 2003; Hawk et al., 2002; Heekeren et al., 2004; Poje & Filion, 2021). The fact that active designs enhance startle PPI only with continuous prepulses and longer SOAs suggests that these stimulus parameters are more amenable to the recruitment of attentional mechanisms. However, discrete prepulses are more effective at eliciting startle PPI than continuous ones (Braff et al., 2001; Poje & Filion, 2021; Wynn et al., 2000), which is consistent with the broader evidence that startle PPI is predominantly driven by processes that are independent of higher-level, attentional mechanisms.

1.1.1 Mechanism of startle PPI

1.1.1.1 Pathway in rodents

Early animal, and particularly rat studies have led to an extensive model of the acoustic startle and PPI pathways. The primary startle pathway (see figure 1.1 below) involves the spiral ganglion cells of the cochlea which directly inputs to the cochlear root neurons (CRNs). The CRNs then innervate giant neurones in the caudal pontine reticular (PnC) that project to spinal, facial, and cranial motoneurons (MN) leading to the muscle contractions of startle 6 - 10 ms post stimulus presentation (Fendt et al., 2001; Lee et al., 1996).

The literature suggests PPI is mediated by numerous pathways (Gomez-Nieto et al., 2020). Of these, Fendt et al's (2001) conceptualisation is the most prominent - they propose that in addition to the startle pathway, acoustic prepulses are processed through the inferior colliculus (IC), activating the superior colliculus (SC; known to receive inputs from prepulses in acoustic, visual and tactile modalities). From the SC, its projections to the pedunculopontine tegmental nucleus (PPTg) result in cholinergic projections to the PnC which inhibit the startle response (see Figure 1; Fendt et al., 2001). While the literature supports that these neural areas are central to the inhibitory pathway of PPI, the majority of PTTg neurones are GABAergic and glutamatergic, not cholinergic (Li et al., 2009; Wang & Morales, 2009). Moreover, since Fendt et al's (2001) proposal, optogenetic studies (Azzopardi et al., 2018) and studies using selective cholinergic lesions of the PPTg (MacLaren

et al., 2014) have identified that activating the PTTg cholinergic neurones contrarily facilitates startle and reduces PPI, while the non-cholinergic neurons mediate PPI. These findings suggest that earlier models require revision and further investigation into the proposed inhibitory role of the PTTg cholinergic neurons in PPI is needed. Of these revisions, Yeomans et al. (2006) provide evidence that two parallel pathways exist. Their findings indicate that a faster auditory pathway from the IC to the PTTg, and a slower multimodal SC pathway better account for latency discrepancies between brain areas and partial PPI reductions after SC lesions (Yeomans et al., 2006).

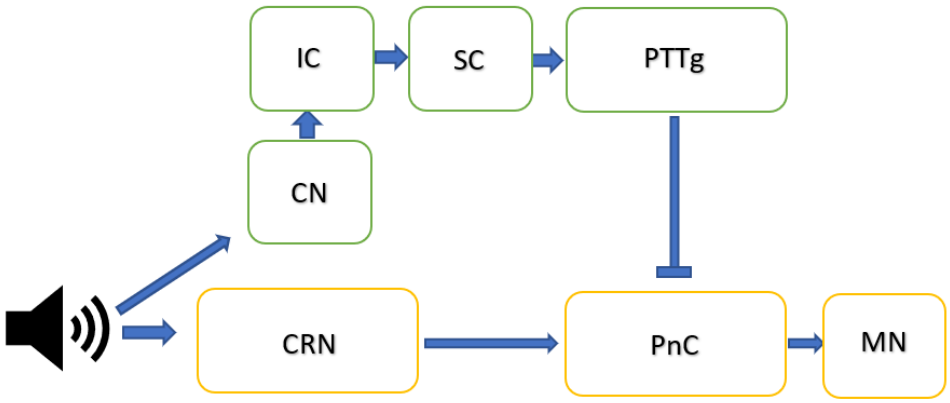

Figure 1.1. *Animal Acoustic Startle PPI Pathway. Arrows represent excitatory connections, while flatline represents inhibitory. Yellow = The primary startle pathway comprised of the cochlear root neurones (CRNs), caudal pontine reticular neurones (PnC) and spinal motor neurones (MN). Inhibition caused by the prepulse is said to occur at the PnC. Green = Prepulses are processed via the cochlear nucleus (CN) and the inferior colliculus (IC). From the IC the information is projected to the superior colliculus (SC) and the pedunculopontine tegmental nucleus (PTTg). Lastly, the PTTg is proposed to send cholinergic inhibitory projections to the PnC which mediate PPI (adapted from Fendt et al., 2001).*

Growing evidence also indicates that additional neural areas not within the commonly held mediating pathway contribute to startle PPI. For example, direct and indirect projections from the substantia nigra to the PnC have been shown to mediate PPI (Li et al., 2009; Koch et al., 1993). Gómez-Nieto et al. (2014) also identified a pathway that can explain how startle PPI is observed at very short intervals (15 - 20 ms) via cholinergic

projections from the ventral nucleus of the trapezoid body (VNTB) to the CRNs. This is said to occur via bypassing of the slower multimodal circuit when acoustic stimuli are used, consistent with Yeomans et al. (2006) suggestion that two parallel pathways exist. Lastly, the locus coeruleus (LC) has been implicated in the mediation of PPI via projections to the CRN (Hormigo et al., 2014). However, the LC also impedes PPI under high tonic output of noradrenaline (Alsene & Bakshi, 2011). Moreover, Alsene and Bakshi's (2011) finding that stimulating cholinergic receptors in the locus coeruleus, which indirectly activates noradrenergic neurons, reduced PPI and facilitated startle is consistent with those of Azzopardi et al. (2018) in suggesting that a cholinergic-specific inhibitory pathway is unlikely responsible for PPI. The LC's location in the brainstem and known role in regulating cognitive, arousal, sensory, and attentional processes (Aston-Jones & Cohen, 2005; Sara, 2009) offer it significant potential to modulate the transmission of sensory information and render it a prime candidate for mediating PPI. The LC may mediate PPI via its inhibitory projections to the CRN (Hormigo et al., 2014), but reduce PPI under enhanced noradrenaline activation of the final moto-neurone in the startle pathway (Noga et al., 2011; Szabadi, 2012).

Evidently research with rodents has led to many insights and strong support for the existence of multiple midbrain pathways mediating PPI. Whether they act independently or in tandem is yet to be confirmed. The existence of multiple pathways in the mechanism of startle PPI is supported by its sensitivity to various stimulus parameters, such as intensity and SOA. This sensitivity implies that different test parameters might not only affect the overall response but also highlight the involvement of specific pathways over others. For instance, the rapid acoustic pathway, as identified by Yeomans et al. (2006) and Gómez-Nieto et al. (2014), is particularly active at shorter latencies, as indicated by PPI using shorter SOAs. This pathway responds swiftly to auditory stimuli. On the other hand, the pathway proposed by Fendt (2001) appears to be more engaged during longer latency periods and when the experiment uses multimodal stimuli. This suggests that depending on the nature and timing of the stimuli, different neural pathways are recruited, each playing a distinct role in modulating the startle PPI response.

Although rodent studies have progressed PPI and startle pathway models, and multiple similarities between species have been observed (see Geyer et al., 2001 and

Swerdlow et al., 2001 for review), there are also many differences (Swerdlow et al., 2001). Even lower-level brain regions which regulate startle differ significantly across species (Swerdlow et al., 2001). Thus, while rat studies provide models for understanding the neural pathways of startle and startle PPI, it would be rash to assume that rat pathway models directly translate across species (e.g. to human neural pathways). Human studies are required to provide support for translational models and insights into human specific startle and startle PPI pathways (Swerdlow et al., 2001).

1.1.1.2 Human studies

Non-human mammalian studies have provided a wealth of speculative insights into the human startle PPI pathways. These insights are particularly compelling given the findings of consistencies in PPI regulatory mechanisms across mammalian species, including humans (Swerdlow et al., 2001). However, these pathways are still speculative, as the ASR pathway in humans is yet to be conclusively mapped. Nevertheless, growing evidence from behavioural, fMRI, pharmacological, and psychophysiological experiments is converging towards a widespread network branching from the brainstem to limbic and frontal areas (Naysmith et al., 2021).fMRI studies have added some support for the suggestions of Swerdlow et al. (2001) in implicating a cortico-striatal-pallido-thalamic (CSPS) circuit comprising the prefrontal cortex, thalamus, amygdala, hippocampus, nucleus accumbens, striatum, ventral pallidum and globus pallidum in human PPI (Cambell et al., 2007; Goldman et al., 2006; Hazlett et al., 2001; Kumari et al., 2007; Li et al., 2009). These studies have also evidenced differences in BOLD activity depending on the SOA used (30 and 120 ms; Kumari et al., 2003; Kumari et al., 2008). Kumari et al. (2003) reported that on PPI trials (compared to pulse-alone trials), BOLD activity was observed in the globus pallidus/putamen, caudate, thalamic, insula, inferior frontal, temporal, hippocampal, and inferior parietal regions at a 120 ms SOA. In contrast, 30 ms SOA trials produced increased BOLD activity in these same areas, with the addition of increased activity in the temporal gyrus. Similarly, Kumari et al. (2008) observed increased BOLD activity in the superior temporal gyrus at 30 ms SOAs compared to pulse-alone trials, while 120 ms SOAs saw increased BOLD activity in the inferior parietal cortex branching to the inferior frontal gyrus compared to pulse-alone trials. Studies employing the attention-to-prepulse design have demonstrated an increased BOLD response in the thalamus (Hazlett et al., 2001) and frontal-striatal-thalamic circuitry

(Hazlet et al., 2008) in 'attend' to prepulse conditions when compared to 'ignore' or unattended prepulse conditions at 120 ms SOAs. Notably, attention-to-prepulse designs differ significantly from 'standard' PPI studies; they predominantly use a continuous prepulse (durations of 2 seconds plus) which terminates at or after the pulse presentation (Hazlet et al., 2001; Hazlet et al., 2008; Poje & Filion, 2021). Startle PPI is typically less effective under continuous prepulse methods compared to when the prepulse is discrete (Braff et al., 2001; Poje & Filion, 2021; Wynn et al., 2000). Nevertheless, these findings suggest the thalamus is central to attentional enhancements of PPI when using a continuous prepulse and longer SOAs, likely due to induced cortical arousal, consistent with known functions of the thalamus (Schiff, 2008).

In combination, the fMRI literature supports propositions drawn from rodent studies (Swerdlow et al., 2016), and highlights the likely involvement of top-down processes which increase in influence as SOA increases above 30 – 60 ms, and when a continuous prepulse is used (Hazlett et al., 2001). However, Li et al. (2009) raises valid concerns about interpreting fMRI data, particularly at short latencies such as those used in PPI. At short SOAs, it is uncertain whether fMRI is sensitive or reliable enough to separate representations of sensory gating (elicited by the prepulse) from sensory processing of the stimuli. This becomes a particular issue in fMRI studies that use prepulse durations of several seconds such as those required for attentional enhancement of PPI (Hazlet et al., 2001; Hazlet et al., 2008; Li et al., 2009). That is, fMRI data comparing the 'with prepulse' to 'pulse-alone' conditions may depict the activation of gating pathways by the prepulse or simply the difference in stimulus energy (Li et al., 2009). While it can be reasonably assumed that startle PPI is occurring during fMRI studies, to-date fMRI machines limit researchers' ability to record startle PPI simultaneously (Hazlet et al., 2008). Being able to compare trials where the prepulse elicited PPI to those where it did not would minimise some of the current fMRI concerns and provide better insights into the neural correlates of human PPI (Li et al., 2009).

Evidently the processing and inhibitory pathways of the brain provide a complex picture, even when looking at a simple reflex and limitations exist with each chosen method. While recording fMRI and startle PPI may be difficult, the literature does indicate that cortical activity might be important for a reflex and its inhibition (Hazlet et al., 2001; Hazlet et al., 2008; Li et al., 2009). If this is the case, cortical activity should be critical for tasks

which involve reporting perceptual experiences, such as perceived intensity. Not only are perceptual experience methods easier to implement simultaneously with fMRI (Langers et al., 2007), but the prepulse is also known to alter the perceived experience of the stronger pulse-stimulus, reducing its perceived intensity in a similar manner to startle PPI (Swerdlow et al., 2005). Therefore, a broader understanding of the processing and inhibitory pathways of human sensory gating may be gained by investigating it at the perceptual and cortical levels.

1.2 Prepulse Inhibition of Perceived Stimulus Intensity

Peak (1939) first reported that when a weak auditory stimulus is presented 177 ms before a loud auditory stimulus, the perceived intensity of the second stimulus was reduced by approximately 25%. This phenomenon is known as prepulse inhibition of perceived intensity (PPIPSI; Swerdlow et al., 2005). In comparison to startle PPI, bar a handful of foundational experiments, PPIPSI has received little research attention and is often studied as an auxiliary in startle PPI experiments (Cohen et al., 1981; Swerdlow et al., 2005).

Of the limited studies, PPIPSI (like PPI) has been observed in acoustic (Perlstein et al., 1993; Swerdlow et al., 1999; Swerdlow et al., 2005; Swerdlow et al., 2007), tactile (Cohen et al., 1981), and electrotactile (Blumenthal et al., 2001) modalities. Studies have also evidenced that the prepulse and pulse can be of different modalities, demonstrating multimodal PPIPSI. For example, Cohen et al. (1981) and Swerdlow et al. (1999) found that acoustic prepulses significantly reduced the perceived intensity of tactile pulse stimuli (knee tap and 40 psi air puff, respectively). However, the majority of the PPIPSI experiments use within-modality stimuli (prepulse and pulse of the same modality) and particularly acoustic PPIPSI is the most extensively researched (Blumenthal et al., 1996; Perlstein et al., 1993; Swerdlow et al., 1999; Swerdlow et al., 2005; Swerdlow et al., 2007). Overall, multimodal PPIPSI is less reliable than within-modality PPIPSI (Blumenthal et al., 1996; Flaten et al., 2016), and findings of around 9 - 12% reductions are most common multi-modally (Krauter et al., 2012; Swerdlow et al., 1999), whereas within-modality typically reduces perceived intensity by approximately 25% (Blumenthal et al., 2001; Peak, 1939; Swerdlow et al., 2005; Swerdlow et al., 2007). Detailed experiments by Swerdlow et al. (2005; 2007) highlight that like PPI, PPIPSI is sensitive to test parameters such as prepulse intensity, duration,

frequency, pulse intensity, and SOA. Considering that the optimal parameters for PPIPSI have only been studied in the acoustic modality, this sensitivity has likely contributed to inconsistent, weak, or non-significant findings in previous studies such as Flaten et al. (2016).

Due to PPI and PPIPSIs sharing a fundamental principle of a weak stimulus inhibiting the response to a subsequent stronger stimulus, early explanations postulated that they may be directly related. In Neumann et al. (2006), referencing Blumenthal et al. (1996), it is suggested that participants' intensity ratings might be influenced by their self-perceived physical reactions to the pulse-stimulus. Specifically, because the startle or blink reflex is reduced during 'with prepulse' trials, participants may factor in their motor response when assigning an intensity rating. However, this explanation has been called into question, as Neumann et al. (2006) reported a stronger correlation between PPIPSI and response amplitude than response probability (no blink response). Because response probability is associated with the eye-blink not occurring, if participants were interpreting their physiological response, it would be expected that perceived intensity correlates more strongly with response probability than response amplitude (Neumann et al., 2006). Other studies have proposed that PPI and PPIPSI are directly related, but at the mechanistic level – that is, the reduction in perceived intensity is a downstream effect of PPI on lower-level circuits (Swerdlow et al., 1999). Support for this perspective comes from paradigm assessments by Swerdlow et al. (2005).

In their experiments, Swerdlow et al. (2005) manipulated acoustic stimulus intensity and stimulus onset asynchrony (SOA) to investigate their effects on PPIPSI and PPI concurrently across three separate “sessions.” The “interval session” focused on testing an array of SOAs (10, 20, 30, 60, and 120 ms) using a 105 dB(A) 40 ms noise burst for the pulse and an 86 dB 5 ms noise burst for the prepulse. The “test-retest session” focused on the test-retest reliability, using a pulse intensity of 105 dB and two prepulse intensities (82 dB and 86 dB, both 20 ms in duration). Lastly, the “intensity session” investigated the effect of prepulse intensity using the same 105 dB pulse and two prepulse intensities (82 dB and 86 dB). Consistent with their previous study (Swerdlow et al., 1999), both PPI and PPIPSI were maximal at higher stimulus intensity settings (86 dB prepulse and 105 dB pulse), under which a strong positive correlation was observed in their “interval session” ($r > .72$;

Swerdlow et al., 2005). A similar intensity response profile and strong positive correlation are consistent with PPI and PPIPSI sharing underlying mechanisms. Notably, however, during their “intensity session,” they did not observe a significant correlation between startle PPI and PPIPSI (Swerdlow et al., 2005).

The stronger association between PPI and PPIPSI in the “interval session” may be attributed to the broader array of temporal intervals used in this session, engaging more consistent neural mechanisms and avoiding a ceiling effect. In contrast, the intensity session's focus on “higher” intensity prepulses (82 and 86 dB) at a constant interval may have caused a ceiling effect, limiting variability in PPI responses and resulting in a weaker association with PPIPSI (Swerdlow et al., 2005). This explanation is supported by previous correlational findings between PPIPSI and PPI when a greater range of prepulse intensities was used (74, 78, 82, and 86 dB; Swerdlow et al., 1999). Nevertheless, the lack of correlation suggests that PPIPSI and PPI do not measure identical underlying processes. Coupled with differences in time-course of activation and experimental designs (discussed in the paragraph below), further questions are raised about the extent to which PPI and PPIPSI share underlying mechanisms and where they may diverge (Swerdlow et al., 2005).

1.2.1 Differences between PPIPSI and PPI

PPIPSI and startle PPI differ in two primary ways: their time-course of activation and the nature of experimental designs (PPI typically employs a passive design, whereas PPIPSI uses active procedures). Although the literature is quite limited, there is a consistent pattern of rarely observing PPIPSI with SOAs below 120 ms (Swerdlow et al., 2005; Swerdlow et al., 2007). In their paradigm assessment, Swerdlow et al. (2005) found that significant PPI emerged at 30 ms SOA, while PPIPSI only became significant at 60 ms and reached its peak at 120 ms SOA. It is important to note that while PPIPSI peaked at 120 ms SOA, this was also the longest SOA Swerdlow et al. (2005) tested. Therefore, it is entirely possible that SOAs even longer than 120 ms may produce greater PPIPSI. However, since further studies of this possibility have not been conducted, based on the available literature, the current thesis assumes that acoustic PPIPSI is maximal at SOAs of 120 ms+.

The emergence of startle PPI at a shorter SOA is consistent with conceptualisations that it is subcortically mediated. As discussed previously, such brief SOAs are unlikely to

provide the prepulse sufficient time to engage higher-level processes such as attention (Swerdlow et al., 2005). Conversely, the finding that PPIPSI is not observed below 60 ms and is maximal at 120 ms indicates that PPIPSI may only occur at temporal intervals that are sensitive to attentional manipulation (Swerdlow et al., 2005). Adding to this, unlike typical startle PPI investigations, PPIPSI experiments use an active procedure: participants are required to attend to the pulse in each condition, appraise the stimuli, and report an intensity rating. That is, PPIPSI experiments require participants to make relative judgements about the intensity of their experiences. This focus directed toward the stimuli to make relative perceptual judgements has been said to involve higher-level processes such as attention (directed towards the pulse), self-monitoring, memory, and decision making (Swerdlow et al., 2005; Swerdlow et al., 2007). The extended SOA in PPIPSI might offer the necessary time for these processes to be actively engaged in the task.

In summary, the literature evidences that startle PPI and PPIPSI share similar intensity response profiles, and when studied simultaneously, strong positive correlations have been observed (Swerdlow et al., 1999; Swerdlow et al., 2005). However, experiments have also failed to find a correlation ("intensity session"; Swerdlow et al., 2005), the nature of their experimental designs differs (active vs passive), and the time-course of their activation profiles is not identical. These similarities and differences suggest that startle PPI and PPIPSI are conceptually similar phenomena, that share some, but do not have identical underlying psychophysical processes. Swerdlow et al. (2007) highlighted that both are dependent on ascending sensory input and the activation of an inhibitory mechanism; however, startle PPI is regulated by midbrain and brainstem mechanisms (supported by its passive design and short latencies), while PPIPSI requires the involvement of higher-level processes to form a conscious percept (reflected by its task design and reliance on longer SOAs). One possibility that aligns with these similarities and differences is that the gating mechanism activated by the prepulse is lower-level (shared with startle PPI pathway), but its effects flow to higher-level areas that make PPIPSI possible. However, the extent to which the brain can access the information coming from the lower-level mechanisms requires a top-down attentional shift towards the pulse and its internal representation. This top-down attentional shift may be facilitated or explained by PPIPSI requiring a longer SOA which provides more time for these processes to be engaged and oriented towards the pulse.

Moreover, even if indirectly, one function of the prepulse may be acting as a cue that facilitates this attentional shift towards the pulse in PPIPSI (see below, section 1.2.3).

1.2.2 Role of the prepulse

The prepulse, as conventionally understood according to Graham (1975), serves as an activator for protective processes. These processes aim to prevent the processing of a stimulus from being overpowered by a subsequent, more intense stimulus and the response it elicits (e.g. startle). This is known as the protection of processing theory (Graham, 1975). Norris and Blumenthal (1996) found that participants' accuracy in detecting the presence of the prepulse is higher on trials where startle is effectively inhibited (PPI occurred) as opposed to when it is not, supporting that PPI results in greater prepulse processing. Similarly, Wynn et al. (2004), using visual prepulses and trials containing backward masking—a phenomenon where the perception of a stimulus is obscured by a subsequent stimulus—found that the degree of PPI elicited was linked with recovery from backward masking, suggesting stronger prepulse processing. However, other studies have failed to find a relationship between prepulse processing and PPI (Elden & Flaten, 2002; Postma et al., 2001). Postma et al. (2001) tested the effect of acoustic prepulses on acoustic pulses at SOAs of 30, 60, and 120 ms. Participants were tasked with reporting whether a trial contained one or two stimuli. Participants' accuracy increased with SOA increases, but the amount of PPI had no effect on task accuracy. Elden and Flaten (2002) implemented a more complex task, a tone was presented 4 s prior to a prepulse 10-20 ms shorter in duration, followed by an acoustic startle stimulus at SOAs ranging from 30-420 ms. Approximately half of the participants were tasked with determining whether the duration of the second tone (prepulse) was the same as the first. Again, no relationship was found between task accuracy and startle PPI. Differences in task difficulty have been suggested to explain the non-significant findings of Elden and Flaten (2002) and Postma et al. (2001). That is, Elden and Flaten's (2002) task likely required a high level of cognitive load to hold a representation of the initial sound's duration for 4 seconds (in their working memory), identifying the following prepulse and making a comparison judgement. This is reflected in the average task accuracy (60-65%; Elden & Flaten, 2002). In Norris and Blumenthal (1996), participants had to report whether the prepulse frequency in a trial was low, high or no-prepulse. While Postma et al. (2001) used a simpler detection task, not requiring representations to be held,

or compared. Combined, these three studies (Elden & Flaten, 2002; Norris & Blumenthal, 1996; Postma et al., 2001) suggest a relationship between PPI and prepulse detection accuracy whereby cognitive load affects PPI when at moderate levels, but not when it is too low or too high (Blumenthal et al., 2015). Due to the limited number of studies testing whether PPI occurs to protect prepulse processing, the answer is inconclusive.

Researchers have since extended the protection of processing hypothesis to more than just the prepulse itself, and towards ongoing processes more generally (Blumenthal et al., 2015). Notably, these experiments focus on the interruption aspect of the theory more so than the specific role of the prepulse. Blumenthal et al. (2015) studied PPI within an attention network task (ANT), here, reaction time (RT) is recorded in response to a target stimulus that is either presented alone or preceded by a visual cue (which may be considered a prepulse of sorts). Studies have found that when the target stimulus is presented simultaneously with a startle stimulus, RT is decreased, suggesting that the startle stimulus facilitates processing and motor responses (Valls-Sole et al., 1999; Valls-Sole et al., 2005). Instead of presenting the startle stimulus simultaneously with the target stimulus Blumenthal et al. (2015) presented it 200 ms prior, to see if it or the startle response interrupts reaction time and task accuracy. They found that when the cue (prepulse) was present, the startle stimulus decreased RT (155 ms faster), but the startle response lengthened RT. That is, processing of the startle stimulus speeded the voluntary motor response to the target, but the involuntary response (startle reflex) slowed the voluntary motor response. Moreover, greater inhibition of the startle response (more PPI) corresponded with faster RT of the voluntary response by the pulse (Blumenthal et al., 2015). These findings support the hypothesis that the startle response interrupts not only prepulse processing, but subsequent information processing and behaviours too. They also support the proposition that PPI (activated by the prepulse) protects the following processes from the interrupting effects of the startle response (Blumenthal et al., 2015). Lastly, at least within the ANT methodology, they suggest that the prepulse inhibits the startle response but not processing of the startle stimulus (pulse) entirely, because the startle stimulus improved reaction time maximally when the cue (prepulse) inhibited the startle response entirely.

1.2.3 Prepulse as temporal cue/facilitator of processing

In startle PPI studies researchers have explored the role of the prepulse. One consideration is whether the presence of the prepulse inhibits startle because it acts as a warning stimulus or temporal cue, signalling the imminent arrival of the startling stimulus (Blumenthal, 2015). In these experiments, certain parameters, such as the SOA (Stimulus Onset Asynchrony) and the frequency of trials where a prepulse precedes a startling stimulus, play a significant role. Most startle stimuli in these studies do not have a preceding prepulse, making the prepulse a low-probability event (Blumenthal, 2015). This rarity makes it unlikely that the prepulse primarily serves as a cue for the startling stimulus in startle PPI. However, studies in conditioning (Nees et al., 2009; Schächinger et al., 2013) show that when the prepulse consistently precedes the startle stimulus it can indeed become a predictor. In other words, if the prepulse often signals the coming of the startle stimulus, learning effects can develop (Nees et al., 2009; Schächinger et al., 2013). However, startle PPI is observed on the first trial (before conditioning or learning can occur) and at short SOAs, further indicating that predicting a startle stimulus is not a crucial function of the prepulse in startle PPI. It might be that the prepulse primes the sensory pathways, preparing the system for processing the upcoming stimulus, which also triggers inhibitory mechanisms. These mechanisms might counteract responses that would interfere with subsequent stimulus processing, such as the startle response. However, categorising this priming effect simply as a cueing phenomenon is likely an oversimplification or misinterpretation of the prepulses' role.

Within PPIPSI experiments, the prepulse as a cue may be more of a factor, as most prepulses are followed by a strong stimulus making it a high-probability warning cue (Swerdlow et al., 1999; Swerdlow et al., 2005; Swerdlow et al., 2007). Additionally, the SOA required for acoustic PPIPSI may indicate that greater processing of the prepulse is needed for it to be a successful cue for when attentional resources are most required to be directed towards sensory channels. The possibility that the prepulse works as a cue aligns PPIPSI with other paradigms such as the accessory stimulus effect (ASE) and motor preparations studies in a way consistent with suggestions by Brunia (1993) that motor and attention processes use similar mechanisms. In ASE studies, a preceding cue (prepulse) in a different modality to the target stimulus is known to speed RT in response to the target stimulus (Nakano, 1997). In motor preparation studies, it has been found that responses can only be held in a high

state of preparation for approximately 100 - 300 ms (Alegria, 1975; Muller-Gethmann et al., 2003); these responses are optimally prepared when the warning stimulus is presented 200 ms prior to the imperative stimulus to act. Thus, while in PPIPSI the presentation of a pulse stimulus within a trial is randomised, making it difficult to maintain optimal cognition to perceive the pulse, the prepulse may act as a cue, signifying when the allocation of these resources should be directed towards monitoring a particular sensory channel. The cueing effect of the prepulse may also be indirect, or stimulus driven. Instead of intentionally directing attention towards relevant sensory channels when the prepulse is processed, its presence may spark a form of automatic attention which broadly facilitates processing of temporally close stimuli. This may be particularly effective when the prepulse and pulse are of the same modality, as the processing and attention captured by the prepulse may pre-activate attention towards pulse processing channels. Such a proposition would also suggest that the prepulse facilitates processing of the pulse, consistent with Blumenthal et al.'s (2015) findings of startle PPI in the ANT paradigm.

One issue with the proposition that the prepulse acts as a temporal cue for the allocation of resources to monitor particular sensory channels is the expectation that this would lead to greater processing of the pulse. However, this may appear difficult to reconcile with the fact that PPIPSI is a misjudgement that the pulse in the 'with prepulse' condition is less intense than the 'pulse alone' when they are the same intensity. What this would suggest is that the prepulse's function of activating a gating mechanism and its function as a temporal cue for directing attention towards relevant processing channels operate at different levels. Consistent with startle PPI, where cueing is less relevant (discussed above), the prepulses' activation of a gating mechanisms may occur prior (I.e., subcortically) to cueing processes which are activated in PPIPSI, meaning that although the prepulse aids the allocation of attentional resources towards processing the pulse, the received information is already gated. The function of the prepulse as a temporal cue may be a unique aspect of PPIPSI that guides participants' attention towards the pulse, and/or internal processes such as the representation of the pulse. This apparent contradiction could be resolved by interpreting the impaired accuracy — perceiving the pulse alone as more intense — as a necessary trade-off to enhance efficiency in processing and responding, which in the context of potentially threatening stimuli is likely more important.

Understanding what occurs at the cortical level during PPIPSI is one way we might gain insight into questions regarding the role of the prepulse (where does gating occur? Is it a cue?) and attention.

1.3 Cortical PPI

A prepulse also inhibits the cortical response to a subsequent, more intense stimulus, referred to as cortical PPI (Ford et al., 1999). Specifically, a prepulse has been found to reduce event related potentials (ERP; P50, N1, P2, P300), theta (Kedzior et al., 2006), alpha, and gamma (Kedzior et al., 2007) responses to a pulse stimulus, compared to when it is presented alone. Like PPIPSI, this phenomenon has only been extensively studied in the acoustic modality. In these studies, cortical inhibition is greatest in frontal and central areas, while occipital (visual processing) and temporal (auditory processing) locations display limited, or no PPI (Kedzior et al., 2006; Kedzior et al., 2007). Fronto-centro-parietal theta oscillations are frequently implicated in processes relating to focussed (selective) attention (Ishii et al., 2014), memory (Herweg et al., 2020; Miller et al., 2018), sensorimotor integration, and spatial learning (Caplan et al., 2003). While gamma oscillations in these areas have been linked to bottom-up and top-down driven object representations (Bertrand & Tallon-Baudry, 2000), attention and memory (Jensen et al., 2007). Findings of cortical PPI specific to these fronto-central areas are consistent with propositions that PPI engages higher-order information processing mechanisms (Annic et al., 2014; Blumenthal, 2015). Early studies suggested that the N1 represents initial detection, selection, processing, and encoding of stimulus characteristics or physical attributes such as intensity (Davis & Zerlin, 1966; Hillyard et al., 1973). Since then, enhanced N1 has been attributed to early sensory perception (vigilance) and attention to a stimulus (Mishra & Hillyard, 2009; Mingming et al., 2018). For example, Tiitinen et al. (1993) found that when participants are instructed to attend to an auditory stimulus, greater N1 ERP magnitudes are recorded as opposed to when instructed to ignore the stimulus. The P2 component has been proposed as the resolving response of the N1, and thus a measure of the same processes, this is supported by the high correlation typically found between the two responses (Mulert et al., 2005; Paiva et al., 2016). However, under specific experimental contexts, evidence suggests the P2 may be more associated with initial stimulus classification and decision-making processes (conscious experience), while the N1 is more driven by physical characteristics of the

stimulus (Annic et al., 2014; Crowley & Colrain, 2004; Garcia-Larrea et al., 1992; Näätänen, 1992). Regardless, both are indicative of higher order processes.

Studies investigating startle and cortical PPI simultaneously are yet to identify a correlation between these two responses while they co-occur on a trial (Ford et al., 1999; Kedzior et al., 2006, 2007; San-Martin et al., 2018). This supports the distinction emphasised by Blumenthal (2015) between the startle response processing and stimulus processing. More specifically, startle, and startle PPI are sensorimotor responses activated at very short intervals (20 ms) and largely mediated by brainstem and midbrain structures (e.g., subcortical processing; Fendt et al., 2018; Blumenthal, 2015). Whereas cortical indices, such as the N1 and P2 ERPs demonstrate gating at longer intervals post-stimulus (100 – 200ms) and are products of neural activity that index higher-order sensory processing of the stimulus (Kedzior et al., 2006; San-Martin et al., 2018). While most cortical PPI (N1-P2 inhibition) studies use higher intensity pulse-stimuli (90 – 115 dB; Kedzior et al., 2006, 2007; San-Martin et al., 2018), studies have also observed N1-P2 gating using lower intensities (70 dB; Ford et al., 1999). It is important to note that majority, if not all cortical PPI studies have measured startle PPI simultaneously – which has likely contributed to it being studied using high intensity pulse-stimuli. N1-P2 threshold studies have shown that 30, 40, and 60 dB stimuli consistently elicit the N1-P2 response (Lightfoot & Kennedy, 2006). Thus, in addition to their lack to correlated when studied in parallel (Ford et al., 1999; Kedzior et al., 2006, 2007; San-Martin et al., 2018), the two measures may also be separable based on sensitivity. Put another way, the underlying mechanisms of cortical PPI may have a lower threshold of activation than startle PPI. That said, acoustic startle has been reported at lower intensities (e.g., 60 - 70 dB; Blumenthal & Goode, 1991), though the broader literature suggests it is less reliable, resulting in more trials on which no startle occurs – making motor PPI difficult to measure. The comparable intensities used in Ford et al. (1999) and Blumenthal and Goode (1991) leave this possible distinction based on sensitivity between cortical PPI and startle PPI open to future investigation.

Furthermore, the time-course of optimal N1-P2 inhibition by a leading prepulse is largely unknown, with considerable variability between study methods and paradigms; however, studies have observed it at SOAs of 50 – 400 ms (Annic et al., 2014; Ford et al., 1999; San-Martin et al., 2018). Although it was not analysed, visual inspection of San-Martin

et al.'s (2018) data suggests shorter SOAs (50 – 80 ms) may inhibit the N1-P2 response more than longer SOAs (140 ms). This may indicate a similarity between cortical PPI and startle PPI, but specific investigation is required. Studies outside the startle PPI literature have uncovered an intriguing negative relationship between N1 magnitude and startle inhibition. Budd and Michie (1994) conducted an experiment in which a series of 80 dB acoustic pulses were presented in quick succession. The SOAs varied from 100 to 1000 ms. They found an enhanced N1 response at SOAs shorter than 300 milliseconds, coinciding with inhibited eye-blink (startle) responses. This suggests a link where greater startle inhibition is associated with a larger N1 response, implying more intensive processing of the stimulus when the startle reflex is suppressed. Although Budd and Michie's (1994) experiment differs from typical PPI methods, it aligns with the proposition that the startle response interrupts ongoing cognitive processes. These processes might include those responsible for encoding prepulse and startle stimulus characteristics, as suggested by Blumenthal (2015).

1.3.1 Unknown relationship between PPIPSI and cortical PPI

Considering that cortical PPI and PPIPSI are both measures of ongoing processes post stimulus, which also share their occurrence at later latencies than startle PPI, it is possible that they are related processes. This has been suggested by independent studies looking at PPIPSI or cortical PPI separately (Swerdlow et al., 2007; Kedzior et al., 2007). Swerdlow et al. (2007) noted magnitude and temporal sensitivity similarities between PPIPSI and cortical PPI (Swerdlow et al., 2007). Within the acoustic modality, prepulses have the greatest inhibitory effect on perception (Swerdlow et al., 2007) and theta oscillations (Kedzior et al., 2007) at SOAs of 120 ms. Given that cortical responses are linked to cognitive processes such as detection, attention, memory and encoding of stimulus properties the reductions seen in cortical PPI may contribute to PPIPSI. These similarities from acoustic studies support this possibility, however, simultaneous recording of cortical PPI and PPIPSI is required to provide empirical evidence of their relationship. Moreover, PPIPSI and cortical PPI are observed in modalities other than acoustic (e.g. tactile and visual), but to date, their speculated relationship is grounded in acoustic experiments (Kedzior et al., 2007; Swerdlow et al., 2007).

Like startle PPI, cortical PPI is observed without attention needing to be directed to either of the stimuli (passive designs; Ford et al., 1999; San-Martin et al., 2018), though

Annic et al. (2014) demonstrated that attention to the prepulse can further inhibit ERP responses to the pulse stimulus. Annic et al. (2014) constructed an experiment in which three types of visual prepulses were used (to-be attended, to-be-ignored, and unexpected) to investigate the effect different attentional processes have on cortical PPI (N1 and P2 ERPs) of a 110dB acoustic pulse. Specifically, the to-be-attended prepulse was goal-directed, participants were instructed to make a motor response with their right index finger as quickly as possible only when a probe letter "X" occurred immediately (approximately 1400 ms) after a letter "A" (prepulse/cue letter), on some trials the pulse was presented after an SOA of either 400 or 1000 ms. The to-be-ignored prepulses involved letters not including A (X and O) in a sequence where no instructions were given to participants. Lastly, the unexpected stimulus (participants were uniformed of its occurrence) was used to manipulate stimulus-driven attention, via the presentation of a meaningless symbol that filled the screen (Annic et al., 2014). They found that at the 400 ms SOA, compared to baseline, the unexpected (stimulus-driven) prepulse elicited the greatest inhibition of the N1 ERP compared to to-be attended and to-be-ignored conditions, which did not differ significantly from each other, though also elicited gating. The to-be-attended (goal-directed) prepulse elicited greater P2 inhibition than the to-be-ignored and unexpected prepulses. There were no significant differences between prepulse conditions at 1000 ms SOA. Based on these findings, Annic et al. (2014) concluded that gating of the N1 response to the pulse is associated with and enhanced by stimulus-driven attention to the prepulse. Moreover, that early sensory gating processes are stimulus-driven, in that non-goal-oriented attention directed towards the prepulse initially modulates processing of the pulse stimulus' characteristics, such as its physical representation (Annic et al., 2014; Rosburg et al., 2008). Goal-directed attention on the other hand influences sensory gating more at later processing stages (the P2 window; Annic et al., 2014). Specifically, they suggest that P2 reflects higher-order integrative and evaluative processing of the pulse stimulus which influence PPI via goal-directed attention to the prepulse (Annic et al., 2014). Notably, their data presents no significant difference in P2 amplitude between unexpected (stimulus-driven) and to-be-attended (goal-directed) prepulse conditions, indicating that further research into this distinction is required. While studies have suggested that N1 and P2 are independent, distinct components (Crowley & Colrain, 2004), if N1 represents encoding of a stimulus' physical characteristics, and P2 cognitive evaluation of the stimulus, they are likely

due to interrelated processes, consistent with the strong correlation typically observed between them (Mulert et al., 2005; Paiva et al., 2016).

PPIPSI experiments differ from attention to prepulse studies significantly in that PPIPSI experiments entail explicit directed attention to the pulse stimulus, not the prepulse (Swerdlow et al., 2005). Thus, it may be considered that the pulse is the goal-directed stimulus in PPIPSI, not the prepulse. The prepulse still likely recruits some level of stimulus-driven attention, however, not in the same manner or degree as the methods used for attention to prepulse studies. Moreover, attention to prepulse studies typically use a continuous prepulse, while PPIPSI and startle PPI use discrete (Swerdlow et al., 2005; Poje & Filion, 2021). Given these differences and conceptualisations of PPIPSI as a higher-order measure of sensory gating, understanding its relationship with cortical gating may provide insights into the processes entailed by PPIPSI. Being that perception may be considered the end product of cognitive processes, and the similarities noted by Swerdlow et al. (2007) between PPIPSI and cortical PPI, PPIPSI may be dependent on attention being directed towards these processing channels or signals. However, the similarities between cortical PPI and PPIPSI noted by Swerdlow et al. (2007) are yet to be empirically tested.

1.3.2 Possible role of attention in cortical PPI, PPIPSI and their relationship

While a significant body of literature supports the notion that N1 and P2 cortical responses represent encoding of stimulus characteristics such as intensity and classification (Annic et al., 2014; Crowley & Colrain, 2004; Davis & Zerlin, 1966; Garcia-Larrea et al., 1992; Hillyard et al., 1973), debate exists around the extent to which they represent encoding of attentional processes, and their link to conscious perception (Muller-Gass and Campbell, 2002; Näätänen & Winkler, 1999). Particularly focussed on N1, Näätänen (1992) conceptualises it as an exogenous ERP, automatic encoding of stimulus features, which are non-representative of attentional processes, or conscious perception. They propose that attention occurs at a later processing stage and is directed by a perceptual mechanism that brings the representation into the focus of conscious perception. Findings that cortical PPI occurs in passive-design studies, when attention is not instructed to be directed towards any of the stimuli are consistent with this proposition (Ford et al., 1999; San-Martin et al., 2018). Conversely, Muller-Gass and Campbell (2002) posit that N1 is endogenous, and representative of attention directed to a stimulus, whether the stimulus is task-relevant or

not. Support for Muller-Gass and Campbell's (2002) theory can be found in evidence that selective attention enhances the N1 response for attended stimuli compared to unattended/ignored stimuli (Tiitinen et al., 1993; Mishra & Hillyard, 2009), and increases N1-P2 inhibition when directed towards the prepulse (Annic et al., 2014). It must be highlighted that PPIPSI differs from these methods because it is assessed in an active paradigm, attention is directed towards the pulse-stimuli, and not instructed towards the prepulse. Therefore, it may be argued that attention is directed equally to the task relevant stimuli required to make comparisons with. Consequently, if a relationship exists between cortical PPI and gating of perception, and attention is a facilitatory process, the standard PPIPSI design would make it difficult to infer at what stage of processing attention is incorporated.

The literature indicates that attention is a finite resource (Petersen & Posner, 2012; Swallow & Jiang, 2013). Therefore, manipulating attentional load should provide insights into the specific influence(s) attention has on cortical and perceptual gating. This may be done by introducing a secondary task that induces attentional load concurrently with the PPIPSI task. If N1-P2 represents attentional allocation to a stimulus (as suggested by Muller-Gass & Campbell, 2002), attentional load should modulate this cortical response, and the effect of the prepulse. Alternatively, if the N1-P2 response is exogenous, and pertains to processes of stimulus trace or complete representation (Näätänen & Winkler, 1999) it is likely unaffected by attentional load. Similarly, if attentional processes are involved in PPIPSI, manipulating attentional load should modulate its occurrence. If it does not, then this would provide an indication that PPIPSI is more a by-product of lower level, preattentive processes, and that attention is not always necessary for conscious perception.

1.4 Predictability may facilitate attention and modulate the time-course of PPIPSI

As discussed, previous studies suggest that PPIPSI engages attentional processes which startle PPI does not (Swerdlow et al., 2005). These studies propose that PPIPSIs reliant on longer SOAs (60 ms+ and maximal at 120 ms+), may be due to attention and self-monitoring processes requiring more time to be sufficiently engaged to perceive that gating has occurred. Moreover, as I previously discuss (Section 1.2.2) the prepulse may act as a temporal cue for the timely allocation of limited attentional resources in PPIPSI. The idea

that temporal predictability may improve allocating attention towards the pulse and its processing channels parallels PPIPSI with motor preparation, perception, and attention studies (Alegria, 1975; Nobre & van Ede, 2018; Nakayama & MacKeben, 1989). In visual perception, cues presented shortly before a target enhance the target's cortical representation and mitigate distractor interference (van Ede et al., 2018). Similarly, a cue or warning stimulus reduces reaction times by optimising the motor systems' preparedness to respond (Alegria, 1975; Mondor & Breau, 1999; Muller-Gethmann et al., 2003). Furthermore, temporal predictability attenuates participant's auditory attentional blink. Specifically, researchers have found that participants' abilities to perceive a second target stimulus (S2) presented closer in succession to an initial target stimulus (S1) are enhanced when the stimuli are temporally predictable (Shen & Alain, 2012; Visser et al., 2014). The above findings from different research domains suggest a common mechanism may be involved. If attention directed towards perceiving the pulse (monitoring the sensory input channels) is a central component of PPIPSI, one challenge is that the pulses temporal unpredictability within a trial make it unlikely that attention will be at an optimal level when most needed. This is because attention is a finite resource (Petersen & Posner, 2012; Swallow & Jiang, 2013), and like motor preparation, likely cannot be held at an optimal level when the target presentation is uncertain. However, this also suggests that greater temporal predictability of the pulse onset may lead to more PPIPSI observations, and possibly enhanced PPIPSI at shorter SOAs, by facilitating a more efficient use of attention.

1.5 General summary

Startle PPI is one of the dominant operational measures of gating and is used to make inferences about how the brain filters incoming sensory information (Blumenthal, 2015). While startle PPI has been fruitful in providing knowledge about underlying mechanisms, clinical populations, and transspecies models of gating, its reliance on a reflexive motor response and subcortical mediation likely limits its utility to provide inferences and further understanding about the higher-level (conscious perception) aspects of sensory gating (information processing). It is well researched that both startle, and startle PPI pathways involve midbrain and brainstem areas (Fendt et al., 2001; Gomez-Nieto et al., 2020). These areas, though associated with cortical areas of the brain, typically do not regulate higher level processes such as attention or perception directly. Additionally, startle PPIs

observation in infants (Graham et al., 1981), sleeping adults (Silverstein et al., 1980) and even decorticated rats (Ison et al., 1991) highlight how separated startle PPI can be from conscious processes. PPIPSI is proposed to be a more direct method of studying gating of conscious perception (Swerdlow et al., 2005), however compared to startle PPI, little research has been conducted. Of the limited studies, paradigm assessments by Swerdlow et al. (1999a; 2005; 2007) indicate that unlike startle PPI, PPIPSI requires the engagement of higher order (likely attentional and self-evaluative) processes. This proposition is based on PPIPSIs use of an active design and its time-course of activation (Swerdlow et al., 2005; 2007). As opposed to startle PPI, in PPIPSI participants are explicitly instructed to pay attention to the pulse stimulus so that an intensity rating can be assigned. This active design is said to inherently require the engagement of attentionally sensitive mechanisms (Swerdlow et al., 2005). Consistent with the task design, the time-course of PPIPSI (emerges at 60 ms and peaks at 120 ms SOA) suggests that it is only observed using intervals which allow for sufficient activation of attentional processes (Swerdlow et al., 2005). Lastly, experiments have found a positive correlation between startle PPI and PPIPSI (Swerdlow et al., 1999a; "interval session", Swerdlow et al., 2005), while also failed to observe a correlation ("intensity session", Swerdlow et al., 2005).

The findings that startle PPI and PPIPSI are correlated in some settings, but not others indicate that they likely share some, but not identical underlying processes. Moreover, knowing that they share some underlying processes does not tell us which processes, or how their effects reach conscious perception. Understanding the processes which influence PPIPSI may provide insight into how gating of conscious perception occurs. At present, preliminary evidence suggests that attention is involved in PPIPSI, but this has only been studied in the acoustic modality (Swerdlow et al., 2005). Further support would come from evidence in other modalities and manipulating attention directly. Another way of investigating the higher-level processes contributing to gating of conscious perception is via PPIPSIs relationship with measures of cortical activity (e.g. the N1-P2 complex) which provide indications of sensory processing and encoding (Annic et al., 2014; Crowley & Colrain, 2004; Davis & Zerlin, 1966; Garcia-Larrea et al., 1992; Hillyard & Picton, 1979). Lastly, if attention is a key process in the observation of PPIPSI, and contributes to PPIPSIs requirement of longer SOAs, then temporal predictability which is known to improve the

allocation of attention (Alegria, 1975; Nobre & van Ede, 2018; Nakayama & MacKeben, 1989), may also enhance PPIPSI.

1.6 General purpose and outline

The current thesis seeks to address the above-mentioned gaps in the sensory gating literature. Specifically, the overall aim of this thesis is to further develop the knowledge of sensory gating at the perceptual level, using PPIPSI for the following reasons.

1. Limited acoustic studies indicate the time-course of PPIPSI suggests attentional mechanisms are required. Specific investigations into the optimal parametric settings for PPIPSI in other sensory modalities have yet to be conducted to further this proposition. In chapter 2, we present findings from electrotactile modality.
2. Investigate the currently unknown relationship between PPIPSI and cortical PPI, and the role of attention (chapter 3).
3. Extend knowledge of attentions role in observing gating of conscious perception (PPIPSI) and develop a possible model of contributing processes (e.g. temporal predictability and cortical activity; chapter 4).

This thesis comprises five chapters. The first chapter has provided an overview of the relevant, startle PPI, PPIPSI, and cortical PPI literature and the current issues that will be addressed throughout as well as the theoretical approach taken during this research. Chapters two through five each comprise a standalone scientific work. Chapter two examines the effects of prepulse amplitude and SOA on the observation of electrotactile PPIPSI. Electrotactile PPIPSI is found to be optimal with a 2x perceptual threshold prepulse amplitude and 200 – 600 ms SOA and is proposed to be consistent with acoustic PPIPSI in requiring attentional processes that startle PPI does not. These new parameters are then used to further investigate the processes underlying gating of conscious perception (PPIPSI). In chapter three, the relationship between electrotactile and acoustic PPIPSI (Experiment 1A and 1B respectively) and cortical PPI (N1 and P2 ERPs) are examined. Moreover, in this chapter, I examine the effect attentional load has on acoustic PPIPSI and cortical PPI and provide a novel interpretation of what this suggests about the relationship between the two forms of sensory gating. Chapter four examines the relationship between temporal

predictability and the time-course of PPIPSI. Finally, in chapter five, I summarise the main findings of this thesis, provide an overall conclusion in the context of the literature introduced in chapter one, and present future research directions.

CHAPTER TWO: THE EFFECT OF PREPULSE AMPLITUDE AND TIMING ON THE PERCEPTION OF AN ELECTROTACTILE PULSE

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2.0 Abstract

The perceived intensity of an intense stimulus as well as the startle reflex it elicits can both be reduced when preceded by a weak stimulus (prepulse). Both phenomena are used to characterise the processes of sensory gating in clinical and non-clinical populations. The latter phenomenon, startle Prepulse Inhibition (PPI), is conceptualised as a measure of pre-attentive sensorimotor gating due to its observation at short latencies. In contrast, the former, Prepulse Inhibition of Perceived Stimulus Intensity (PPIPSI), is believed to involve higher-order cognitive processes (e.g., attention) which require longer latencies. Although conceptually distinct, PPIPSI is often studied using parameters that elicit maximal PPI, likely limiting what we can learn about sensory gating's influence on conscious perception. Here, we tested an array of stimulus onset asynchronies (SOA; 0 – 602ms) and prepulse intensities (1 – 3x perceptual threshold) to determine the time course and sensitivity to the intensity of electrotactile PPIPSI. Participants were required to compare an 'unpleasant but not painful' electric pulse to their left wrist that was presented alone with the same stimulus preceded by an electric prepulse, and report which pulse stimulus felt more intense. Using a 2x perceptual threshold prepulse, PPIPSI emerged as significant at SOAs from 162 - 602ms. We conclude that evidence of electrotactile PPIPSI at SOAs of 162ms or longer is consistent with gating of perception requiring higher-level processes, not measured by startle PPI. The possible role of attentional processes, stimuli intensity, modality-specific differences, and methods of investigating PPIPSI further are discussed.

2.1 Introduction

2.1.1 Sensory Gating

Each day, our brains are tasked with navigating a complex and ever-changing environment. An environment filled with sensory information. This endeavour requires us to focus on relevant information while suppressing less relevant information - a task that for most seems automatic and effortless. One mechanism contributing to the regulation of incoming information is called sensory gating. Sensory gating is not a singular process, but rather, a set of neural processes that allow for or suppress the further processing of incoming sensory stimuli. Here we were interested in understanding how sensory gating influences conscious perception.

2.1.2 Sensory gating of reflexes: Prepulse inhibition (PPI)

Initially, sensory gating was examined in the context of lower-level stimulus processing by studying startle prepulse inhibition (PPI) - a phenomenon where the amplitude of a startle reflex elicited by an intense stimulus (known as the pulse) is reduced when shortly preceded by a weaker prepulse stimulus (Blumenthal, 2015; Graham, 1975). Due to the stimuli affecting a physiological response, PPI is considered an expression of sensorimotor gating (Blumenthal, 2015; Graham, 1975). PPI is highly sensitive to test parameters, particularly the time gap between the prepulse onset and pulse onset, known as the stimulus onset asynchrony (SOA). The phenomenon's sensitivity to test parameters is useful in making inferences about the involved neural mechanisms, particularly its time-course of activation (Graham & Murray, 1977). Acoustic startle PPI, where both an acoustic prepulse and pulse stimulus, is the most extensively researched (Blumenthal, 2015). Within this modality, time-course studies show that PPI emerges at SOAs of 15 - 30ms, peaking at around 60 – 240ms SOAs (Blumenthal et al., 1999; Graham, 1975; Graham & Murray, 1997; Swerdlow et al., 2005). The shortness of the SOA required to observe PPI (15 - 30ms) and the response that it acts upon (eye-blink reflex) have led to its mechanisms being proposed as pre-attentive (Blumenthal, 2015; Bohmelt et al., 1999; Swerdlow et al., 2005). That is, attentional mechanisms are unlikely to be involved at this level of sensory gating. This is further supported by PPIs presence in infants (Graham et al., 1981), sleeping adults (Silverstein et al., 1980) and even decorticated rats (Ison et al., 1991).

Human studies have found that explicitly directing participants' attention to the prepulse, either by telling the participant to focus on or report identification that a prepulse was present, does enhance startle PPI. However, it has been extensively shown that this enhancement only begins to influence startle PPI at SOAs ≥ 120ms, before which its effects are inconsistent (Ashare et al., 2007; Dawson et al., 1993; Elden & Flaten, 2002; Filion & Poje, 2003; Hawk et al., 2002; Heekeren et al., 2004). Suggesting that prior to 120ms SOAs, attentional mechanisms are less involved, supporting that they are not a requirement for startle PPI, which is observed at SOAs of 15 -30ms.

2.1.3 Sensory gating of perception: Prepulse inhibition of perceived stimulus intensity

In addition to the sensorimotor effects of PPI on the excitability of startle circuits, it has been subsequently demonstrated that PPI also modulates conscious perception – reflected by a reduction in perceived intensity of the intense stimulus (referred to as Prepulse Inhibition of Perceived Stimulus Intensity, PPIPSI; Swerdlow et al., 2005). Initial theories suggest that PPIPSI and PPI are directly related, stating that the reduction in perceived intensity is a downstream effect of PPI on lower-level circuits (Blumenthal et al., 1996). For example, Blumenthal et al. (1996) proposed that participants' perceived reduction in intensity (PPIPSI) is based on their perception of the reduced startle response (PPI), referred to as self-perceived startle. Consistent with the hypothesis that PPIPSI is a downstream effect of PPI are the findings of Blumenthal et al. (2001), where the perceived intensity of a subjectively painful electric shock (*M* = 160V) was reduced by the presence of a weak prepulse (1x and 1.25x perceptual threshold) at SOAs of 40 and 60ms. Observing PPIPSI at such short an SOA aligns with time-courses of preattentive lower-level mechanisms (Blumenthal et al., 2001). However, at high intensities, the separability of PPI and PPIPSI is limited by the fact that startle, and subsequently PPI co-occur (Blumenthal et al., 2001). In fact, some studies have evidenced that startle is not a requirement for PPIPSI. At the trial level, significant PPIPSI is observed without the presence of startle PPI (Swerdlow et al., 2005) and using stimuli intensities sub-optimal for eliciting startle (Cohen et al., 1981; Peak, 1939). These, and more detailed parametric experiments discussed below suggest that PPI and PPIPSI are related, yet separable phenomena – such that PPI and PPIPSI are both driven by basic gating mechanisms at the lower level, but the manifestation of a perceivable reduction in intensity during PPIPSI is dependent on higher-level (e.g., attentional)

processes. This hypothesis is based on core findings of the strong correlation between PPI and PPIPSI when high-intensity stimuli are used, differences in their design requirements relating to directed/undirected attention and their time-course of activation (Swerdlow et al., 2005).

Detailed paradigm assessments by Swerdlow et al. (2005) investigated the effects of varying high-intensity acoustic stimuli (both prepulse and pulse) and SOAs on PPI and PPIPSI simultaneously. Both PPI and PPIPSI were found to be best elicited by higher intensity stimuli (80dB prepulse and 105dB pulse), under these conditions a strong positive correlation was observed (All r >.72; Swerdlow et al., 2005). This relationship suggests PPIPSI and PPI likely share underlying mechanisms. However, their results from manipulation of SOA (10, 20, 30, 60 and 120ms) indicate a difference in the time-course of activation. PPI was observed from 30 ms+ SOAs, but PPIPSI was non-significant until 60 and maximal at 120 ms SOAs. This difference in time-course is consistent with conceptualisations of PPI as preattentive, and indicative that PPIPSI only occurs at temporal intervals that are sensitive to attentional manipulation (Swerdlow et al., 2005). PPIPSIs time-course also appears to align with when PPI becomes enhanced by directed attention (120ms+; Ashare et al., 2007; Dawson et al., 1993; Elden & Flaten, 2002; Filion & Poje, 2003; Hawk et al., 2002; Heekeren et al., 2004). Consistent with the possible role of attentional mechanisms in PPIPSI, by design, PPIPSI requires cognitive appraisal of the pulse stimulus. This requirement is said to explicitly involve directed attention towards the pulse stimulus (Swerdlow et al., 2005). Conversely, PPI occurs under conditions widely considered preattentive (20 – 30ms) and does not require the active engagement of the participant to be observed (Dawson et al., 1993; Graham et al., 1981; Ison et al., 1991; Silverstein et al., 1980).

These findings indicate that, while there is evidence supporting the association between PPI and PPIPSI, differences in the time-course of effects suggest that additional (likely attentional) mechanisms are involved for PPIPSI (Swerdlow et al., 2005). One hypothesis is that lower-level sensorimotor effects during PPI do contribute, but the degree to which the brain can access this lower-level information requires top-down attentional shift toward the pulse. The observation of PPIPSI may therefore be shaped by time – likelihood of observing PPIPSI may increase as SOAs become longer, as there is more time to orient to the pulse. Moreover, the observation of PPIPSI also appears to be shaped by

prepulse intensity (Swerdlow et al., 2005), where the presentation of a more intense prepulse may facilitate the proactive shift of attention towards the prepulse-pulse pair.

However, one limitation of using intense, startle, and PPI eliciting stimuli is that they leave the degree to which PPI and PPIPSI are separable largely unknown. Independent studies have observed PPIPSI with sub-optimal startle intensities and stimuli modalities (Blumenthal et al., 1996; Cohen et al., 1981; Peak, 1939), but to date, the time-course of PPIPSI is only known using intense acoustic stimuli (Swerdlow et al., 2005).

2.1.4 Current study

In the current study, we sought to characterise the nature of electrotactile PPIPSI - by conducting 3 experiments examining how PPIPSI is influenced by parameters such as time (SOA between the prepulse and pulse) and intensity (of the prepulse). In experiments 1 and 2, we examine PPIPSI under short and long SOAs. In experiment 3, we explore the effect of prepulse intensity at 202ms SOA where PPIPSI was prominent in experiments 1 and 2.

2.2 Methods

2.2.1 Participants

In all three experiments, participants were Curtin University undergraduate volunteers, who participated in exchange for course credit. We ran an a priori power simulation based on pilot data from five participants. This identified that for a repeated measures GLMM analysis with a power of 0.90 and $\alpha = .05$, 19 participants were required. Consequently, a final sample of 25 participants (16 female, 1 non-binary) were recruited (age mean = 23.5, SD = 6.5, range = 18 – 49) for Experiment 1. An independent sample of 23 participants (12 female) volunteered for Experiment 2 (age mean = 22.8, *SD* = 5.9, range = 18 – 45). For experiment 3, 24 participants (17 female) were recruited (age mean = 22.1, SD = 6.5, range = 18 – 46). All participants reported having normal or corrected-to-normal vision, with no known neurological conditions or injuries. In accordance with the Declaration of Helsinki and with approval from the Curtin University human research ethics committee, prior to participation, informed written consent was provided by all participants.

2.2.2 Experimental task and stimuli

2.2.2.1 Experiment 1. Participants were seated at a desk with their head ~57 cm away from a 24-inch BenQ LCD monitor (1920×1080 resolution; 120 Hz refresh rate), with their arms rested on the desk. Two Digitimer DS7A stimulators (separate stimulators to deliver to pulse and prepulse) were then attached to the participants' left wrist at the ulnar styloid process using four Kendall Covidien Ag-AgCl adhesive electrodes. Both stimulators were set to emit a single square wave prepulse or pulse with a duration of 2ms.

Following this, a perceptual threshold (i.e., the weakest identifiable stimulation) was identified using a work-down and work-up procedure. Stimulation started at 0.50 mA and decreased in increments of 0.10 mA until the participant no longer reported feeling the stimulus. The intensity was then increased using finer increments of 0.05 mA until the stimulus was first perceived again – this intensity was defined as the perceptual threshold. Prepulse intensity was set to 2 times the perceptual threshold (e.g., 0.50 mA perceptual threshold = 1.0 mA prepulse intensity). Pulse intensity was determined by a work-up procedure with stimulation starting at perceptual threshold and increasing in 1.0 mA increments until the stimulus was reported to be "unpleasant, but not painful". Descriptive statistics of participants perceptual thresholds, prepulse and pulse test intensities are provided below in Table 2.1.

To familiarise participants with the task, four practice trials were administered. Each practice trial included two types of stimulus presentations: a pulse stimulus alone (pulse-alone condition) and a pulse 'with prepulse' (PPIPSI condition). The SOA for the 'with prepulse' condition was randomised, allowing any of the six SOAs (0, 42, 82, 122, 162, or 202 ms) to be presented. The order of the stimuli conditions in the practice trials was fixed: trials one and three always began with the pulse-alone condition, while trials two and four always began with the 'with prepulse' condition. The interstimulus intervals, timing of prompts, response style (mouse click), and time between selecting a response and the commencement of the next trial were run in the same manner as the actual experiment (detailed below).

Each trial contained two stimulus presentations: pulse stimulus alone (referred to as control) and pulse stimulus preceded by a prepulse (referred to as 'pulse with prepulse')

presented at one of six different SOAs (0, 42, 82, 122, 162 or 202 ms). Each SOA configuration for the pulse with prepulse stimulus was presented 30 times (total number of trials = 180). On 50% of trials, the pulse-alone was delivered first. The order of stimulus presentation (i.e., pulse-alone or pulse with prepulse first) and the SOA condition were randomised. Within each trial, the time interval between the first (S1) and second pulse (S2) was randomised to either 2, 4 or 6s. Two seconds after S2 was delivered, participants were prompted to select via mouse clicking: "which shock-stimulus was perceived as more intense (left-click = first stimulus, right-click = second stimulus or middle-click = felt the same)?". Time between responding to the present trial and commencement of the next was also randomised to 1, 2 or 3s.

2.2.2.2 Experiment 2. The same equipment and procedure were used as in Experiment 1, with the only changes being the SOAs investigated (0, 202, 302, 402, 502, and 602ms).

2.2.2.3 Experiment 3. The equipment and procedure used were the same as those in Experiment 1, with the following exceptions. Three different prepulse intensities were investigated: 1, 2 and 3 times the perceptual threshold. Participants completed three blocks of 40 trials each, with a different prepulse intensity for each block. Block order was counterbalanced between participants. A 202 ms SOA between prepulse and pulse was used throughout the experiment. The results of Experiment 1 indicated that PPIPSI was most prominent at 202 ms, and Experiment 2 showed that this was followed by a plateau. Although PPIPSI at 402 ms SOA was slightly elevated compared to 202 ms, we selected 202 ms because this interval coincides most closely to the shorter SOA's typically examined in the PPI protocols.

Table 2.1

Means, Standard Deviations and Ranges for Stimuli Intensities in Experiment 1, 2 and 3

Stimulus	Experiment 1		Experiment 2		Experiment 3	
	M(SD)	Range	*M(SD)*	Range	*M(SD)*	Range
Threshold	0.62 (0.44)	0.20 – 1.75	1.20 (1.01)	0.3 – 1.75	0.25(0.11)	0.10 – 0.5
Prepulse	1.24 (0.89)	0.4 – 3.5	1.24 (0.89)	0.6 – 3.5	*	*
Pulse	6.64 (3.55)	2 - 15	6.26 (6.17)	1 - 20	5.81(2.46)	1 – 20

Note. Unit of measurement = milliamps (mA). Prepulse intensity was manipulated in Experiment 3, thus descriptive statistics were 1, 2 and 3x perceptual threshold*

2.2.3 Statistical Analysis

All statistical analyses were conducted using R statistics (v3.5.1; R Foundation for Statistical Computing, Vienna, Austria). We conducted generalised linear mixed models (GLMM) analyses using a logistic regression to model the proportion of prepulse-pulse trials perceived less intense, with SOA as a fixed-effect predictor (for Experiments 1 and 2) or prepulse intensity (for Experiment 3), and participant ID as the random factor. The GLMM's were conducted at the trial level using the 'gamljGlmMixed' function the 'gamlj' package (Gallucci, 2019). To facilitate the interpretation of the data, we excluded 'unbiased' trials where the participant responded, "felt the same". Descriptive statistics of the excluded 'unbiased' trials for each experiment are provided in Table 2.2. Given the binary nature of the outcome variable, we used a binomial family distribution for the model. Follow-up pairwise comparisons with Holm's adjustment for multiple comparisons and estimated marginal means for plots were extracted from the model output provided by the 'gamlj' R package.

Table 2.2

Mean Percentage and Standard Deviation of Unbiased Trials Removed for each Experiment

Experiment No.	% Unbiased responses removed
	M(SD)
Experiment 1	30.20 (14.69)
Experiment 2	35.00 (16.65)
Experiment 3	21.64 (11.10)

2.3 Results

2.3.1 Experiment 1: 42 – 202ms SOAs

The GLMM analysis revealed a statistically significant main effect of SOA ($X^2(5, N = 25) = 103$, $p = .0001$*). The pattern of results depicted in Figure 2.1A showed that the proportion of trials where the 'pulse with prepulse' was perceived less intense than the 'pulse alone' increased with SOA. On the control condition (No Gap), participants performed at chance,

reporting on average that ~49% of 'pulse with prepulse' was less intense (*M* = 0.49, *SE* = 0.04). Interestingly, at a 42ms SOA, there was a statistically significant bias towards facilitation - reporting on average ~40% of trials that the 'with prepulse' was less intense (*M* = 0.40, *SE* = .04), meaning ~60% of trials 'with prepulse' was perceived more intense – relative to No Gap ($z(5) = 2.86$, $p < .05$). At 82 and 122ms SOA's, participant responses returned to chance-levels (SOA-82, *M* = 0.52, *SE* = 0.04; SOA-122, *M* = 0.55, *SE* = 0.04) and were not statistically significantly different than No Gap (82 vs. No Gap; $p > .05$; 122 vs. No Gap; $p > .05$). At 162 and 202ms SOA, a statistically significant perceptual bias emerged towards prepulse inhibition – reporting on ~62% and ~69% of trials that 'pulse with prepulse' was less intense compared to 'pulse alone' (SOA-162: *M* = 0.62, *SE* = 0.04; SOA-202: *M* = 0.69, *SE* = 0.04) – relative to No Gap (162 vs. No Gap: ($z(5) = -3.92$, $p < .001$; 200 vs. No Gap: ($z(5) = -6.24$, $p < .001$. Pairwise comparisons between SOA-162 and SOA-202 did not reveal a statistically significant differences in perceptual bias ($z(5) = -2.48$, $p = 0.07$).

2.3.2 Experiment 2: 202 – 602ms SOAs

The GLMM analysis revealed a statistically significant main effect of SOA ($X^2(5, N = 23) = 38.7$, $p = .0001$*). On the control condition (No Gap), participants performed close to chance (*M* = .47, *SE* = .04). As depicted in Figure 1B, the results show a consistent pattern of perceptual bias towards prepulse inhibition at 202-502ms SOA's with average reports that on ~63-66% of trials, the 'pulse with prepulse' was less intense (SOA-202: *M(SE)* = 0.64(0.04); SOA-302 = 0.63(0.04); SOA-402 = 0.66(0.04); SOA-502 = *0*.63(0.04)) with a slight decrease in bias at 602ms (*M* = .58, *SE* = .04). Follow-up pairwise comparisons revealed that the response bias towards prepulse inhibition for all SOA's was significantly greater compared to the No Gap condition (all $p < .01$). Although a slight decrease at 602ms SOA can be observed in Figure 2.1B, no statistically significant difference in response bias was observed between any SOA pair (all $p > .15$).

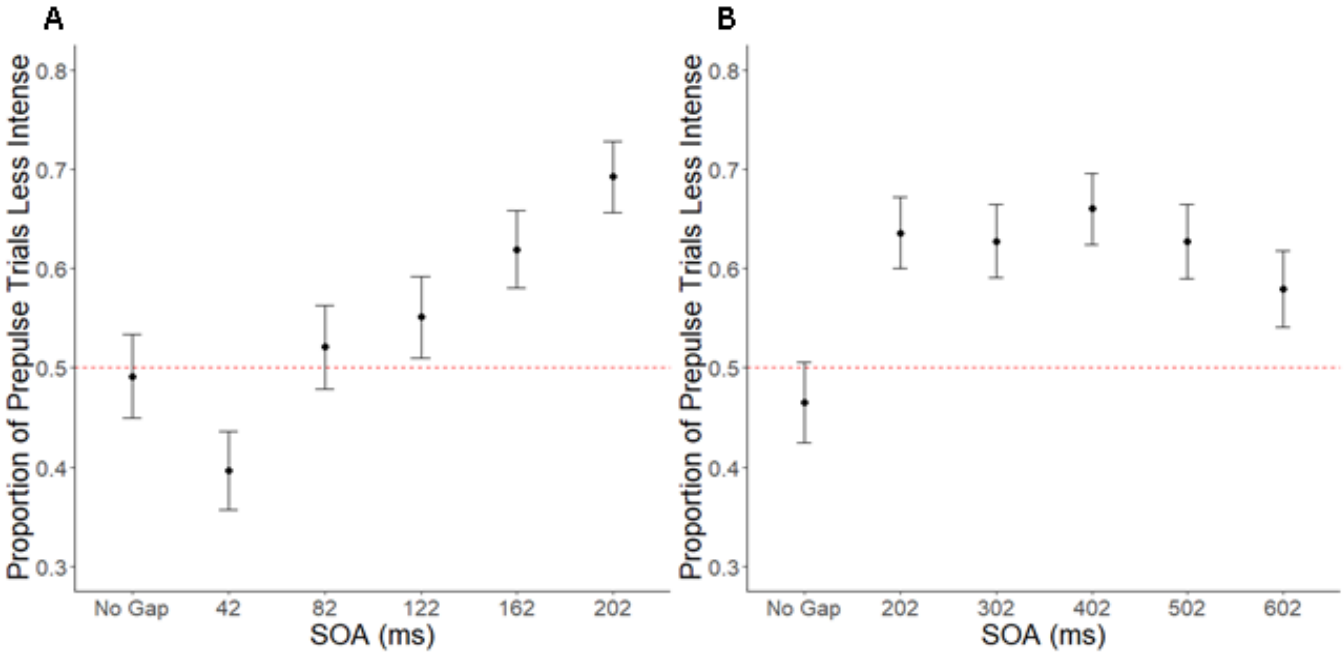

Figure 2.1. *Estimated marginal mean proportion of trials perceived less intense for each SOA investigated in Experiments 1(A) and 2(B). Red dotted line represents chance level. Bars represent the standard error (SE) for each condition. 2.1A shows that as SOA increased, presence of the gating mechanism (PPIPSI) increased, with 162ms and 202ms being the only conditions significantly higher than the control condition (No Gap). 2.1B demonstrates that for all conditions, the presence of gating mechanism (PPIPSI) was significantly higher than the control condition (No Gap).*

2.3.3 Experiment 3: Prepulse Intensity (1x, 2x, and 3x perceptual threshold)

The GLMM analysis revealed a statistically significant main effect of prepulse intensity on PPIPSI ($X^2(2, N = 24) = 15.9$, $p = .0003$*). As illustrated in Figure 2.2, the proportion of 'pulse with prepulse' trial reported as less intense was maximal when prepulse intensity was set to 2x the perceptual threshold ($M = .70$, $SE = .04$). Follow-up pairwise comparisons revealed this was significantly greater compared to 1x and 3x perceptual threshold conditions (1x: $M = .62$, $SE = .04$; 1x vs. 2x: ($z(2) = -2.77$, $p = 0.01$; 2x vs. 3x: $M = .59$, $SE = .04$; ($z(2) = -3.88$, $p = 0.0003$). No statistically significant difference in the proportion of PPIPSI between 1x and 3x threshold conditions was observed ($z(2) = 0.96$, $p = 0.34$).

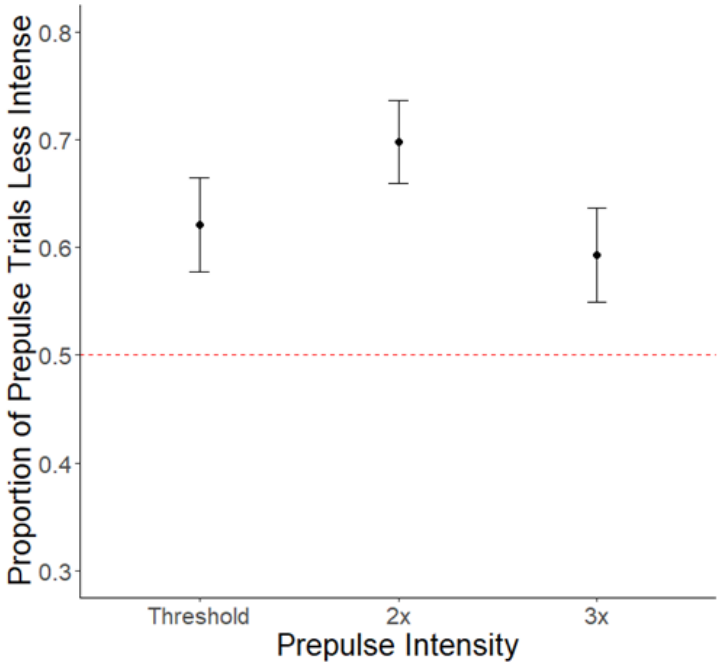

Figure 2.2. *Estimated marginal mean proportion of trials perceived less intense for each prepulse intensity investigated in Experiment 3. Red dotted line represents chance level. Bars represent the SE for each condition. The graph shows that the proportion of PPIPSI was significantly higher in the 2x threshold condition compared to 1x and 3x conditions, where no significant difference was found between 1x and 3x perceptual threshold conditions.*

2.4 Discussion

In the current study, we sought to characterise the nature of PPIPSI by examining how it is modified as a function of SOA and prepulse intensity. With respect to timing, we predicted that PPIPSI would not be observed at shorter SOAs and would emerge after ~100 ms, reflecting the dependence of PPIPSI on the reorientation of attention. In Experiment 1, No PPIPSI was observed in the No Gap condition. Interestingly, the prepulse led to an increase in perceived intensity at 42 ms which could reflect a form of priming or summation (Neumann et al., 2004), followed by a gradual shift towards inhibition with increasing SOA. PPIPSI was observed ~62-69% of trials at 162 and 202 ms. In Experiment 2, we investigated whether the proportion of PPIPSI would increase beyond SOAs of 202 ms. We observed that the proportion of trials with PPIPSI remained consistent between 202-602 ms (~58-66%).

With respect to prepulse intensity, we predicted that the proportion of trials where PPIPSI is observed would increase with prepulse intensity – as this may facilitate the re-

orientation of attention towards the pulse. We focused on an SOA of 202 ms when exploring the effect of intensity as PPIPSI was most prominent at this timing (~64-69%). Although Experiment 2 showed that PPIPSI was comparable between 202-602 ms, focusing on 202 ms limits the potential influence of voluntary processes that may be evident at longer SOAs. In this last experiment, a prepulse 2 times (2x) stronger than the perceptual threshold elicited the greatest proportion of PPIPSI (~70%), compared to perceptual threshold (1x) and 3x perceptual threshold (~59-62%).

2.4.1 PPIPSI at SOA > 162 ms suggests the involvement of attentional processes.

Collectively, our findings align with conceptualisations of PPIPSI being reliant on attentional and self-monitoring mechanisms - which require greater time between the prepulse and pulse to take effect. Swerdlow et al. (2005) found that the magnitude of perceived intensity reduction increased with SOA, we too found that the proportion of trials where PPIPSI was observed increased with SOA. In their paradigm assessment, Swerdlow et al. (2005) studied the time-course of acoustic PPIPSI at SOAs of 10, 20, 30, 60 and 120 ms – finding that PPIPSI only emerges and is maximal at intervals susceptible to attentional control (approximate reduction: 25% at 120 ms). The attentional control range being 120 ms and above (Dawson et al., 1993). Consistent with these findings, we did not observe a significant proportion of electrotactile PPIPSI until SOAs within the suggested attentional range (~62% at 162 – 602 ms), providing further evidence that PPIPSI requires the engagement of attentionally sensitive mechanisms that are not required for startle PPI (Swerdlow et al., 2005; Swerdlow et al., 2007).

2.4.2 Mechanism of perceived intensity reduction by prepulses

While the time-course and experimental design of PPIPSI indicate the involvement of attentional and higher cognitive evaluative mechanisms, there are a few ways by which the prepulse might influence these mechanisms leading to perceived intensity reductions. These include mechanisms of prepulse inhibition and perceptual assimilation. In startle PPI, studies show that the prepulse activation (depending on its modality) travels through the inferior and superior colliculus to the pedunculopontine tegmental nucleus (PPTg) where it results in suppression of the primary startle pathway (for detailed reviews see: Azzopardi et al., 2018; Fendt et al., 2001). Given the strong correlation found between startle PPI and PPIPSI

(Swerdlow et al., 1999), the inhibitory effect of PPTg activation by the prepulse may also project to higher processing areas, resulting in inhibited processing of subsequent stimuli. Similarly, though via a different pathway, electrotactile prepulses may activate the lower pain gate in the spinal cord, which then limits the projection of intensity information for the following pulse stimulus, resulting in reduced perceived intensity. The reduced, or lack of PPIPSI observed at SOAs as brief as those that elicit startle PPI may be because attention requires more time to (even if driven indirectly by the prepulse) to monitor inputs to the cortex. Note that although participants are likely attending to the somatosensory channel throughout the entire trial, it is difficult to maintain a high level of attention when the exact timing of the stimuli is random (see Bendixen et al., 2009). Therefore, in addition to inhibiting the input to the cortex, the prepulse might serve as a temporal cue to allocate additional resources to monitor particular sensory channels. This model is consistent with Brunia's (1993) proposal that motor and attention processes use similar mechanisms. More precisely, because motor responses cannot be held in a high state of preparation for long periods (100 – 300 ms; Alegria, 1975; Muller-Gethmann et al., 2003), responses are maximally prepared when the warning signal is presented around 200 ms before the imperative stimulus to act. In PPIPSI, the participants similarly cannot stay in a high state of attention to perceive the pulse, because the timing of pulse presentation is uncertain.

PPIPSI resembles phenomena known as 'loudness enhancement' and 'loudness decrement', though these are observed in considerably different procedures (Elmasian et al., 1980). In these experiments, the target stimulus's perceived loudness increases when preceded by a louder conditioning stimulus and decreases when preceded by a weaker stimulus (Elmasian et al., 1974; Elmasian et al., 1980; Zwislocki & Ketar, 1972). These effects are attributed to assimilation, a form of perceptual averaging that occurs when processing two similar and temporally overlapping stimuli makes them difficult to distinguish, resulting in a combined percept (Elmasian et al., 1980). This combined percept typically shifts in the direction of the preceding stimulus's intensity. The assimilation process hypothesis suggests that assimilation should be maximal when: 1) the stimuli overlap in time, 2) their similarity is greatest, and 3) the intensity disparity between them is greatest (Elmasian et al., 1980).

The observation of prepulse facilitation (PPF) at the short SOA of 42 ms using brief 2 ms electric stimulation for both the prepulse and pulse meets two of the criteria for

assimilation. However, it draws greater parallels with findings from startle/sensorimotor gating experiments. Neumann et al. (2004) reported an increased eye-blink magnitude (PPF) in response to a 105 dB white noise burst using 1000-Hz tone, tactile, and visual prepulses at SOAs of 0-30 ms. This short SOA facilitation is typically attributed to temporal summation, where the prepulse primes the response pathway, and at short intervals, this priming overlaps and sums with the processing of the subsequent stimulus (Boelhouwer et al., 1991; Neumann et al., 2004). This suggests that at short SOAs, where processing overlaps, participants' intensity judgments might be based on the sum (rather than the average) of the prepulse and pulse, either due to difficulty separating the two, because perception is fused into a single summed stimulus, or both.

Furthermore, the broader patterns of the data are inconsistent with the third criterion of assimilation (Elmasian et al., 1980). Our findings that 2x threshold prepulses produce greater PPIPSI are incompatible with this proposition because the disparity between stimuli was greatest in the 1x threshold condition. Additionally, findings that PPIPSI is observed with cross-modal stimuli (English & Drummond, 2021; Swerdlow et al., 1999) indicate that perceptual averaging alone is unlikely to explain our results.

2.4.3 The role of stimuli intensity

Although consistent with the broader PPIPSI literature in supporting that longer SOAs provide greater direction of attention to perceive sensory gating effects, several differences between our experiments and these studies offer nuanced insights into PPIPSI, but also limitations.

The broader PPIPSI literature uses fixed stimulus intensities across participants and a Visual Analog Scale (VAS; assigning a numeric perceived intensity rating) to measure PPIPSI (Swerdlow et al., 1999; Swerdlow et al., 2005; Swerdlow et al., 2007). The VAS method yields a percentage difference value between pulse conditions (with/without prepulse; Swerdlow et al., 2005). However, the use of a percentage reduction method requires a high intensity pulse-alone stimulus to allow room to observe a significant reduction in perceived intensity in the prepulse-pulse condition. This is evident from Swerdlow et al's (2005) calibration session, where 90dB and 95dB pulse-alone conditions yielded perceived intensity scores of 10/100 and 20/100 respectively, while the 105dB pulse-alone yielded an

approximate score of 80/100. In their case, pulses below 100dB would have likely been susceptible to a floor effect, limiting the ability to observe a percentage difference in SOAs and subsequently altering PPIPSI's time-course. An ethical requirement of our study was that stimuli be non-painful, this, in combination with evidence that electrotactile stimuli are more subjectively aversive than acoustic (Sperl et al., 2016), led us to opt for individualised intensities as opposed to predetermined ones. Informed by the evidence from Swerdlow et al. (2005) calibration session, a concern of using individualised intensities was that participants may select intensities in ranges below those required to observe meaningful differences between conditions using a percent reduction method. Thus, we selected a comparison between pulse (with/without prepulse) conditions method, which yields a more general proportion of trials perceived less intense metric.

Using these fixed intensity settings and the VAS, the literature typically finds that PPIPSI increases as prepulse intensity increases to some threshold, after which PPIPSI begins to decrease with further increases in prepulse intensity (Swerdlow et al., 1999; Swerdlow et al., 2007). Despite our use of individualised intensity settings and proportion method, we identified a similar non-linear pattern of prepulse intensity effects as previous studies. We observed an increase in PPIPSI with increased prepulse intensity from 1x to 2x, followed by a reduction in PPIPSI in the 3x perceptual threshold condition.

The literature also suggests PPIPSI is maximal with higher pulse intensities (e.g., Swerdlow et al., 2005). A limitation of our stimulus intensity settings, particularly that the pulse be 'unpleasant, but not painful' and our use of a proportion method is that our study is not well equipped to support inferences about pulse intensity effects. Evidence that PPIPSI increases with pulse intensity could be due to something inherent to the gating mechanisms, or a product of the VAS method requiring high intensities to be sensitive (discussed further below). An additional possibility is that the use of proportion may have limited our ability to identify differences in effects between 202 – 602 ms SOAs. The VAS method may reveal that although the proportion of PPIPSI doesn't change at these intervals, the pattern of percentage reduction between conditions might. To resolve these limitations, a future study may validate the sensitivity of the VAS at lower intensities, and by testing an array of objectively set low to high intensities and array of SOAs.

2.4.4 Modality specific differences in PPIPSI

Building to the PPIPSI literature, our study provides evidence of possible modality specific differences in the time-course of PPIPSI. When compared to acoustic PPIPSI (Swerdlow et al., 2005), our findings suggest that electro-tactile PPIPSI has a longer time-course of activation. Swerdlow et al. (2005), using high intensity/startling acoustic stimuli (85dB prepulse / 105dB pulse) identified PPIPSI at 60 and 120 ms SOAs. Whereas our findings evidence electrotactile PPIPSI requires SOAs > 122 ms (162 ms – 600 ms based on measured SOAs). A possible explanation for this is that like PPI, PPIPSI contains modality specific processing pathways, of which a faster auditory and slower tactile pathway exist (Yeomans et al., 2006; Gomez-Nieto et al., 2020). This intuitively suggests that faster processing of stimuli reduce the time-course at which attentional mechanisms are recruited and can be directed towards the relevant sensory channels. However, there is evidence to suggest pulse intensity may modulate the time-course of PPIPSI, which may account for this small difference in SOA between our two studies (Swerdlow et al., 2005). Additionally, the differences in the length of afferent pathways for the ear and wrist, and the corresponding time taken for the signal to arrive in the brainstem and higher centres, could further explain the observed differences. Auditory signals, which travel a shorter and faster pathway, reach the brainstem quicker than tactile signals from the wrist, likely contributing to the shorter SOAs observed for acoustic stimuli.

Within the same modality as our study (electro-tactile), though with painful electric shocks (*M* = 160V), Blumenthal et al. (2001) observed PPIPSI at SOAs of 40 and 60 ms using 1x and 1.25x perceptual threshold prepulses. These SOAs are well within the “preattentive” range, and with shorter SOAs than the acoustic modality used by Swerdlow et al. (2005). One possible explanation for these findings is that the high intensity of the pulse in Swerdlow et al. (2005) and particularly Blumenthal et al.’s (2001) work may have made participants more sensitive to the effect of the prepulse. That is, in line with the findings that PPIPSI increases with stimuli intensity and the VAS being more sensitive to high intensity stimuli, the effect of the prepulse may be greater for high intensity pulses due to the dynamic range of the perceptual system. There is more room for the reduction of a large signal than a small signal. For example, a 20% reduction of 100 is 20, but a 20% reduction of 10 is 2. To gain more conclusive insight into possible modality specific pathways and the role

pulse intensity plays in the time-course of PPIPSI, a future study using a range of pulse intensities (particularly high ones) and the VAS would allow for a more direct comparison.

2.4.5 Separability of PPIPSI and startle PPI

Due to startle being the index of motor PPI, it is common to use stimuli intensities above or equal to 90dB for acoustic (Blumenthal et al., 1999; Swerdlow et al., 1999) and 40mA for electrotactile (Bufacchi et al., 2017; Sambo et al., 2012; Sambo et al., 2012). Notably, acoustic startle has been reported at lower intensities (e.g., 70dB; Blumenthal & Goode, 1991), though the broader literature suggests it is less reliable, resulting in more trials on which no startle occurs - making motor PPI difficult to measure. In the current study, we show that PPIPSI can be elicited with pulse stimuli as weak as 2mA, well below that which reliably elicits startle. Meaning PPIPSI may be a useful measure of sensory gating where motor responses may interfere or confound data. For example, In Blumenthal et al. (2001), it was difficult to disentangle whether PPIPSI simply reflected the perception of perceived startle response. Our findings also provide tentative evidence that PPIPSI and startle may be separable based on intensity requirements and time-course. A future study could directly look at this relationship using similar non- magnitude estimation methods, as magnitude estimate methods appear to require high intensities to be sensitive (Swerdlow et al., 1999).

Multiple studies have reported evidence of cortical PPI (Dawson et al., 2004; Kedzior et al., 2007; San-Martin et al., 2018). When the prepulse is present, the N1 and P2 event related potentials (ERP) responses to the pulse are reduced (Dawson et al., 2004; Kedzior et al., 2007; San-Martin et al., 2018). Interestingly, studies measuring startle PPI and cortical PPI simultaneously find weak or no correlation (Kedzior et al., 2007; San-Martin et al., 2018). This may not seem surprising given startle PPI is a motor response typically used as an indicator of subcortical activation (Blumenthal, 2015; Fendt et al., 2001), while N1 and P2 ERPs are products of neural activity which provide information about cortical processing of stimuli (San-Martin et al., 2018). However, given the current and other studies indicating that PPIPSI requires attentional mechanisms, a higher-order process, it may be possible that PPIPSI correlates with these ERPs. For example, enhanced N1 has been attributed to early sensory perception (vigilance) and attention to a stimulus (Mishra & Hillyard, 2009; Mingming et al., 2018). Since PPIPSI and cortical PPI appear to focus on processing information rather than responding to stimulation (as startle PPI does), PPIPSI may correlate

more strongly with cortical PPI. This potential relationship may lend further support for the involvement of higher-order, likely attentional, mechanisms in PPIPSI.

2.4.6 Role of attention

Our study and the literature suggest that based on the time-course and design of experiments, PPIPSI requires the engagement of attentional mechanisms to be observed. While stimuli intensity may influence the activation time of attentional mechanisms, strong evidence for their involvement in PPIPSI would be shown by manipulating attention directly. A possible avenue for future research would be to divide attention - by giving participants a secondary task to perform, if attention is crucial to PPIPSI it would be expected that participants perceived intensity of the 'pulse with prepulse' condition would be affected in this condition compared to when there is no secondary task.

2.4.7 Conclusion

In the present study, the parameters which elicited the greatest proportion of trials where the 'pulse with prepulse' was perceived less intense were found to be a 2x perceptual threshold prepulse presented at an SOA of 202ms before the pulse. The current results demonstrate that from 0ms, except for 42ms, as SOA increases so does the observation of PPIPSI. However, it is important to note that while PPIPSI was first observed at 162 ms, and was non-significant at 122 ms, one weakness of using discreate values with a continuous variable (e.g. time) is that we cannot conclusively say at which SOA between 122 and 162 ms PPIPSI becomes observable above chance levels. It is possible that an SOA of 125 ms or 130 ms may effectively elicit PPIPSI. Nevertheless, even when using a conservative estimate from the data, the range (> 122 ms – 600 ms+) at which PPIPSI becomes observable is within those considered to be influenced by attentional processes (Dawson et al., 2004). Consistent with Swerdlow et al. (2005), we conclude that this relationship supports conceptualisations of PPIPSI requiring attentional and self-monitoring processes – which the longer SOAs allow greater activation of. Our findings also provide evidence that PPIPSI can be elicited using less intense stimuli, something that may be useful for those seeking to investigate the mechanisms involved using physiological measures, such as EEG.

CHAPTER THREE: N1-P2 EVENT-RELATED POTENTIALS AND PERCEIVED INTENSITY ARE ASSOCIATED: THE EFFECTS OF A WEAK PRE-STIMULUS AND ATTENTIONAL LOAD ON PROCESSING OF A SUBSEQUENT INTENSE STIMULUS

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3.0 Abstract

A weak stimulus presented immediately before a more intense one reduces both the N1-P2 cortical response and the perceived intensity of the intense stimulus. The former effect is referred to as cortical prepulse inhibition (PPI), the latter as prepulse inhibition of perceived stimulus intensity (PPIPSI). Both phenomena are used to study sensory gating in clinical and non-clinical populations, however little is known about their relationship. Here, we investigated 1) the possibility that cortical PPI and PPIPSI are associated, and 2) how they are affected by attentional load. Participants were tasked with comparing the intensity of an electric pulse presented alone versus one preceded 200ms by a weaker electric prepulse (Experiment 1), or an acoustic pulse presented alone with one preceded 170ms by a weaker acoustic prepulse (Experiment 2). A counting task (easy vs. hard) manipulating attentional load was included in Experiment 2. In both experiments, we observed a relationship between N1-P2 amplitude and perceived intensity, where greater cortical PPI was associated with a higher probability of perceiving the 'pulse with prepulse' as less intense. Moreover, higher attentional load decreased observations of PPIPSI but had no effect on N1-P2 amplitude. Based on the findings we propose that PPIPSI partially relies on the allocation of attentional resources towards monitoring cortical channels that process stimulus intensity characteristics such as the N1-P2 complex.

3.1 Introduction

When a weak stimulus is presented immediately before a stronger one, the motoric (e.g., startle and blink reflex) and cortical (electrophysiological) response to and perceived intensity of the stronger stimulus are reduced compared to presenting the strong stimulus alone (Graham, 1975; San-Martin et al., 2018; Swerdlow et al., 2005). These phenomena are broadly referred to as prepulse inhibitions (PPI) and are operational measures of sensorimotor and sensory gating. Sensory gating involves the cortical process that permits or suppresses the further processing of incoming stimuli. Although the underlying mechanisms and protocols to elicit both types of gating (motor and sensory) overlap, it is likely that these two phenomena are affected by different brain processes. Here, we were interested in understanding the processes which influence gating of conscious perception.

Startle PPI is a measure of motor gating: the presence of a weaker preceding stimulus (prepulse) reduces the blink reflex to an intense stimulus (pulse; Blumenthal, 2015). It is observed shortly after the pulse at short gaps between prepulse and pulse onset (SOA). SOAs from 15 – 300 ms will elicit startle PPI, and SOAs of 60 – 120 ms are where inhibitory effects of the prepulse on the blink reflex are maximal (Blumenthal, 2015; Swerdlow et al., 2005). Because the blink reflex has a short onset latency, and the SOA required to elicit startle PPI is also very short, startle PPI is mostly informative about the lower-level gating mechanisms (Fendt et al., 2001). That is, the short latencies suggest that the blink reflex and startle PPI occur so quickly that there is little time for the involvement of higher-order processes with longer cortical loops. While explicitly instructing participants to pay attention to the prepulse does enhance startle PPI, these studies differ significantly from typical startle PPI experiments: they utilise longer SOAs (120ms+) and a continuous prepulse (Ashare et al., 2007; Dawson et al., 1993; Elden & Flaten, 2002; Filion & Poje, 2003; Hawk et al., 2002; Heekeren et al., 2004; Poje & Filion, 2021). Typical studies of startle PPI use short SOAs (e.g., 60 ms) and discrete prepulses, settings which are not optimal for the observation of attentional enhancement of PPI (Poje & Filion, 2021). Furthermore, evidence that gating of reflexes is driven by brainstem and midbrain structures supports the conceptualisation that startle PPI is mediated by lower-level gating mechanisms (for detailed reviews see, Azzopardi et al., 2018; Fendt et al., 2001). Combined with findings that startle PPI is observed in infants (Graham et al., 1981), sleeping adults (Silverstein et al.,

1980) and even decorticated rats (Ison et al., 1991), the broader literature suggests that the gating of reflexes is largely driven by processes that are independent of attention. However, conscious perception requires the engagement of attentional processes (Noah & Mangun, 2020), and we are yet to understand the ways by which lower-level mechanisms may contribute to gating of conscious perception.

Sensory gating of perception has been proposed to be more directly measured by a related phenomenon known as prepulse inhibition of perceived stimulus intensity (PPIPSI; Swerdlow et al., 1999; Swerdlow et al., 2005). PPIPSI is measured by the reported reduction in the perceived intensity of the pulse stimulus when a prepulse is present (Swerdlow et al., 1999; Swerdlow et al., 2005). Meaning, participants are required to make relative judgments about the intensity of their experiences. Studies measuring startle PPI and PPIPSI simultaneously have reported strong positive correlations (r = .72 - .75; Swerdlow et al., 1999; Swerdlow et al., 2005). These findings indicate that gating of perception (measured by PPIPSI) likely shares underlying mechanisms with gating of reflexes (Swerdlow et al., 2005). Subcortical signals (those activated by startle PPI) may propagate to perceptual areas of the cortex where perceived intensity is processed (Swerdlow et al., 2005). However, there is little direct evidence for this, and studies show that the time-course of startle PPI and PPIPSI activation differ (Favero et al., 2022; Swerdlow et al., 2005; Swerdlow et al., 2007). While startle PPI is observed at short SOAs (>15ms), Swerdlow et al. (2005) found that for acoustic stimuli, the prepulse has no effect on perception at SOAs below 60 ms and maximally reduces perceived intensity at 120 ms. Moreover, in a previous study, we found that electrotactile PPIPSI requires SOAs of 160 – 600ms (Favero et al., 2022). In line with the task requirements of PPIPSI, that participants direct their focus to the pulse stimuli (with *vs.* without prepulse) and provide an intensity rating or comparison, it has been proposed that the requirement of longer SOAs is because attentional mechanisms are required to experience sensory gating of perception (Favero et al., 2022; Swerdlow et al., 2005; Swerdlow et al., 2007). More specifically, longer times are required to direct attention to the sensory inputs which reflect the inhibitory effects of the prepulse. These data suggest that, although gating of perception may be partially shaped by subcortical processes, this is unlikely to be the complete picture – attention and perception are higher order processes and likely associated with or represented by cortical activity.

Although time-course data and task requirements provide some insight into the involvement of higher order processes in perceptual gating, stronger evidence of this may come from studies specifically measuring cortical activity such as an electroencephalogram (EEG). The presence of a prepulse is known to correspond with inhibited N1 and P2 event related potentials (ERP) at central and centroparietal areas in human subjects — reflecting what is known as cortical PPI (Dawson et al., 2004; Kedzior et al., 2007; San-Martin et al., 2018). Researchers have suggested that the N1 and P2 ERP reductions might be due to cortical encoding of the processes which contribute to PPIPSI (Swerdlow et al., 2007). Indeed, cortical PPI and PPIPSI share similar magnitude reductions and temporal sensitivities (Kedzior et al., 2006; Swerdlow et al., 2007). Furthermore, studies have evidenced the N1 and P2, or N1-P2 complex represent functionally relevant processes to PPIPSI, such as those involved in processing the physical characteristics of the stimulus (e.g., intensity; Annic et al., 2014; Garcia-Larrea et al., 1992). For example, N1 and P2 magnitude both increase as a function of stimulus intensity (Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008).

While the N1-P2 may represent encoding of stimulus intensity and classification, the literature indicates that perceptual and decisional processes are not contained within this processing stage or time window, but that they provide specific feature traces, or possibly complete representations of a stimulus, which perceptual and decisional processes may access (Näätänen & Winkler, 1999). One possibility is that perceptual and decisional processes can access cortical representations of sensory stimuli via attentional mechanisms such as selective attention. Directing attention to the stimulus is said to facilitate conscious perception by bringing its cortical representation into focus (Näätänen & Winkler, 1999). The above findings suggest a relationship between cortical PPI and PPIPSI where inhibition of the N1 and P2 cortical responses, which represent encoding of stimulus features, contribute to the perceptual experience of reduced perceived intensity. Moreover, they indicate that this relationship is modulated by selective attention, which brings the inhibited cortical representation into conscious perception. Such a model is consistent with previous propositions that PPIPSI requires higher order (attentional and self-monitoring) mechanisms (Favero et al., 2022; Swerdlow et al., 2005). However, this relationship is yet to be investigated more directly, and while PPIPSI is observed in other sensory modalities (e.g.,

tactile), current propositions of its similarities with cortical PPI have only been based on acoustic data (Kedzior et al., 2007; Swerdlow et al., 2007).

Additionally, the extent to which N1 represents encoding of attentional processes is debated. According to Näätänen's (1992) model of auditory processing, N1 is considered a predominantly exogenous ERP, shaped by stimulus characteristics (e.g., particularly intensity) and representing encoding of its feature traces. In this model, N1 is preattentive (unaffected by and non-representative of attentional processing), and even if unattended, or not entering conscious perception, its contained information (stimulus trace or representation) is still encoded (Näätänen & Winkler, 1999). For these authors, attention is directed post-N1 via a perceptual mechanism. Alternatively, Muller-Gass and Campbell (2002) suggest N1 is endogenous and represents attentional allocation to a stimulus, whether task relevant or not. Indeed, selective attention has been found to modulate N1 and P2 cortical responses, enhancing their magnitude for attended as opposed to unattended stimuli (Tiitinen et al., 1993; Mishra & Hillyard, 2009), and increasing cortical PPI when directed towards the prepulse (Annic et al., 2014). Assessment of PPIPSI differs from these paradigms in that attention is directed toward each pulse-stimulus in a trial, thus even if a relationship was found between cortical PPI and PPIPSI, inferring at what stage attentional processes are recruited, and their effects would not be possible. However, given that attention is widely held to be a finite resource (Petersen & Posner, 2012; Swallow & Jiang, 2013), we can gain insight into the cortical mechanisms of PPIPSI by manipulating attentional load. If N1-P2 represents attentional allocation to a stimulus, presenting a secondary task which induces attentional load would likely modulate this cortical response, and the inhibitory effect of the prepulse. Conversely, if the N1-P2 response is unaffected by attentional load, this would align best with Näätänen and Winkler (1999), suggesting that N1-P2 is encoding of stimulus representation, and that attention is directed towards this channel at a later stage of processing via a perceptual mechanism which may result in PPIPSI.

In this study, we sought to investigate the relationship between gating of perception (PPIPSI) and the net neural response of the cortical system at the N1-P2 timeframe (~50-250 ms) in both tactile (Experiment 1) and acoustic (Experiment 2) modalities. The N1-P2 complex reflects the initial cortical processing of sensory stimuli, and the cortical responses

of this complex provide an index of the net neural activity at a critical time for perception that can be compared by measuring ERPs with and without prepulses. To extend this further, in Experiment 2 we also manipulated attentional load, providing insight into the influence attentional processes have on PPIPSI and cortical PPI.

3.2 Methods

3.2.1 Participants

Participants were Curtin University undergraduate students who participated in exchange for course credit and volunteers. We ran an a priori power simulation based on pilot data from five participants. Our sample sizes were based on our prior study using the same protocol we employed in the current study (Favero et al., 2022), where we collected between 22 and 25 participants. This range is similar to that of a related study by San-Martin et al. (2018), which recruited 22 participants to examine cortical PPI. For Experiment 1, 26 participants (21 female) were recruited (age M(SD) = 21.79(4.46) years, range = 18 – 38 years). However, EEG data from two participants was not collected due to software error, resulting in a final sample of 24 participants (20 female), age M(SD) = 21.74(4.55), range = 18 – 38. For Experiment 2, a separate sample of 24 pa rticipants (20 female) were recruited (age M(SD) = 24.04(7.02) years, range = 18 – 48 years). All participants self-reported having normal or corrected-to-normal vision, with no known neurological conditions or injuries that may affect their performance in the experiment. In accordance with the Declaration of Helsinki and with approval from the Curtin University human research ethics committee (Approval Code: HRE2018-0257) informed written consent was provided by all subjects prior to participation.

3.2.2 Pre-Experiment Procedures

In both experiments we used a within-participant repeated measures design. Consistent with our previous work (Favero et al., 2022), participants were seated at a desk 57 cm from a 24-inch BenQ LCD monitor (1920×1080 resolution; 120 Hz refresh rate), with both arms rested on the desk.

3.2.2.1 Experiment 1 – Tactile

Two Digitimer STIMULATOR-DS7As – one to deliver the prepulse and one to deliver the pulse – were then attached to participants' left wrist around the ulnar styloid process, via four Kendall Covidien Ag-AgCl electrodes. Both stimulators were set to emit a single square wave prepulse or pulse with a duration of 2 ms. Perceptual thresholds (weakest identifiable stimulation) were then identified and documented via the following process: starting at 0.50 mA and decreased in increments of 0.10 mA until participants no longer reported feeling the stimulus, intensity was then increased using finer increments of 0.05mA until first perceived again – this value was defined as their individual perceptual threshold. Once perceptual threshold was identified, the prepulse intensity was set by doubling this (e.g., 0.50 mA perceptual threshold = 1.0 mA experiment prepulse intensity). Pulse intensity was set by starting at perceptual threshold and rising in 1 mA increments until the pulse was reported to be "unpleasant, but not painful" by the participant. Descriptive statistics of participants perceptual thresholds, prepulse and pulse test intensities are provided below in Table 1.

Table 3.1

Means, Standard Deviations and Ranges for Stimuli Intensities in Experiment 1

Stimulus	Experiment 1	
	M(SD)	Range
Threshold	0.35 (0.17)	0.1 – 0.8
Prepulse	0.70 (0.39)	0.2 – 1.6
Pulse	4.63 (2.54)	2.0 – 12.0

Note. Unit of measurement = milliamps (mA).

3.2.2.1 Experiment 2 – Acoustic

Acoustic stimuli were generated by the motherboard of the computer used to run the experiments and presented binaurally through stereophonic headphones (Model: HD25-1 II). The background noise was set at 60 dBA. The stimuli consisted of a brief white noise burst (50 ms duration with a rise and fall time < 1.5 ms) generated in MATLAB using the "cgsound" function. The volume of the generated noises was calibrated using the

"AttenuateSound" function to achieve the desired decibel levels for the pulse (100 dB) and the prepulse (80 dB), consistent with the optimal intensity range reported by Swerdlow et al. (1999, 2005) and cortical PPI studies by San-Martin et al. (2018). The volume settings were adjusted using the "cgsound('vol', channel, volume)" function to ensure that each sound channel was set to full volume (1), providing maximum output. An audiometer was used to measure the output volume from the headphones. Positioned between the headphones, the audiometer ensured accurate measurement. The code was adjusted iteratively until the volume settings matched the desired loudness levels as recorded by the audiometer. This final step was repeated before each participant commenced the experiment to ensure accuracy and consistency across participants.

3.2.3 Procedures

3.2.3.1 Experiment 1: Tactile perceptual task

In each trial, participants were instructed to compare two pulses: the pulse-alone (control) against the 'pulse with prepulse' (PPIPSI condition). A 200 ms SOA was used for the PPIPSI condition. The task consisted of 90 trials (i.e., 90 comparisons of 'pulse alone' with 'pulse with prepulse' conditions). Stimulus conditions were randomised with an equal number of 'pulse alone' and 'with prepulse' first trials. To commence the experiment, a prompt stating "press any button to start" was displayed on the screen. After participants pressed a key, the delivery of the first stimulus was randomised to 1, 2 or 3 s. Within each trial, the time interval between the first stimulus (S1) and the second stimulus (S2) was randomised to either 3, 4 or 5 s. 1 s after both S1 and S2 were delivered, participants were prompted to select via mouse clicking: "which shock-stimulus was more intense (left-click = first stimulus; S1, right-click = second stimulus; S2 or felt the same = middle-click)?". Participants were told there was no correct response and that we were purely interested in comparing their perception with brain responses. The commencement of the next trial was randomised to 1, 2 or 3 s after the mouse response, thus time between trials varied but was at least 1 s, but the effective window including response time was about 5 s. We opted for a comparison between pulse (with/without prepulse) conditions method as opposed to the visual analogue scale (VAS; assigning a numeric perceived intensity rating) for consistency with our previous study (Favero et al., 2022), and to avoid the possibility that our ethical requirement

of non-painful stimuli intensities may result in participants selecting intensities below those that the VAS can record meaningful differences from (see Favero et al., 2022 and Swerdlow et al., 2005 for further detail).

3.2.3.2 Experiment 2: Acoustic perceptual task and attentional load

In Experiment 2, participants completed the same perceptual comparison task as in Experiment 1, with an additional counting task to manipulate attentional load and the following stimulus interval differences. A SOA of 170 ms (interstimulus interval: 120 ms) was used for the PPIPSI condition informed by previous studies (San-Martin et al., 2018; Swerdlow et al., 2005). The experiment consisted of 60 trials, stimulus conditions were randomised with an equal number of 'pulse alone' and 'with prepulse' first trials. Attentional load was divided into two levels of task difficulty (easy and hard) and presented in blocks of 30. Block order was randomised between participants. To manipulate attentional load, numbers were presented in the centre of the screen for a duration of 1 second. In the easy task, these numbers were a series of 1s (11 in total, same number of 1s/numbers on each trial), and in the hard task numbers were pseudorandomised and ranged from -9 to +11. Participants were instructed to add these and report the sum via keyboard input after reporting their perception.

To commence the experiment, a prompt was displayed on screen stating, "press enter to start", 1 s after the participant pressed the enter key the first number would appear, displayed for 1 s and then be replaced by a focus point (dot). Acoustic S1 was set to randomly deliver between 3.5 – 4.5 s into a trial, and S2 was set to be randomly delivered between 12.5 – 13.5s into the trial. Thus, the interval between S1 and S2 was randomised between 8 – 10 seconds. Presentation of visual and acoustic stimuli were offset so as not to be presented at the same time. After the last number of the counting task had been presented a screen prompt for the perceptual comparison would appear: "which loud-stimulus was more intense (left-click = first stimulus; S1, right-click = second stimulus; S2 or felt the same = middle-click)?". Following reporting of perception, participants were asked to report the sum from the counting task via the number pad and press enter to record the response and start the next trial. Time between responding to the present trial and commencement of the next was also randomised to 1, 2 or 3 s post entering number response, thus time between trials varied but was at least 1 s.

It may be noted that these presentation timings and interstimulus intervals differ from those used in Experiment 1. However, these timings were selected to ensure that the attentional load task was sufficiently challenging and engaging. It was necessary to present an adequate number of numbers at a perceptible rate to maintain participants' engagement with the task, thereby preventing disengagement and ensuring that the manipulation of attentional load was effective. Additionally, the timing of S1 and S2 was offset from the visual (counting) stimuli to avoid simultaneous presentation, which could confound the data by introducing unintended overlaps in stimulus processing. Furthermore, compared to Experiment 1, the interstimulus interval in Experiment 2 was longer. This adjustment was made to ensure participants were adequately engaged with the task under sufficient attentional load, while also preventing the S1 and S2 from being presented so closely in time that participants might prioritise one task over the other. Lastly, pilot data indicated that the N1-P2 response to the acoustic stimuli was considerably larger than that elicited by the electrotactile pulse (evident in Figure 3.1). Therefore, lengthening the interstimulus interval was also used to minimise the risk of ERP overlaps or reduced responses due to refractory periods between S1 and S2.

3.2.4 EEG Acquisition & Pre-processing

EEG data were recorded continuously for the duration of the experiment. Data were acquired using a Biosemi ActiveTwo EEG system and ActiView (ver. 7.07) at a sampling rate of 1024 Hz with a 100 Hz low-pass online filter. Data were recorded from 64 scalp electrodes arranged according to the 10-5 system with additional electrodes placed adjacent to the outer canthi of both eyes and on the left infraorbital region. For online referencing, the Biosemi EEG system uses active electrodes with common mode sense (CMS) and driven right leg (DRL) electrodes providing a reference relative to the amplifier reference voltage.

The EEG data were processed offline in MATLAB 2021a using EEGLAB (Delorme & Makeig, 2004) and SASICA plugins (Chaumon et al., 2015). The data were re-referenced to the average of the 64 scalp electrodes, filtered from 0.1 – 40 Hz using separate low- and high-pass filters using the ‘pop_eegfiltnew’ function in EEGLAB and then down-sampled to 256 Hz. Two epochs were extracted per trial, time-locked to the presentation of the pulse for each stimulus condition. Epochs spanned from -1000 to 1000 ms and amplitudes were baseline corrected to a short pre-stimulus period prior to and avoiding the prepulse: -400 to

-200 ms (Experiment 1) and -300 to -200 ms (Experiment 2). Independent Component Analysis was conducted and independent components (ICs) containing artifacts were manually identified with the guidance of SASICA and removed to correct for blinks, horizontal saccades and other artifacts. In Experiment 1, an average of 13.88 (SD = 4.69) ICs were removed. In Experiment 2, an average of 12.88(SD = 6.06) ICs were removed. Note that the number of IC artifacts removed does not result in the removal of trials. However, trials containing voltages on analysed channels exceeding ± 100 μV were excluded, M(SD)excluded = 3.21(8.22) trials (Experiment 1), and 4.50(5.34) trials (Experiment 2).

Using algorithms described in Perrin et al. (1989) we applied a surface Laplacian filter (smoothing factor = $1e^{-5}$, order of Legendre polynomial = 10), which then transformed our data to reference-free current source density (CSD). CSD transformation reduces volume conduction effects in EEG sensor space and increases spatial resolution of the signal (Gevins et al., 1995; Kayser & Tenke, 2015). In our context, because each trial contained two temporally overlapping stimuli of interest (the pulse stimuli), the surface Laplacian was applied to prevent later ERPs to the first stimulus from masking early ERPs to the second stimulus. This process aimed to emphasise the signal we were interested in (N1/P2 complex). Voltages were measured at the central midline (Cz) based on previous cortical PPI studies of maximal inhibition (Abduljawad et al., 1999; Ford et al., 1999; San-Martin et al., 2018) as well as inspection of scalp density plots highlighting larger activation in these areas (see Figure 3.1).

In both experiments, we focused on the peak-to-peak amplitude difference. Peaks were defined using the mean amplitude of a short time window (25 ms either side) surrounding the peak of N1 and P2 components. In Experiment 2, the SOA and stimulus intensities resulted in temporal overlap of prepulse and pulse ERPs in the ‘with prepulse’ condition. To resolve this, we used the peak amplitude timings of the ‘pulse alone’ condition for both conditions. That is, instead of focussing on the specific peaks of response to the pulse in the ‘with prepulse’ condition, which are morphed by the prepulse, we focussed on the net neural response of the system at the time frames corresponding to the N1 and P2 of the ‘pulse alone’ condition. The logic here is that the processing (N1 response) of the pulse in the ‘with prepulse’ condition is still happening at this time-point, only the processing of the prepulse is added on top. Thus, the net neural response at this time may represent key

processing differences between the 'pulse-alone' and pulse 'with prepulse' which are associated with how the stimuli are perceived. For consistency we applied this method to both experiments. Therefore, we searched for the maximal peak on the grand-average data at Cz (between 50 – 170 for N1 and 140 – 300 ms for P2). The measured windows for Experiment 1 were, N1 (71 – 121 ms) and P2 (143 – 193 ms). For Experiment 2, the measured windows were N1 (91 – 141 ms) and P2 (179 – 229 ms).

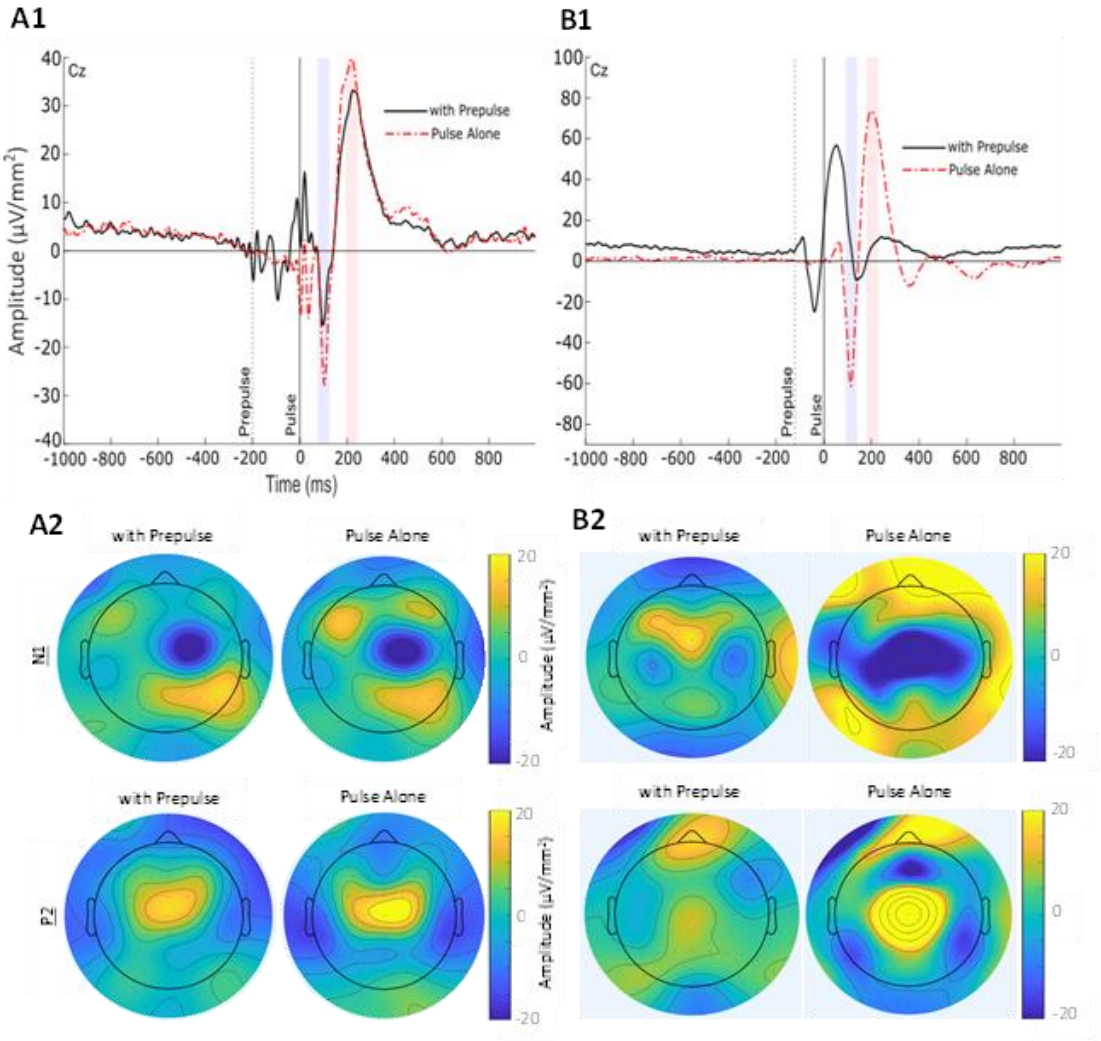


Figure 3.1. *Waveforms, and Scalp Map Distributions for N1 and P2 of Both Conditions (with Prepulse vs Pulse Alone) in Experiment 1(A) and Experiment 2(B). Note. Grand-average ERP waveforms for each stimulus condition (with prepulse = black, pulse alone = red), in both Experiment 1 (A1) and Experiment 2 (B1), with shaded areas depicting N1 and P2 measurement intervals (blue = with prepulse, red = pulse alone).* Experiment 1 (A2) and Experiment 2 (B2) *topographical plots of the grand average waveform across 'with prepulse'*

and 'pulse alone' trials for N1 and P2 over an average of the measured time intervals. All amplitudes are CSD-transformed (μV/mm^2).

3.2.4 Statistical Analysis

3.2.4.1 Experiment 1 – PPIPSI and Cortical PPI (Tactile)

All statistical analyses were conducted using R software (v3.5.1; R Foundation for Statistical Computing, Vienna, Austria). We aimed to investigate whether a relationship existed between cortical PPI (N1-P2 magnitude reduction) and PPIPSI. Because an N1-P2 response is elicited by both pulse conditions in a single PPIPSI trial, to aid interpretation of their relationship with perceived intensity, we created a N1-P2 amplitude trial difference variable by subtracting the N1-P2 response to the 'with prepulse' condition from the N1-P2 response to the 'pulse alone' condition. We fit multinomial baseline logit models using the 'mblogit' function from the 'mclogit' package 0.8.5.1 (Elff, 2020) to model the predicted odds of participants perceived intensity choice (three levels: pulse alone more intense, pulse with prepulse more intense or felt the same) as a function of Cz N1-P2 amplitude difference on a given trial. 'Pulse alone more intense' was the reference category as it was the most frequent category and reflects the occurrence of PPIPSI, and participant ID was entered as the random factor to account for subject-level variation and repeated measurement.

3.2.4.2 Experiment 2 – PPIPSI, Cortical PPI, and Attentional Load (Acoustic)

Statistical analyses were conducted using the same software as Experiment 1. A final sample of 24 participants (20 female; age M(SD) = 24.04(7.02), range = 18 – 48) were used for analyses. We conducted a trial-level multinomial baseline logit analysis to model the relationship between attentional load (levels: easy and hard), Cz N1-P2 amplitude difference, and perceived intensity responses, with participant ID as the random factor. Again, 'Pulse alone more intense' was used as the reference category as it was the most frequent category and reflects the occurrence of PPIPSI.

To investigate the possible effect of attentional load on Cz N1-P2 magnitude, we conducted a linear mixed model (LMM) analysis using a logistic regression model at the trial level. Attentional load ('Block') was set as the fixed effect predictor, and participant ID as the random factor. For this LMM we used the 'gamljMixed' function from the 'gamlj'

package (Gallucci, 2019). To gain further insight into the effect (or lack thereof) attentional load has on N1-P2 magnitude, Bayesian analyses were conducted using the 'generalTestBF' function from the 'BayesFactor' package (*v0.9.12*; Morey et al., 2018).

3.3 Results

3.3.1 Experiment 1 – Tactile

3.3.1.1 Association between Cortical PPI and PPIPSI

In this experiment, the 'pulse-alone' condition was perceived more intense on 43.19% of trials (chance level = 33.33%), providing evidence of perceptual gating. The analysis that follows seeks to determine whether cortical responses can influence perception. The multinomial logit model revealed that Cz N1-P2 magnitude difference was a statistically significant predictor of perception in both baseline comparisons. In the first comparison, 'with prepulse' more intense vs 'pulse alone' more intense the estimate for Cz N1-P2 magnitude difference was -.0059 (SE = 0.001, z = 4.40, p < .001; OR = 0.994, 95% CI [0.990, 0.999]), indicating that as Cz N1-P2 magnitude difference increases, the odds of perceiving 'pulse alone' more intense also increase. In the second comparison, 'same' vs 'pulse alone' more intense the estimate for Cz N1-P2 magnitude difference was -.0043 (SE = 0.001, z = -3.35, p < .001; OR = 0.996, 95% CI [0.992, 0.999]). Similar to the first comparison, as Cz N1-P2 magnitude differences becomes more positive the odds of perceiving the 'pulse alone' more intense increase, and the odds of perceiving the pulse-stimuli as the same decrease. The pattern of results depicted in Figure 2 shows that when the N1-P2 difference is more negative (meaning the N1-P2 response was larger in the 'with prepulse' condition) the probability of perceiving the 'pulse with prepulse' more intense is higher. Conversely, when the N1-P2 difference was more positive (meaning the N1-P2 response was larger in the 'pulse alone' condition) there is a higher probability of perceiving the 'pulse-alone' as more intense. These patterns are consistent with our hypothesis that inhibition of the N1-P2 response to the pulse, elicited by the prepulse, is associated with PPIPSI.

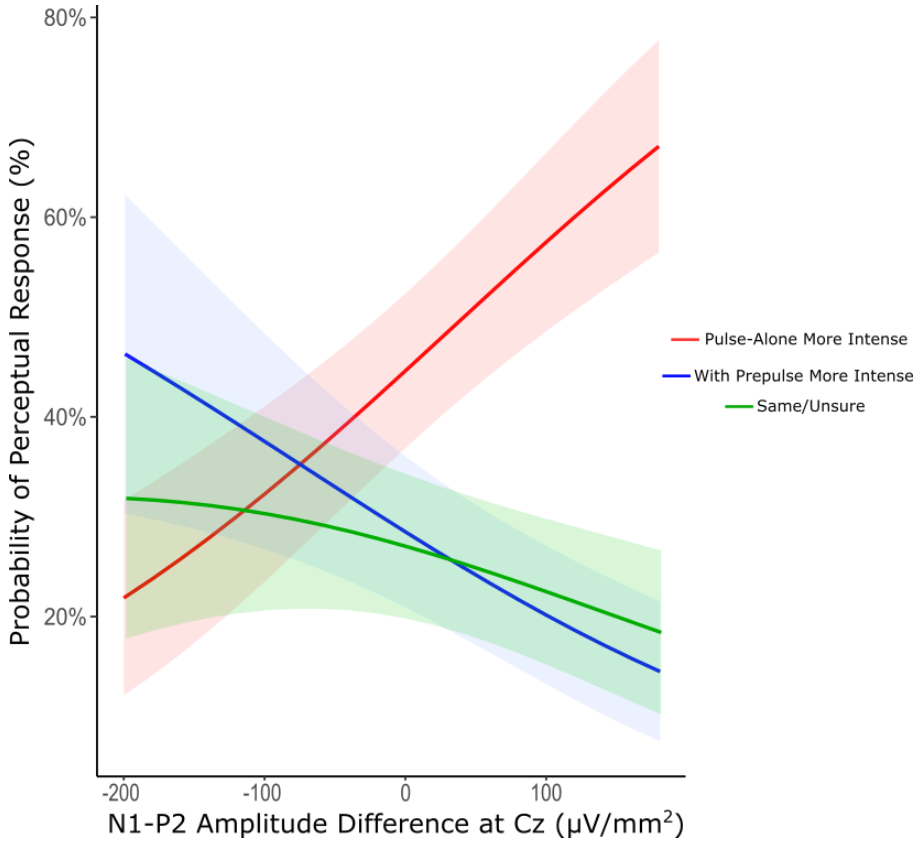


Figure 3.2. *Predicted Probabilities and Standard Error (SE) for each Perceptual Response Option as a Function of Cz N1-P2 Magnitude Difference (CSD-transformed = μV/mm²). Note. The figure demonstrates that when N1-P2 magnitude difference is more negative, the probability of perceiving the 'with prepulse' condition more intense or perceiving them the 'same' is higher. Alternatively, the probability of perceiving the 'pulse-alone' more intense increases as the N1-P2 magnitude difference becomes more positive.*

3.3.2 Experiment 2 – Acoustic

3.3.2.1 Association between Cortical PPI and PPIPSI

Here, the 'pulse-alone' condition was perceived more intense on 51.60% of trials (chance level = 33.33%), evidencing perceptual gating. The analysis that follows seeks to determine whether cortical responses can influence perception. Results from the multinomial logistic regression evidenced that Cz N1-P2 magnitude difference was not a statistically significant predictor of perception in the first comparison, 'with prepulse' more intense vs 'pulse alone' more intense (z = -0.89, p = 0.37; OR = 0.999, 95% CI [0.996, 1.002]). However, Cz N1-P2 magnitude difference was a statistically significant predictor of perception between 'same'

vs ‘pulse alone’ more intense, estimate = -0.005 (SE = -0.001, z = -3.84, $p < .001$; OR = 0.995, 95% CI [0.992, 0.999]). As depicted in Figure 3, the results indicate a relationship whereby, the more positive the Cz N1-P2 magnitude difference, the higher the probability of perceiving the ‘pulse-alone’ more intense.

3.3.2.2 Attentional Load Influences the Observation of PPIPSI

The multinomial logistic regression also found that attentional load (‘block’) was a statistically significant predictor of perception in both comparison equations. In the first comparison, ‘with prepulse’ more intense vs ‘pulse alone’ more intense the estimate effect of attentional load (‘block’) was 0.44 (SE = 0.135, z = 3.26, $p < .001$, OR = 1.552, 95% CI [1.09, 2.22]). In the second equation, ‘same’ vs ‘pulse alone’ more intense, the estimate effect of attentional load (‘block’) was 0.676 (SE = 0.15, $z = 4.61$, $p < .001$; OR = 1.96, 95% CI [1.32, 2.74]). For both comparisons, the results indicate that the probability of observing PPIPSI (‘pulse-alone’ more intense perceptions) decreased with increasing attentional load.

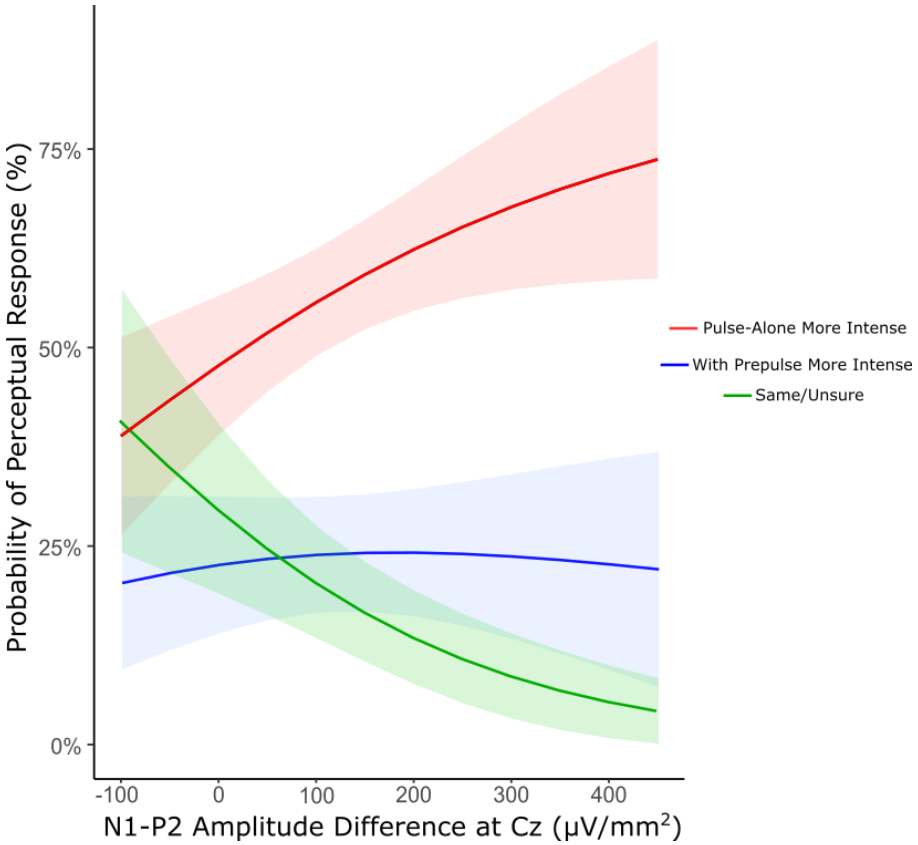


Figure 3.3. *Predicted Probabilities and Standard Error (SE) for each Perceptual Response Option as a Function of Cz N1-P2 Magnitude Difference (CSD-transformed = μV/mm²). Note. The figure demonstrates that when N1-P2 magnitude difference is more negative, the*

probability of perceiving both pulses the 'same' intensity is higher. Conversely, as the N1-P2 magnitude difference becomes increasingly positive, the probability of perceiving the 'pulse-alone' more intense also increases.

3.3.2.3 Effect of Attentional Load on Cz N1-P2 Magnitude Difference

The LMM analysis revealed no significant effects of attentional load on Cz N1-P2 amplitude difference (F(1, 1356) = 2.97, p = 0.08), with 'Easy Block' (M(SE) = 111.15 (11.50), and 'Hard Block' (M(SE) = 105.90(11.47). A follow-up Bayesian analysis to investigate the evidence for the null effect of attentional load on Cz N1-P2 amplitude difference produced a BF_{01} of 4.31, providing substantial evidence for the absence of an effect (H0 = 4.31 times more likely than H1; Jeffreys, 1961).

3.4 Discussion

In the present study we investigated the relationship between electrotactile (Experiment 1) and acoustic (Experiment 2) PPIPSI and cortical PPI, as measured by the ERP magnitudes during the N1-P2 complex timeframe. In other words, we examined how the magnitude of cortical suppression, reflected in the reduction of N1-P2 amplitudes to a pulse stimulus when preceded by a prepulse, relates to the perception of the pulse's intensity. In Experiment 2, we also examined the influence attentional load has on cortical responses and perceived intensity. In both modalities we identified that on a given trial, the larger the N1-P2 response magnitude to a pulse-stimulus is, the higher the probability participants will perceive that stimulus as more intense. Specifically, the more effectively the prepulse inhibits N1-P2 response magnitude to the pulse ('with prepulse condition'), the greater the difference will be from the N1-P2 to that same intensity pulse presented alone. As this difference increases, so too does the probability participants will perceive the 'with prepulse' less intense, demonstrating PPIPSI. These findings support previous suggestions that the processes captured in cortical PPI may contribute to the inhibition of conscious perception or perceived intensity seen in PPIPSI (Swerdlow et al., 2007). In Experiment 2, we extended our understanding of the influence attention has on cortical responses and perceived intensity. In more detail, we found that attentional load impedes the observation of PPIPSI but does not modulate the inhibitory effect a prepulse has on the N1-P2 response to a subsequent pulse (cortical PPI).

3.4.1 The Relationship between PPIPSI and Cortical PPI

Cortical PPI at central brain areas (e.g., Cz) has been suggested to represent attentional and encoding processes (Kedzior et al., 2007). Consistent with this, studies evidence that the N1 ERP represents processing of a stimulus' physical characteristics (e.g., intensity), while the P2 represents stimulus classification and decision-making processes (Annic et al., 2014; Garcia-Larrea et al., 1992). Each of these event-related potentials have been hypothesised as reflecting processes that contribute to the phenomenon of PPIPSI (Favero et al., 2022; Swerdlow et al., 2007). Thus, the current findings of a relationship between the gating of these cortical responses (cortical PPI) and PPIPSI support both the functional representation of the N1-P2 complex and their involvement in gating at the perceptual level. In other words, the reduction in these cortical responses, which represent encoding of stimulus characteristics such as intensity, correlate with the reduction in perceived intensity that is PPIPSI. This suggests that the processes captured in the N1-P2 complex are reflecting key factors that affect the perceptual experience of PPIPSI.

3.4.2 The Influence of Attention on PPIPSI, Cortical PPI, and their Relationship

Paradigm assessments by Swerdlow et al. (2005; 2007) and Favero et al. (2022) indicate that PPIPSI relies on attentional and self-monitoring mechanisms. This has been inferred from the task designs in studies of PPIPSI and time-course evidence. In PPIPSI experiments, participants are explicitly instructed to attend to the pulse stimulus to either assign an intensity rating (Swerdlow et al., 2005), or to compare and decide which pulse they perceive as more intense (with or without prepulse; Favero et al., 2022). Therefore, studies of PPIPSI employ an active design involving directed attention to the pulse and self-monitoring of perceived intensity to make relative judgements. Additionally, PPIPSI peaks at longer SOAs than startle PPI, which does not require active engagement by participants (Graham et al., 1981; Ison et al., 1991; Silverstein et al., 1980). Acoustic PPIPSI is maximal at a SOA of 120 ms+ (Swerdlow et al., 2005; 2007), and electrotactile PPIPSI emerges at SOAs greater than 122 ms (160 ms+; Favero et al., 2022). Consistent with these timings, attentional processes are said to be engaged around 120 ms after stimulus onset (Dawson et al., 1993). These findings led us to propose that PPIPSI is likely observed at longer SOAs than startle PPI because to perceive the effects of the prepulse on the subsequent pulse stimulus requires attention to be directed towards monitoring sensory inputs to the cortex. Moreover, that

attention itself requires greater time, or a larger gap between prepulse onset and pulse onset to be sufficiently ready to monitor relevant sensory channels (Favero et al., 2022). The current study extends these propositions in two ways, first by providing evidence that attentional mechanisms are engaged in PPIPSI - manipulation of attentional load significantly affects the observation of PPIPSI. Specifically, when attentional load was higher, there was a significant increase in the number of trials where 'with prepulse' more intense and 'same' were perceived, and a reduction in 'pulse alone' more intense (PPIPSI) perceptions. Secondly, our findings provide evidence that attentional resources required for PPIPSI might be used to access stimulus traces or representations reflected within the N1-P2 cortical response.

We found a relationship between PPIPSI and N1-P2 magnitude that is consistent with the functional representation of the N1-P2 complex. These are the processing or encoding of a stimulus' physical characteristics (e.g. intensity), and stimulus classification (Annic et al., 2014; Kedzior et al., 2007; Garcia-Larrea et al., 1992). Of course, it is possible that the additional attentional load could have impacted the magnitude of the N1-P2 complex, rather than making it more challenging to monitor them as we hypothesized. Our finding that the N1-P2 magnitude was unaffected by attentional load, whereas PPIPSI was clearly impacted by our manipulation renders this explanation unlikely. In a cortical PPI study, Annic et al. (2014) observed an effect of stimulus-driven, and goal-directed attention to the prepulse on the N1 and P2 cortical responses. They found the N1 response to the pulse was inhibited more by stimulus-driven attention to the prepulse, while P2 was inhibited by goal-directed attention to the prepulse, when compared to a 'do not attend' condition. At first, our lack of an effect of cognitive load on the N1-P2 complex might seem contradictory to Annic et al's. (2014) findings. However, differences in the designs of the two studies might explain this discrepancy. First, we manipulated attentional load, not goal or stimulus-driven attention. In addition, attention is directed towards the pulse in PPIPSI paradigms, while in Annic et al. (2014) attention was directed towards the prepulse, and the pulse was considered irrelevant. One possible synthesis of these differences is that Annic et al. (2014) investigated how allocation of attention to a prestimulus affects the cortical response to a subsequent, more intense stimulus; thus, demonstrating that the inhibitory effect of a prepulse on the N1 and P2 cortical responses to a subsequent stimulus is

enhanced by stimulus-driven and goal-directed attention to the prepulse. This indicates that attention driven by stimulus properties (stimulus-driven) and goal-directed attention to the prepulse influence PPI by modulating the pulse stimulus's sensory characteristics (e.g., intensity) and cognitive evaluation (Annic et al., 2014). In our experiment, we manipulated the availability of attentional resources to be allocated towards the pulse-stimuli (sensory inputs), appraising their characteristics (i.e., intensity) and evaluating these characteristics in comparison to each other. When attention is goal-directed or stimulus-driven by the prepulse, the cortical response to the pulse is further inhibited (Annic et al., 2014), but general manipulation of the availability of attentional resources does not affect the cortical response (as shown here in Experiment 2). These results suggest that attention to the prepulse enhances the inhibitory effects of the prepulse, but attentional load has little effect on the information that reaches the cortex. Conversely, attentional load appears to impair PPIPSI. This finding suggests that PPIPSI may partially rely on the allocation of attentional resources to monitor cortical responses so that accurate perceptual inferences can occur.

It may be argued that the attentional load tasks were not difficult enough to interfere with N1-P2 attentional processing, or that participants prioritised the perception task. To check this, we conducted a paired t-test to compare counting task performance between the Easy and Hard conditions. The results revealed that the average percentage of correct responses was significantly higher in the Easy Task (M = 91.42, SD = 27.22) compared to the Hard Task (M = 29.44, SD = 45.60), $t(1439) = 46.80$, $p < .001$, 95% CI [0.60, 0.65]. The high percentage correct in the Easy Task indicates that participants were engaging with the attentional load task. It is also evident that participants performed worse in the Hard Task, suggesting it was sufficiently difficult to recruit more attentional resources. These data, combined with the finding that attentional load influenced PPIPSI observation, make these alternative explanations unlikely. The current findings are consistent with Näätänen and Winkler's (1999) model of auditory processing. The N1-P2 complex likely reflects pre-attentive encoding of a stimulus trace or representation. Furthermore, the link between cortical responses and conscious perception appears to be via the perceptual mechanisms directing attention towards cortical processes. This direction of attention towards the

cortical responses then brings their contained information into conscious perception (Näätänen and Winkler, 1999).

3.4.3 Prepulse as Temporal Cue

One further way attention may modulate PPIPSI is by the prepulse acting as a temporal cue for the timely allocation of attentional resources. Annic et al. (2014) demonstrated that a salient prepulse recruits' stimulus-driven attention, enhancing cortical PPI. Although we did not manipulate attention to the prepulse directly, it is likely that a prepulse of perceptible intensity, at an SOA which makes it perceivably distinct from the pulse, engages a degree of stimulus-driven attention. Consistent with this, we previously proposed that in combination with inhibiting processing of the pulse, in PPIPSI, the prepulse may facilitate directing attention towards monitoring inputs to the cortex (Favero et al., 2022). Our findings of a relationship between PPIPSI and cortical PPI, and the effect of attentional load support the proposition that attentional resources are required for more reliable observation of PPIPSI.

Experiments in other paradigms have demonstrated that temporal predictability facilitates the allocation of cognitive resources to task relevant processes (Nobre & van Ede, 2018). For example, in motor preparation experiments where a response to a target stimulus must be made as fast as possible, the introduction of a warning stimulus reduces reaction time (RT; Alegria, 1975; Muller-Gethmann et al., 2003). This is said to occur because the resources used to hold motor responses in a high state of preparation are finite, only optimal 100 – 300 ms prior to target stimulus onset (Alegria, 1975; Muller-Gethmann et al., 2003). Thus, presenting a warning signal approximately 200 ms prior to the target stimulus facilitates the optimal allocation of resources towards motor preparation, reducing reaction time. Moreover, when a movement is being prepared, suppression of corticospinal excitability occurs, known as preparatory suppression (Hasbroucq et al., 1997). However, under time constraints which limit movement preparation, preparatory inhibition does not occur, leading to greater response disruption by external stimuli (McInnes et al., 2021). Similarly, studies have evidenced that attentional orienting facilitated by a cue is most effective when presented 100 – 200ms prior to a target (Nakayama & MacKeben, 1989; Egeth & Yantis, 1997). In visual perception, anticipatory cues presented 100 ms before a target enhance visual target representations and delay interference by distractor stimuli

on the target's cortical representation (van Ede et al., 2018). van Ede et al. (2018) interpret this enhanced target detection and minimised interference by distractor stimuli as indication that cued anticipation aids perception by enabling a 'protective temporal window' from distractor interferences (van Ede et al., 2018). The above findings from different research domains suggest a common mechanism may be involved. Consistent with Brunia's (1993) proposition that motor and attention processes use similar mechanisms, the attention allocated to perceiving the pulse (monitoring the sensory input channels) likely cannot stay in an optimal state the entirety of a trial in PPIPSI paradigms, because the timing of pulse presentations is uncertain. Therefore, the prepulse may (even if indirectly) facilitate the allocation of attention towards monitoring inputs to the cortex which process the pulse-stimulus. This may contribute to why PPIPSI requires longer SOAs than startle PPI, because the attentional shift towards monitoring sensory inputs aided by the prepulse requires greater time.

Here, we demonstrate that increased attentional load hinders PPIPSI. If the time-course of PPIPSI is modulated by the allocation of attentional resources to monitor inputs to the cortex, PPIPSI may be observable at shorter SOAs if attention can be allocated faster or more efficiently. This could be investigated by manipulating temporal predictability. Studies show that expectation assists the allocation of attention (Zhao et al., 2013), and selective attention aids perception by prioritising sensory inputs based on their salience or relevance to tasks aims (Desimone & Duncan, 1995; Nobre & van Ede, 2018; Summerfield & Lange, 2014). Therefore, making the presentation of the prepulse and pulse stimuli temporally predictable (presented at the same time in each trial), might speed directed attention towards monitoring inputs to the cortex. We are not proposing that this is the mechanism by which the prepulse inhibits responses to the pulse, but that this is a way by which cortical changes induced by prepulses might enter consciousness more easily. Cortical PPI at central locations is elicited using SOAs of 50 – 140 ms (San-Martin et al., 2018). Based on our results, indicating that the inhibition of the N1-P2 cortical response is linked to perceived intensity, and previous findings that larger cortical inhibition might be more prominent at shorter SOAs (San-Martin et al., 2018), we propose that the manipulation of temporal predictability using cues could enhance the observation of PPIPSI at shorter SOAs, matching that of cortical PPI.

3.4.4 Similarities and Differences between Tactile and Acoustic modalities

The general finding from the current experiments is that the relationship between N1-P2 magnitude and PPIPSI is observed for both tactile and acoustic stimuli. However, it must be highlighted that in the tactile modality (Experiment 1), N1-P2 magnitude differences were a significant predictor of perceptual responses at both levels of comparison ('pulse-alone more intense' vs 'with prepulse more intense' and 'pulse-alone more intense' vs 'same'). In contrast, in the acoustic modality, N1-P2 magnitude difference was a significant predictor of perceptual response only for the 'pulse-alone more intense' vs 'same' comparison in Experiment 2. Differences in results across experiments may be explained by differences in stimulus parameters (e.g. intensity), and influence of the additional task in Experiment 2. In Experiment 2, the influence of the attentional load task likely affected the relationship between N1-P2 magnitude difference and perceptual responses. This is evident from the increase in 'same' responses between high and low attentional load conditions. One explanation is that attentional load increases perceptual uncertainty resulting in participants selecting 'same/unsure'. Subsequently, weakening the relationship between N1-P2 magnitude difference and perceptual comparisons of 'pulse-alone more intense' and 'with prepulse more intense'. This possibility may be investigated further by reproducing Experiment 2 with a greater number of trials, and no manipulation of attentional load.

Previous studies suggest that startle PPI and PPIPSI are sensitive to prepulse and pulse intensity (Blumenthal et al., 2015; Swerdlow et al., 2005). Acoustic studies have found that both startle PPI and PPIPSI increase with increasing prepulse and pulse intensity, to a certain threshold, after which decrements are observed with further intensity increases (Swerdlow et al., 1999; Swerdlow et al., 2007). In Experiment 1, we used parameters previously identified as optimal for electrotactile PPIPSI (Favero et al., 2022), and because electrotactile stimuli are more subjectively aversive than acoustic (Sperl et al., 2016) this entailed individualised intensity settings as opposed to predetermined ones. By contrast, in experiments 2 we used predetermined intensities for our stimuli, informed by maximal acoustic PPIPSI findings (Swerdlow et al., 2005; 2007). It is possible that the use of individualised intensities in Experiment 1 led to weaker overall stimulus intensities, particularly for the prepulse which was set to 2x perceptual threshold (M(SD) intensity = 0.70mA (0.39) compared to an 80dB prepulse in the acoustic experiments. Although

translating stimulus intensity across modalities is difficult, the N1-P2 magnitudes were larger in the acoustic experiments, indicating the stimuli were physically more intense (Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008). Moreover, the acoustic prepulse appears to have had a greater inhibitory effect on the N1-P2 response to the pulse. Thus, it may be that the intensity of the acoustic stimuli was more effective in eliciting gating, but the link between cortical and perceptual gating is weakened – possibly due to the overlapping of prepulse and pulse N1-P2 signals caused by the higher intensity prepulse and shorter SOA.

3.4.5 Limitations and Considerations

Previous studies have identified sex dimorphism and menstrual cyclicity effects on baseline startle PPI measurements (Swerdlow et al., 1999). As such, the predominantly female sample in the current study deserves consideration. While PPI and PPIPSI may share lower-level gating mechanisms, previous studies have shown that PPIPSI is not affected by sex differences or menstrual cyclicity (Swerdlow et al., 2005). Nonetheless, we found that in both experiments group proportion of PPIPSI trials and directional effects were qualitatively similar between males and females: Experiment 1 (M(SD) proportion of PPIPSI trials for males = 0.57(0.42), and females = 0.57(0.40), and Experiment 2 (M(SD) males = 0.59(0.44), and females = 0.64(0.41). These results suggest the imbalanced sample is unlikely to have affected our findings.

Our application of a surface Laplacian filter which converts the EEG data to CSD should be considered when interpreting and comparing the current data with other studies. Surface Laplacian is a mathematical transformation applied to EEG surface potentials designed to mitigate EEG signals reference dependence and masking of smaller signals by volume conduction (Kayser & Tenke, 2015). Surface Laplacian enhances EEG signals spatial resolution by dampening ERP components with broad spatial distributions which would otherwise mask smaller transient signals in the EEG (Gevins et al., 1995; Nunez & Srinivasan, 2014). We applied this filter because each trial contained two stimuli of interest, and a concern was that the late ERP signals to the first stimulus (which are typically long with broad spatial distributions) could interfere with the early ERPs of the second stimulus, such as the N1/P2 complex which were of specific interest. Consequently, the surface Laplacian was used to emphasise the transient and focal N1/P2 complex by filtering away ERP

components of less interest (broad spatial distributions). Lastly, because surface Laplacian is computed from signal differences which filter out lower frequency components, one further concern is that these transformed signals may become more susceptible to noise (Bradshaw & Wikswo, 2001). Noise, including recording artifacts, tends to be of high spatial frequencies and, therefore, by amplifying higher spatial frequencies, Laplacian can increase noises representation in the signal (Bradshaw & Wikswo, 2001). However, noise added by the surface Laplacian filter is unlikely to be a major issue in the current study due to the high quality of our recorded data (Kayser & Tenke, 2015; see the waveforms and scalp maps for non-transformed data in Appendix A).

3.4.6 Conclusion

In the present study we investigated the relationship between cortical PPI and PPIPSI. We also examined the effect attention has on both by manipulating attentional load. We observed a relationship between N1-P2 magnitude difference and relative judgments of perceived intensity, which produced a pattern of results consistent across both electrotactile and acoustic modalities. When the N1-P2 magnitude was larger for a specific pulse-stimulus, the probability that pulse would be perceived more intense was higher. This means that when the prepulse effectively inhibited the N1-P2 response to the subsequent pulse (cortical PPI), the probability that participants would perceive the 'pulse-alone' more intense increased (demonstrating PPIPSI). Our findings are consistent with studies which attribute the N1-P2 response to processes of encoding stimulus characteristics such as intensity (Annic et al., 2014; Garcia-Larrea et al., 1992; Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008). In addition, our results extend this evidence by demonstrating a link between N1-P2 gating, and gating of conscious perception within the PPI/PPIPSI paradigm. This suggests a relationship by which the processes captured in the N1-P2 response contribute to the perceptual experience of PPIPSI. We identified that increased attentional load impedes the observation of PPIPSI, providing evidence in support of propositions that perceptual gating involves the recruitment of attentional processes (Favero et al., 2022; Swerdlow et al., 2005). Moreover, the finding that attentional load affects PPIPSI, but not cortical PPI further characterises their relationship. It appears that what reaches the cortex (N1-P2) is largely free of attentional processes, but to consciously perceive that gating has occurred requires directing attention to processes captured in these cortical responses. That

is, consistent with Näätänen and Winkler (1999), these cortical processes are likely preattentive and driven by stimuli features, after which attention is used to access this information and form a conscious perception. We conclude that PPIPSI may be less (or not) observed at SOAs as brief as those which elicit startle PPI because, even if driven indirectly by the prepulse, directing attention to the appropriate cortical processes requires more time. Given that cortical PPI is observed using shorter SOAs (50 – 80 ms; San-Martin et al., 2018), we propose that if attention can be directed to these processes faster or more optimally, the time-course of PPIPSI may too be shortened. A future study could investigate this by manipulating temporal predictability, which has been found to enhance the allocation of attentional resources and facilitate perception in other studies (Desimone & Duncan, 1995; Nobre & van Ede, 2018; Summerfield & Lange, 2014; Zhao et al., 2013).

3.5 Appendix A

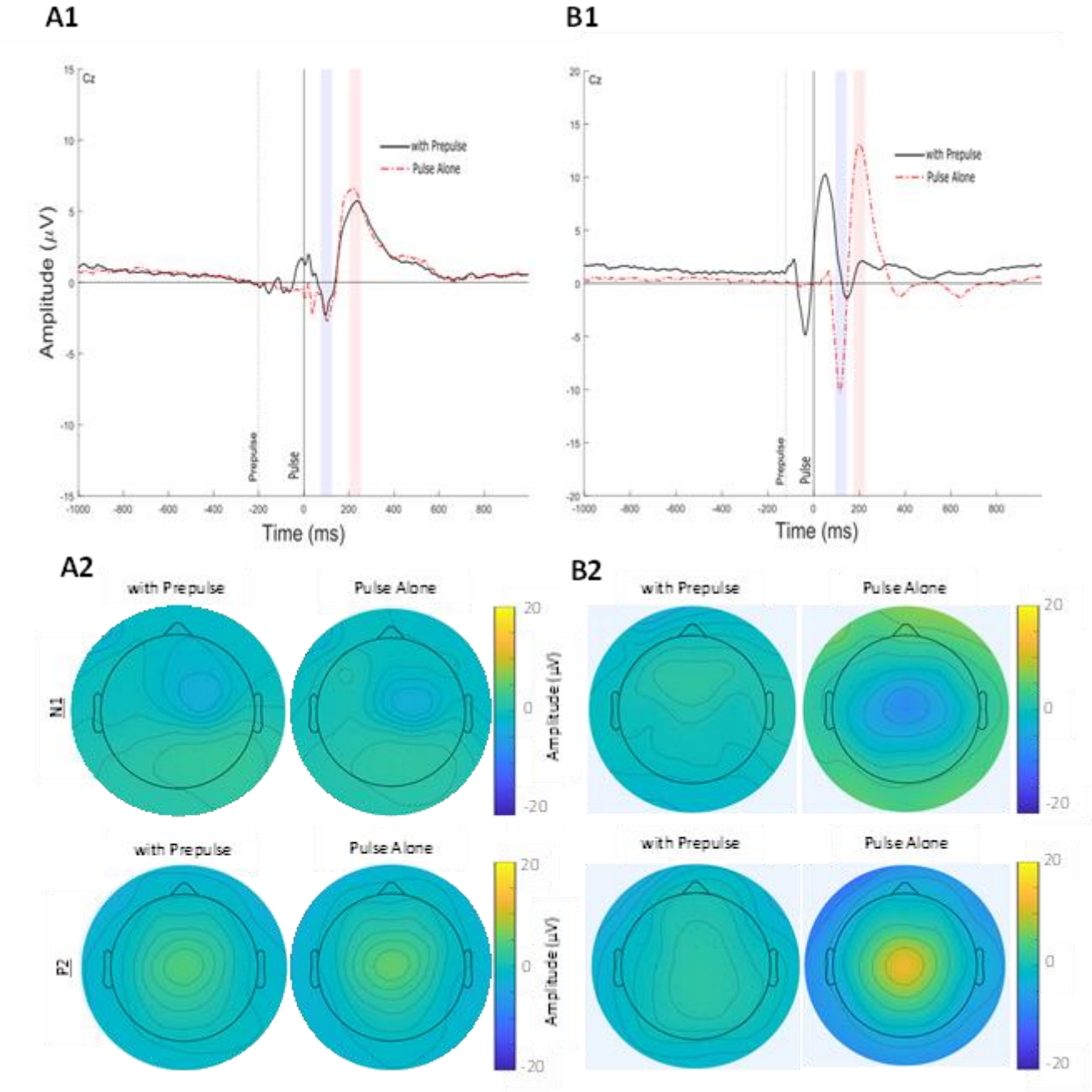


Figure 3.4. *Non-CSD Waveforms, and Non-CSD Scalp Map Distributions for N1 and P2 of Both Conditions (with Prepulse vs Pulse Alone) in Experiment 1(A) and Experiment 2(B). Note. Grand-average ERP waveforms for each stimulus condition (with prepulse = black, pulse alone = red), in both Experiment 1 (A1) and Experiment 2 (B1), with shaded areas depicting N1 and P2 measurement intervals (blue = with prepulse, red = pulse alone).* Experiment 1 (A2) and Experiment 2 (B2) *topographical plots of the grand average waveform across 'with prepulse' and 'pulse alone' trials for N1 and P2 over an average of the measured time intervals. Unit of measurement = microvolts (μV).*

CHAPTER FOUR: THE EFFECT OF TEMPORAL PREDICTABILITY ON SENSORY GATING: CORTICAL RESPONSES INFORM PERCEPTION

4.0 Abstract

Prepulse inhibition of perceived stimulus intensity (PPIPSI) is a phenomenon where a weak stimulus preceding a stronger one reduces the perceived intensity of the latter. Previous studies have shown that PPIPSI relies on attention and is sensitive to stimulus onset asynchrony (SOA). Longer SOAs may increase conscious awareness of the impact of gating mechanisms on perception by allowing more time for attention to be directed towards relevant processing channels. In other psychophysiological paradigms, temporal predictability improves attention to task relevant stimuli and processes. We hypothesised that temporal predictability may similarly facilitate attention being directed towards the pulse and its processing in PPIPSI. To examine this, we conducted a 2 (SOA: 90 ms, 150 ms) X 2 (Predictability: low, high) experiment, where participants were tasked with comparing the perceived intensity of an acoustic pulse-alone against one preceded by a prepulse. The relationship between PPIPSI and cortical PPI (N1-P2 inhibition) was also investigated. Significant main effects of temporal predictability, SOA, and cortical PPI were revealed. Under high temporal predictability, both SOAs (90 ms and 150 ms) elicited greater PPIPSI. The findings indicate that temporal predictability enhances the timely allocation of finite attentional resources, increasing PPIPSI observations by facilitating perceptual access to the gated pulse signal. Moreover, the finding that reductions in N1-P2 magnitude by a prepulse are associated with increased probability of the participants perceiving the pulse 'with prepulse' as less intense, suggests that under various experimental conditions, the link between these cortical processes and perception is similarly engaged.

4.1 Introduction

Prepulse inhibition of perceived stimulus intensity (PPIPSI) is a phenomenon in which the presence of a weaker stimulus (prepulse) immediately before a stronger stimulus (pulse) reduces the perceived intensity of that stronger stimulus (Swerdlow et al., 2005). PPIPSI belongs to a family of sensory gating and sensorimotor gating phenomena. Sensory gating is concerned with the filtering or suppression of incoming sensory information. Because PPIPSI involves perceptual judgments of intensity, it is used as a tool to investigate sensory gating of conscious perception (Favero et al., 2022; Swerdlow et al., 2005). Another form of sensory gating is cortical prepulse inhibition (cortical PPI), where a prepulse is known to inhibit the N1 and P2 event-related potentials (ERP) to a subsequent stimulus (e.g. pulse) at central and centroparietal areas in human subjects (Dawson et al., 2004; Favero et al., 2023; Kedzior et al., 2007; San-Martin et al., 2018). Cortical PPI is believed to provide information about cortical processing of stimuli, such as salience and intensity (Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008; San-Martin et al., 2018).

Previous studies have demonstrated a relationship between cortical PPI and PPIPSI, with greater N1-P2 cortical response inhibition by the prepulse being associated with a higher probability of participants perceiving the pulse-alone condition as more intense (Favero et al., 2023). Favero et al.'s (2023) findings align with previous evidence that the N1-P2 component of the brain's response represents functionally relevant processes to PPIPSI, such as those involved in processing the physical characteristics of a stimulus (e.g., intensity; Annic et al., 2014; Garcia-Larrea et al., 1992). For example, N1 and P2 magnitude both increase as a function of stimulus intensity (Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008). N1-P2's association with PPIPSI in Favero et al. (2023) is also congruent with Näätänen and Winkler's (1999) concept of N1's role in auditory stimuli representations, and how they reach conscious perception. These findings suggest that PPIPSI is informed by processes captured in the N1-P2 cortical response, potentially driven by the prepulse facilitating an attentional shift towards the pulse and its related processing channels (Favero et al., 2023).

PPIPSI involves participants actively making relative intensity judgments and requires longer SOAs compared to other gating phenomena, such as startle PPI, suggesting engagement of attentional processes (*for a discussion see:* Swerdlow et al., 2005; Favero et

al., 2022). This is inferred from the active task design, which directs attention towards the pulse stimuli, and the longer SOA needed to observe PPIPSI, indicating that more time is required for higher-order (e.g., attentional) processes to be sufficiently engaged. To investigate the influence of attention on PPIPSI, Favero et al. (2023) manipulated attentional load and found that increased attentional load reduced the observation of PPIPSI. Specifically, when attention was divided and fewer attentional resources were available, PPIPSI became less frequent. These findings align with the broader literature suggesting that selective attention aids perception by prioritising sensory inputs based on their salience or relevance to task aims (Desimone & Duncan, 1995; Nobre & van Ede, 2018; Summerfield & Lange, 2014).

Based on the findings from Favero et al. (2022; 2023), we propose that PPIPSI's dependence on longer SOAs may be due to the prepulse acting as a cue, allocating additional resources to process the pulse. A large body of evidence, across psychophysical paradigms, indicates that expectation (Zhao et al., 2013) and temporal predictability, optimise the allocation of attention and other cognitive resources to task relevant processes (Alegria, 1974; Nobre & van Ede, 2018). For example, in motor preparation experiments, the neural resources required to keep the prepared response in an optimal state is brief (100 – 300 ms pre target onset; Alegria, 1974; Muller-Gethmann et al., 2003). Here, the use of a 'warning stimulus' (like a prepulse, or cue) presented approximately 200 ms before the stimulus requiring a motor response facilitates the optimal allocation of resources towards motor preparation, resulting in reduced reaction times (RT; Alegria, 1974; Muller-Gethmann et al., 2003). Similarly, visual perception studies have shown that orienting attention is sped up by presenting a cue 100 – 200 ms prior to the target stimulus (Nakayama & MacKeben, 1989; Egeth & Yantis, 1997).

In PPIPSI experiments, the unpredictability of pulse presentation within a trial poses a challenge, as directing attention is a time-consuming process and it cannot be held at peak levels indefinitely due to its finite nature (Petersen & Posner, 2012; Swallow & Jiang, 2013). This is comparable to the challenges encountered in motor preparation studies (Alegria, 1974; Muller-Gethmann et al., 2003), where heightened preparedness to produce a movement can only be maintained for brief periods. Therefore, a prepulse presented well in

advance of the pulse (100 – 200 ms) may facilitate the allocation of attentional resources when they are most needed.

Although it is possible that the prepulse triggers an automatic allocation of attention towards monitoring the pulse, the influence of temporal predictability on PPIPSI is yet to be investigated. Evidence suggests that attention to the pulse is central to perceiving its intensity and inhibition by a prepulse (Favero et al., 2023; Swerdlow et al., 2005). It appears that the SOA range necessary to observe PPIPSI is linked to the time required for this attentional shift. While attention is a finite resource that cannot be shifted without neural delays, temporal predictability may facilitate the allocation of attentional resources in advance and improve the conscious perception of PPIPSI at shorter SOAs (Favero et al., 2023; Nobre & van Ede, 2018). In the present study, we sought to investigate this possibility. More precisely, we examined the influence of temporal predictability on PPIPSI at different SOAs. We also collected EEG data to identify whether the previously found relationship between PPIPSI and cortical PPI in Favero et al. (2023) is consistent across experimental manipulations.

4.2 Methods

4.2.1 Participants

Participants were Curtin University undergraduate students who participated in exchange for course credit. Our sample sizes were based on our prior studies using the same protocol employed in the current study (Favero et al., 2022; Favero et al., 2023), where we collected between 22 and 25 participants. This range is similar to that of a related study by San-Martin et al. (2018), which recruited 22 participants to examine cortical PPI. Subsequently, 24 participants (19 female) were recruited (age M(SD) = 23.66(8.33) years, range = 18 – 56 years). All participants self-reported having normal or corrected-to-normal vision and hearing, with no known neurological conditions or injuries that may affect their performance in the experiment. Informed written consent was provided by all participants prior to participation, in accordance with the Declaration of Helsinki and the experiment protocol was approved by the Curtin University human research ethics committee (Approval Code: HRE2018-0257).

4.2.2 Pre-Experiment Procedures

We used a within-participant repeated measures design. Participants were seated at a desk 57 cm in front of a 24-inch BenQ LCD monitor (1920×1080 resolution; 120 Hz refresh rate), with both arms rested on the desk. This monitor was used to present visual prompts and stimuli to participants during the experiment.

Acoustic stimuli were generated using the computer's motherboard and delivered binaurally through stereophonic headphones (Model: HD25-1 II). The selection of stimulus duration and intensity were based on optimal parameters for PPIPSI as reported by Swerdlow et al. (1999; 2005) and others (San-Martin et al., 2018; Favero et al., 2023). The pulse-stimulus was a 50 ms duration white noise burst (rise and fall time < 1.5 ms), calibrated to 100 dB. The prepulse-stimulus was also a white noise burst (rise and fall time < 1.5 ms), but 30 ms in duration and calibrated to 80 dB.

4.2.3 Procedures

To examine the effects of (1) SOA and (2) temporal predictability on the observation of PPIPSI, we used a 2 (SOA: 90 ms, 150 ms) X 2 (Predictability: low, high) design. The task was the same in all conditions: compare and report which pulse-stimulus (‘pulse-alone’ vs ‘with prepulse’) was more intense. The experiment consisted of 240 trials, 60 trials per condition type. Stimulus conditions were randomised with an equal number of ‘pulse alone’ and ‘with prepulse’ first trials. The SOA presented in each trial (90 ms or 150 ms) was randomised, meaning that trials were not ran in blocks of each SOA level. To commence the experiment, a prompt stating “press any button to start” was displayed on the screen, 1 second after participants pressed a key, a green clocklike circle would appear on the screen. In the high predictability trials, this clock’s centre would initially start out black, and fill frame-by-frame with green starting from the 12:00 position, the clock took 3 seconds to completely fill (return to 12:00 position) at which point the first pulse-stimulus (S1) was presented. After the clock filled and S1 had been presented the screen went blank for 2 seconds, then the clock reset and began to fill again, taking the same 3 seconds duration to completely fill at which point the second pulse-stimulus (S2) was presented. In the low predictability trials, the green clock-like circle would appear prefilled, and remain stationary the entire trial, providing less insight into when acoustic stimuli would be presented. However, the timings

were the same. Therefore, S1 was always presented 4 seconds into a trial (3 seconds from clock appearance), and the interval between S1 and S2 was 5 seconds. 1 second after S2 had been delivered, participants were prompted to select via mouse clicking: “which noise pulse was more intense (left-click = first stimulus; S1, right-click = second stimulus; S2 or felt the same = middle-click)?”. 2 seconds after a response had been selected, a trial number indicator would appear in the centre of the screen (e.g. “trial 2”) for 1 second before the clock-like circle presented on-screen. Therefore, the time between trials was 2 seconds. For a visual representation of trials and timings, see Figure 4.1.

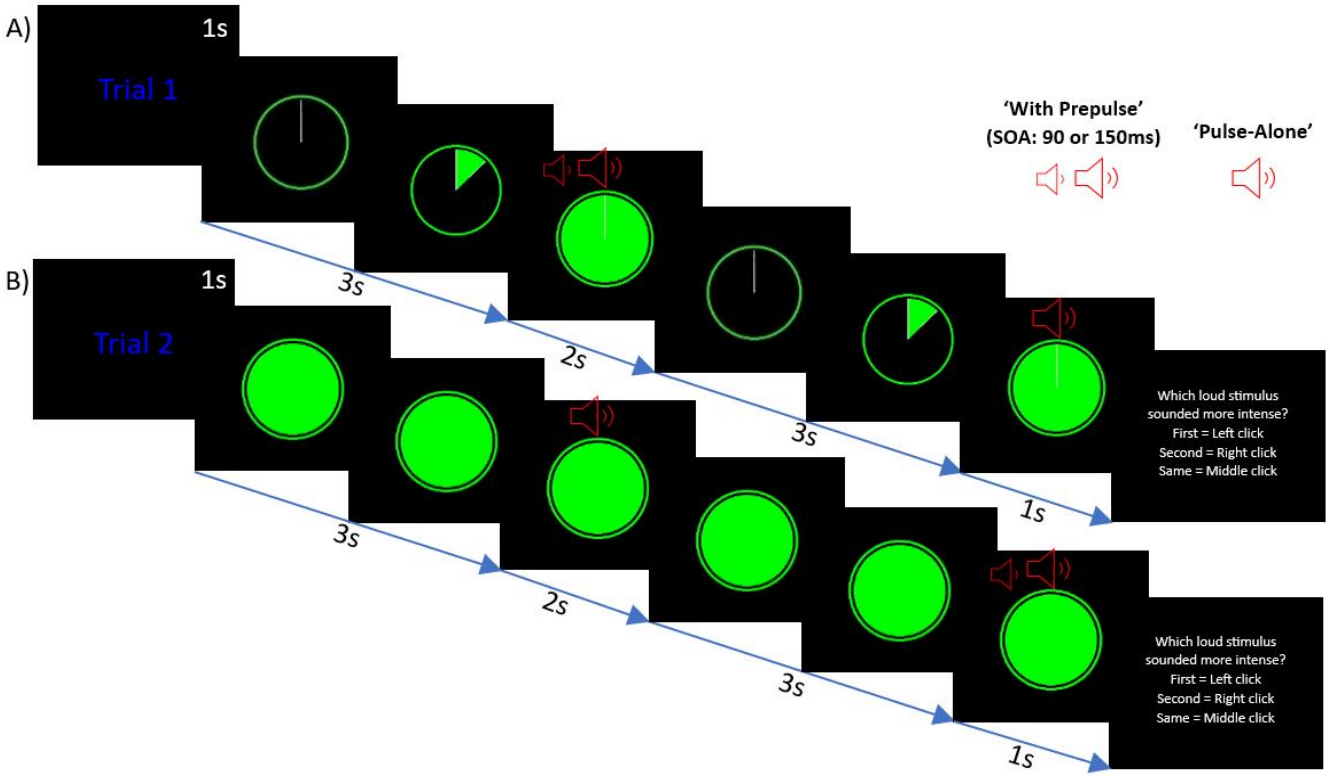


Figure 4.1. *Visual representation of experiment (in actual experiment trial type was randomised). Note: A = high temporal predictability, B = low temporal predictability. In the high predictability trials, pulse stimulus onset in both conditions was synchronised with clock filling completion. Two seconds after S1 of a trial the clock reset and began filling again. In the low predictability trials, an unchanging green circle was onscreen the entire duration, but stimuli were presented at the same time as in the high predictability trials.*

4.2.4 EEG Acquisition & Pre-processing

EEG data were recorded continuously for the duration of the experiment. Data were acquired using a Biosemi ActiveTwo EEG system and ActiView (ver. 7.07), at a sampling rate of 1024 Hz with a 100 Hz low-pass online filter. Data were recorded from 64 scalp electrodes, arranged according to the 20-10 system, with additional electrodes placed adjacent to the outer canthi of both eyes and on the left infraorbital region. For online referencing, the Biosemi EEG system uses active electrodes with common mode sense (CMS) and driven right leg (DRL) electrodes providing a reference relative to the amplifier reference voltage.

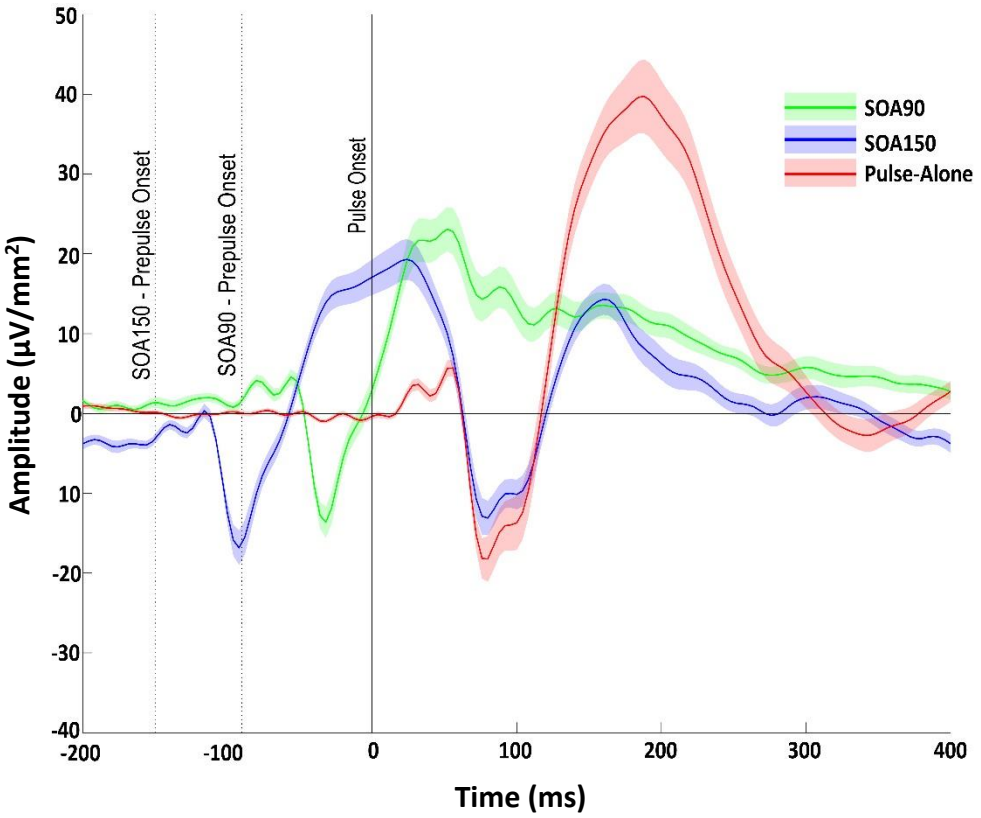
The EEG data were processed offline in MATLAB 2021a using EEGLAB (Delorme & Makeig, 2004) and SASICA plugins (Chaumon et al., 2015). The data were re-referenced to the average of the 64 scalp electrodes, filtered from 0.1 – 40 Hz using separate low- and high-pass filters using the 'pop_eegfiltnew' function in EEGLAB and then down-sampled to 256 Hz. Time-locked to the presentation of the pulse for each stimulus condition, two epochs were extracted per trial. Epochs spanned from -1000 to 1000 ms, and amplitudes were baseline-corrected to a short pre-stimulus period, avoiding the prepulse: -400 to -200 ms. Independent Component Analysis was conducted and independent components (ICs) containing artifacts were manually identified with the guidance of SASICA and removed to correct for blinks, horizontal saccades and other artifacts, M(SD)removed = 11.25 (3.17). Trials containing voltages on analysed channels exceeding ± 75 µV were excluded, M(SD)excluded = 16.12 (18.46) trials.

Using algorithms described in Perrin et al. (1989), we applied a surface Laplacian filter (smoothing factor = $1e^{-5}$, order of Legendre polynomial = 10), which then transformed our data to reference-free current source density (CSD). CSD transformation reduces volume conduction effects in EEG sensor space and increases spatial resolution of the signal (Gevins et al., 1995; Kayser & Tenke, 2015). In our context, because each trial contained two temporally overlapping stimuli of interest (the pulse stimuli), the surface Laplacian was applied to prevent later ERPs to the first stimulus from masking early ERPs to the second stimulus. This process aimed to emphasise the signal we were interested in (N1/P2 complex). Voltages were measured at the central midline (Cz) based on previous cortical PPI studies of maximal inhibition (Abduljawad et al., 1999; Ford et al., 1999; San-Martin et al.,

2018) as well as inspection of scalp density plots highlighting larger activation in this area (see Figure 4.2).

Consistent with our previous experiments (Favero et al., 2023), we focused on the net neural response of the whole system at the time frames corresponding to the N1 and P2 of the 'pulse alone' condition. The rationale for this is taking an additive approach to the signal overlap of prepulse processing on the N1 response to the pulse in the 'with prepulse' condition. Peaks were defined using the mean amplitude of a short time window (25 ms either side) surrounding the peak of N1 and P2 components from the 'pulse alone' condition. Therefore, we searched for the maximal peak on the grand-average data at Cz (between 50 – 150 for N1 and 140 – 300 ms for P2). The measured windows were: N1 (71 – 121 ms) and P2 (143 – 193 ms). We then created an N1-P2 difference variable by subtracting the extracted N1 peak from the P2 peak for each condition at the trial level.

A.



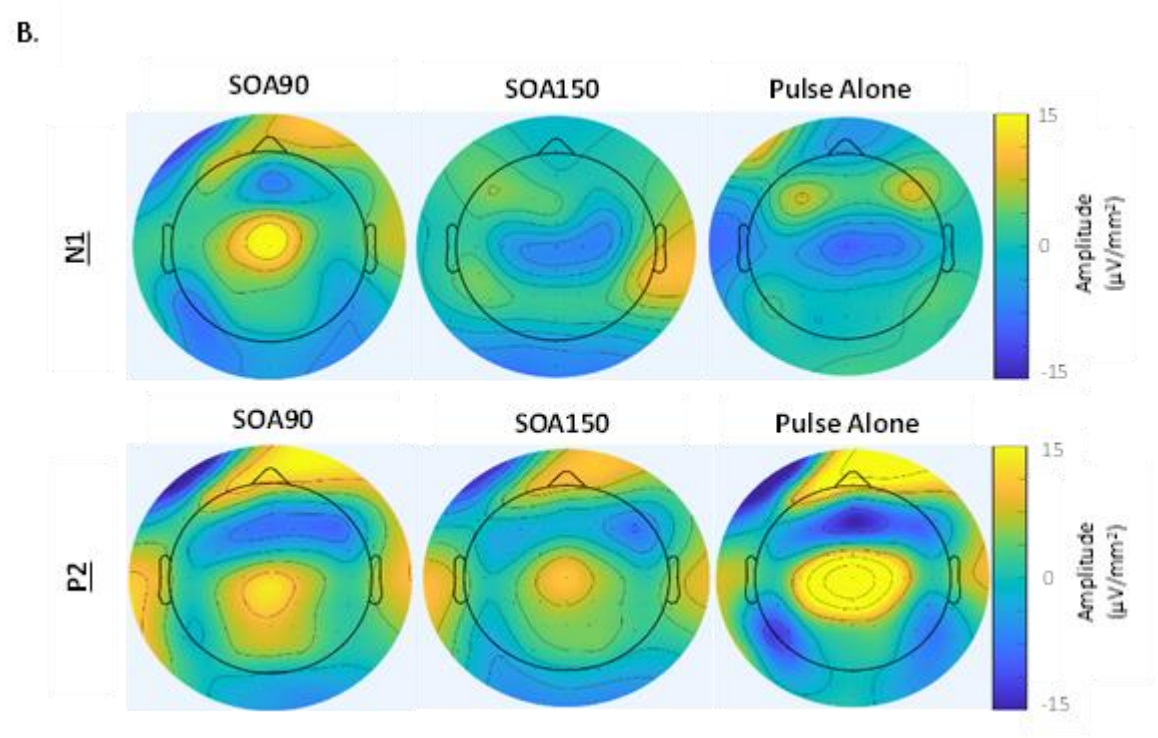


Figure 4.2. *A) Waveforms and Standard Error of the Mean for each SOA (SOA90 = green, SOA150 = blue, Pulse Alone = red), with shaded areas depicting N1 and P2 measurement intervals (blue = N1, red = P2) at Cz. B) Topographical plots of the grand average waveform across 'with prepulse' and 'pulse alone' trials for N1 and P2 over an average of the measured time intervals. All amplitudes are CSD-transformed (μV/mm^2).*

4.2.5 Statistical Analysis

Firstly, because an N1-P2 response is elicited by both pulse conditions in a single PPIPSI trial, we created a N1-P2 amplitude trial difference variable to aid interpretation of their relationship with perceived intensity. This was calculated by subtracting the N1-P2 response to the 'with prepulse' condition from the N1-P2 response to the 'pulse alone' condition. All statistical analyses were conducted using R software (v 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). We fit a trial-level generalised linear mixed model (GLMM) analysis using the 'gamljGlmMixed' function from the 'gamlj' package (v 2.6.1; Gallucci, 2019). This model was employed to predict the odds of participants' perceived intensity choice (two levels: 'pulse alone' more intense and pulse 'with prepulse' more intense or felt the 'same') as a function of Cz N1-P2 amplitude difference (continuous variable), SOA (90 *vs.* 150 ms) and predictability (low *vs.* high). Participant ID was entered in the model as a random factor to account for subject-level variation. Follow-up pairwise comparisons with

Holm's adjustment for multiple comparisons and estimated marginal means for plots were extracted from the model output provided by the 'gamlj' R package.

4.3 Results

4.3.1 Temporal Predictability and SOA

The GLMM analysis revealed a statistically significant main effects of predictability ($X^2(1, N = 24) = 17.28$, $p < .001$) and SOA ($X^2(1, N = 24) = 23.10$, $p < .001$). However, no interaction between predictability and SOA was observed ($X^2(1, N = 24) = .28$, $p = .59$). The pattern of results depicted in Figure 4.3 shows that at both SOAs, the high temporal predictability condition resulted in a greater proportion of trials where the 'pulse alone' was perceived as more intense. The results also exemplify that the observation of PPIPSI was greatest in the 150 ms SOA condition.

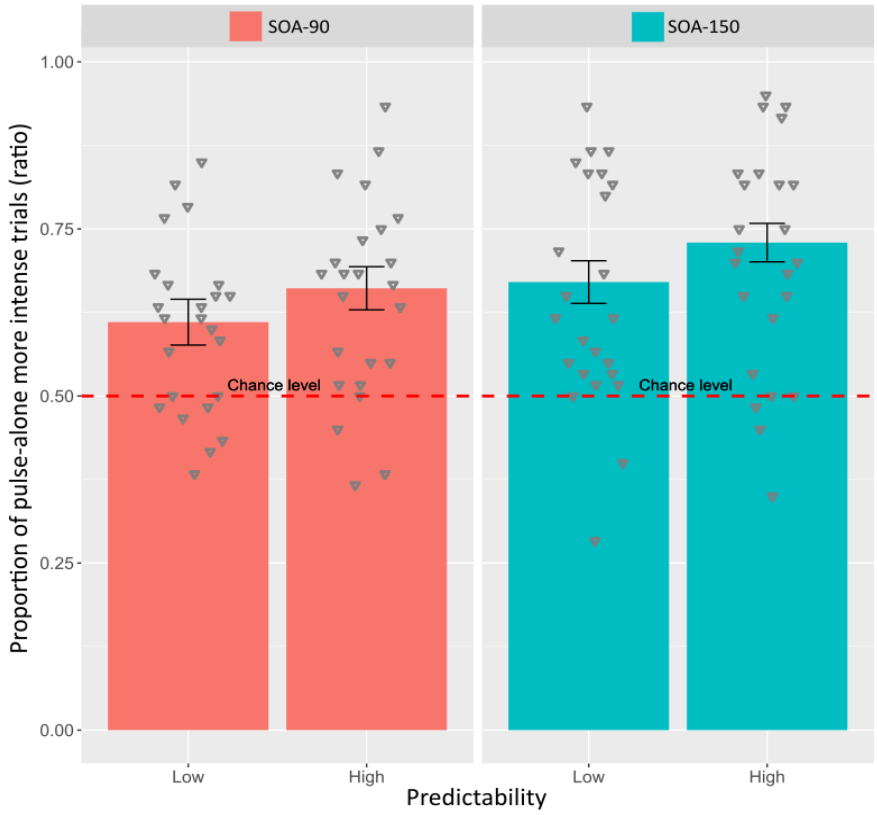


Figure 4.3. *Estimated marginal mean probabilities and standard error (SE; black bars) for the proportion of 'pulse alone' more intense (PPIPSI) trials as a function of temporal predictability (High, Low) and SOA (90 ms = red, 150 ms = green). The red dashed line*

represents the chance level. ▽= Individual data points for each participant within each condition.

4.3.2 Relationship Between Cz N1-P2 Difference and Perception

The GLMM analysis also revealed a statistically significant main effect of Cz N1-P2 amplitude difference ($X^2(1, N = 24) = 9.55$, $p = .002$). As illustrated in Figure 4.4, the model predicts that when the Cz N1-P2 magnitude difference is more positive (meaning the N1-P2 response was larger in the 'pulse alone' condition), there is a higher probability of perceiving the 'pulse-alone' as more intense.

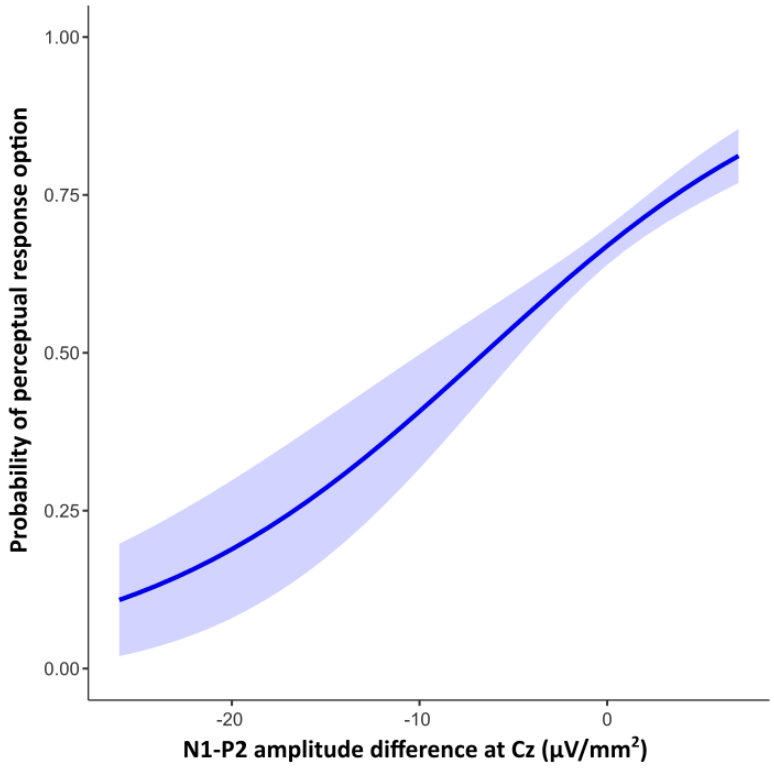


Figure 4.4. *Predicted Probabilities and Standard Error (SE) of Perception ('pulse alone' more intense = 1, 'with prepulse' more intense or 'same' = 0) as a Function of Cz N1-P2 Magnitude Difference (μV/mm²). Note. The predicted probabilities are derived from the GLMM analysis. The model was used to predict the N1-P2 response differences between the 'with prepulse' and 'pulse alone' conditions. The data demonstrates that the more positive the N1-P2 magnitude difference (meaning the N1-P2 response to the 'pulse-alone' was greater on a given trial), the higher the probability of perceiving the 'pulse-alone' more intense (demonstrating greater PPIPSI, consistent with our previous study; Favero et al., 2023).*

4.4 Discussion

In the current experiment, we examined the effect of temporal predictability (high vs. low) on PPIPSI at SOAs of 90 and 150 ms, and also replicated our previous work (Favero et al., 2023 by assessing its impact on cortical PPI (gating of Cz N1-P2 ERP magnitude). In more detail, we previously identified a relationship between PPIPSI and cortical PPI, which suggests that PPIPSI may rely on attentional resources being allocated to monitoring cortical sensory channels (e.g., those captured in the N1-P2 response; Favero et al., 2023). However, cortical PPI has been observed at SOAs of 50 – 140 ms (San-Martin et al., 2018), while PPIPSI typically requires SOAs of 120 ms or more (based on studies where stimulus presentation was randomised, i.e., less predictable than the current study; Favero et al., 2022; Swerdlow et al., 2005; 2007). Based on these findings, we proposed that PPIPSI observations may be increased for shorter SOAs if attention towards cortical responses to sensory input could be facilitated by manipulations of temporal predictability of the stimuli to be compared. Other paradigms suggest that temporal predictability facilitates the allocation of cognitive resources to task relevant processes (Alegria, 1974; Egeth & Yantis, 1997; Muller-Gethmann et al., 2003; Nakayama & MacKeben, 1989; Nobre & van Ede, 2018). Consistent with these previous studies, higher temporal predictability was associated with increased PPIPSI observations at both SOAs (90 and 150 ms). Independent of temporal predictability, SOA also influenced PPIPSI observations, with the longer SOA-150 producing significantly greater PPIPSI than the shorter SOA-90 condition. Our current findings echo a recurring theme across psychophysiological paradigms, demonstrating the pervasive influence of temporal predictability effects on PPIPSI.

Several studies have reported a positive correlation between startle PPI and PPIPSI (Swerdlow et al., 1999; 2005). These findings suggest an overlap in their underlying mechanisms. However, Swerdlow et al. (2005) also noted differences, suggesting that while attention influences PPIPSI, it may not always be essential for startle PPI. Attentional modulation of startle PPI appears to be dependent on experimental design. For example, attention to the prepulse can enhance startle PPI but requires a continuous, as opposed to the typical discreate prepulse (Poje & Filion, 2021). Furthermore, findings that startle PPI occurs in infants (Graham et al., 1981), sleeping adults (Silverstein et al., 1980), and even decorticated rats (Ison et al., 1991) indicate that the gating of reflexes can be observed

under conditions largely free from attentional processes. Conversely, task design, and activation time-courses suggest that attention is a more central process to PPIPSI (Favero et al., 2022; Swerdlow et al., 2005). Favero et al. (2023) found a similar relationship between cortical PPI and PPIPSI, where increased cortical PPI correlated with a higher likelihood of PPIPSI. Interestingly, attentional load was found to impact PPIPSI, but not cortical PPI. These observations imply that both startle PPI and cortical PPI can occur independently of attentional processes, likely operating at subconscious or preconscious levels of sensory processing. However, to observe PPIPSI, attention directed towards the pulse and its processing channels (e.g. aspects like the N1-P2 complex) is critical for awareness of the phenomenon (Favero et al., 2023).

In typical PPIPSI experiments, the exact timing of the pulse within a trial is unpredictable. This unpredictability likely results in a suboptimal allocation of attention to monitor key sensory channels. Given that attention is a finite resource that takes time to be directed and needs to be available at a specific time (Petersen & Posner, 2012; Swallow & Jiang, 2013), unpredictability can significantly affect the perception of events in the environment. In unpredictable settings, we propose that a secondary function of the prepulse is to serve as a stimulus-driven cue, directing attention towards processing the pulse. The prepulse is of perceptible intensity, brief in rise time and duration, and typically presented at an SOA which makes it perceptibly distinct from the pulse, but no explicit instruction is given to attend to it (Favero et al., 2022; Swerdlow et al., 2005). These properties align the prepulse with the rapid (~80 – 120 ms) post-cue onset of stimulus-driven attention, as opposed to the slower (~300 ms), more effortful and sustained engagement of goal-directed attention (Ling & Carrasco, 2006; Muller & Rabbitt, 1989; Nakayama & Mackeben, 1989). Consequently, the prepulse may automatically direct attention to the sensory channels that also process the pulse shortly after (Posner, 1980; Mondor & Breau, 1999). The automatic, stimulus-driven shift in attention likely contributes to decreased PPIPSI at shorter SOAs (Favero et al., 2022; Swerdlow et al., 2005). That is, the prepulses utility as a cue is dependent on there being enough time to process and reallocate attention from the prepulse to the pulse – at shorter SOAs there is less time for the brain to register the prepulse and reorient attention. Our finding of greater PPIPSI in the SOA-150 condition compared to SOA-90 exemplify this point.

To gain further insight into PPIPSI's dependence on longer SOAs being due to attention reallocation limits, we manipulated temporal predictability by delivering the pulse at a predictable time using a clock (in the high predictability condition). In contrast to the stimulus-driven attention captured by the prepulse, the clock engages more effortful goal-directed attention. Our findings demonstrate that high temporal predictability enhances PPIPSI at both SOAs. This effect is likely due to temporal predictability facilitating a voluntary shift of attention (Nobre & van Ede, 2018). The current findings align PPIPSI with the broader literature in which temporal predictability has been shown to improve numerous cognitive processes. For example, temporal predictability has been reported to activate a 'protective temporal window' in both visual perception (van Ede et al., 2018) and motor domains (McInnes et al., 2021). In visual perception, cues presented shortly before a target enhance the target's cortical representation and mitigate distractor interference (van Ede et al., 2018). Similarly, a cue or warning stimulus reduces reaction times by optimising the motor systems preparedness to respond (Alegria, 1974; Mondor & Breau, 1999; Muller-Gethmann et al., 2003). When a movement is being prepared, suppression of corticospinal excitability occurs, known as preparatory suppression (Hasbroucq et al., 1997). McInnes et al. (2021) found that preparatory suppression is not observed under time constraints which limit movement preparation (~350 ms) but emerges at longer intervals (700 – 1400 ms). Consequently, they propose that, like voluntary shifts of attention, preparatory suppression is a form of inhibition that protects motor responses from disruption by irrelevant external stimuli but requires time to develop (McInnes et al., 2021). Such parallels can be drawn with our study, where the clock's 3s lead-interval likely facilitated a more efficient allocation of attentional resources. In essence, when the timing of the pulse is more predictable, attention can be reserved for or pre-allocated to the pulse and its relevant sensory channels in advance. This pre-allocation of attention makes the brain more efficient at accessing the sensory information that subserves PPIPSI, resulting in increased observations at shorter SOAs.

4.4.1 Consistent pattern of relationship between N1-P2 Amplitude Difference and Perception

In our previous study (Favero et al., 2023), we identified a relationship between both electrotactile and acoustic PPIPSI and cortical PPI (gating of the N1-P2 ERP magnitude). We

found that in both modalities, a larger N1-P2 amplitude to a pulse-stimulus is associated with participants perceiving the pulse-stimulus as more intense. Moreover, when the prepulse precedes the pulse (PPIPSI condition), the N1-P2 response is reduced, indicating that cortical gating occurred (Favero et al., 2023; see also San-Martin et al., 2018). On trials where the 'with prepulse' condition corresponded with a greater reduction in the N1-P2 response (cortical PPI), the probability of perceiving the 'with prepulse' stimulus as less intense was significantly higher (Favero et al., 2023), demonstrating an association between cortical PPI and PPIPSI.

Secondly, based on the effects of attentional load we previously reported (Favero et al., 2023), we propose that the attentional resources required for PPIPSI might be used to access stimulus traces or representations reflected in the N1-P2 cortical response, consistent with Näätänen and Winkler's (2011) model of auditory processing and conscious perception. Our analysis of the N1-P2 complex in the current study corroborates this pattern, showing similar results to our previous findings. Therefore, the association between N1-P2 complex inhibition and PPIPSI suggests that similar processes are engaged, regardless of whether we manipulate SOA, temporal predictability, or attentional load (Favero et al., 2023). In other words, these manipulations draw upon overlapping neural resources, affecting the perception of gated stimuli in a similar manner.

4.4.2 Future directions: Exploring a wider range of SOAs and predictabilities

In the present study, we investigated the effects of predictability and SOA on sensory gating using two specific SOAs (90 ms and 150 ms). Our results revealed significant main effects of predictability and SOA, but no interaction between these factors. Interestingly, previous startle research has demonstrated that the inhibitory effect of the prepulse can be reversed, typically at very short (≤20 ms) or very long (1000 ms+) intervals (Graham, 1975; Hsieh et al., 2006; Plappert et al., 2004). Indeed, under less predictable conditions, this has also been observed in PPIPSI, where shorter SOAs (~80 ms) have been associated with an increase in the perceived intensity of the subsequent pulse, compared to when presented alone (Favero et al., 2022). This phenomenon is known as prepulse facilitation (PPF; Graham, 1975). One possible reason for the lack of interaction between SOA and predictability may be because the relationship between these two parameters is affected by time. If a larger array of SOAs were tested, such as those typically associated with PPF and around the SOA

range at which gating begins to diminish, predictability may influence the observed outcomes. Our data tentatively suggest that predictability shortens the SOA at which participants consciously perceive that gating has occurred. It is possible that predictability may also enhance gating at longer SOAs, like those typically associated with the reversal towards PPF (Graham, 1975; Hsieh et al., 2006; Plappert et al., 2004). If an interaction were to be observed using a larger range of SOAs, this would be consistent with our data, and the proposition that the mechanisms underlying sensory gating are not fixed but are flexible and influenced by contextual factors and processes, such as predictability and attention. It is also possible that these longer SOAs where PPF typically occurs produce a type of implicit temporal predictability, in which case it would be expected that temporal predictability would be associated with the reversal from inhibition towards facilitation. Consequently, investigating this possible interaction has the potential to advance theories on the temporal aspects of attention and perception, highlighting how timing and predictability jointly shape sensory experiences. Such investigations would be particularly relevant for better understanding disorders with impaired sensory gating (Braff et al., 1978; Braff et al., 2001; Geyer, 2006; Ludewig et al., 2002; Naegeli et al., 2018), potentially offering new insights into sensory processing and cognitive function through targeted manipulations of predictability and SOA.

Lastly, our temporal predictive method, using a clock-like stimulus, differs from the classical Nobre paradigm (e.g., Coull & Nobre, 1998). In the classical design, visual cues indicate the onset and duration of the delay before target onset, meaning a cue stimulus is not continuously present. In contrast, our visual cue is continuously present, ending at the target stimulus (pulse) onset. It may be argued that audio-visual integration influences our findings due to the continuous visual cue. However, numerous studies show that continuous visual information allows participants to better estimate event timing (Carlsen & MacKinnon, 2010). Indeed, Nobre et al. have used similar methods in some of their studies. For instance, in Rohenkohl and Nobre (2007), a white ball moved diagonally across a computer screen until reaching an occluding band. Temporal expectation was manipulated on a trial-by-trial basis according to whether the ball moved across the screen in a fixed or variable manner. This shares some parallels with our design, where the disk fills until the target stimulus onset (high predictability) or remains stationary (low predictability).

Importantly, the sound only occurs when the clock-hand ceases motion, leaving very limited opportunity for the CNS to integrate auditory information given its timing and duration (40 or 50 ms). This suggests that our effects are more likely influenced by temporal predictability than by audio-visual integration. Moreover, our previous study (Favero et al., 2023), which used only a stationary focus-point (less predictable and less audio-visual integration), yielded a pattern of results consistent with the current study. Specifically, the N1-P2 magnitude was associated with perceived stimulus intensity in both studies, regardless of the continuous temporal cue. Thus, while the current study cannot rule out that a continuous cue stimulus may engage some audio-visual integration mechanisms, this is unlikely to explain the current pattern of results. Nevertheless, future studies could benefit from cross-checking the current findings by implementing the classical Nobre design to further elucidate the effects of different temporal predictability methods and the role auditory-visual integration may play. Such comparisons may provide new insights into the mechanisms underlying temporal predictability, attention, perception, and their interactions.

4.4.3 Conclusion

PPIPSI has been proposed to be a higher order form of sensory gating yet related to startle PPI and cortical PPI (Favero et al., 2022; Favero et al., 2023; Swerdlow et al., 2005; Swerdlow et al., 2007). The SOA at which the prepulse perceivably reduces the intensity of the pulse is considerably longer than that required to observe startle PPI (≥15 ms; Blumenthal, 2015) and cortical PPI (≥50 ms; San-Martin et al., 2018). This difference has been key to propositions that PPIPSI engages attentional processes (Favero et al., 2022; Swerdlow et al., 2005). Here, we provide evidence that temporal predictability facilitates participants conscious awareness of gating, increasing the observation of PPIPSI at each SOA. Consistent with effects in other paradigms (Alegria, 1975; Herbst & Obleser, 2019; McInnes et al., 2021; van Ede et al., 2018), we interpret the findings as indicative that temporal predictability optimises the allocation of finite cognitive resources (e.g., attention) required for the conscious perception of PPIPSI's gating effects.

CHAPTER 5: GENERAL DISCUSSION

5.0 Overall summary

This thesis explores the gating of conscious perception within the PPIPSI paradigm, focusing on the examination of methodological parameters and processes that influence it. PPIPSI, although less researched and with debated mechanisms compared to startle PPI, emphasises the gating of perceived intensity – a higher-order process. This suggests that PPIPSI may offer a more direct way of studying and understanding gating of conscious perception. Some early interpretations of PPIPSI were that it was a downstream effect of the mechanisms underlying startle PPI. For example, Blumenthal et al. (1996), as cited by Neumann et al. (2006) raise the possible explanation that participants' intensity ratings may be affected by their awareness of their physical reactions to the pulse-stimulus. Implying that, because the startle or blink reflex is diminished during 'with prepulse' trials, participants might take their motor response into account when rating intensity. Recent experiments that concentrate on the active experimental procedures used to examine PPIPSI and highlight the apparent necessity of longer SOAs suggest a more refined relationship. These later studies indicate that while PPIPSI shares foundational, lower-level gating mechanisms with startle PPI, additional higher-level processes including and related to attention are also recruited (Swerdlow et al., 2005). PPIPSI's requirement of an active design and longer SOAs provide fundamental support for the involvement of self-monitoring and attentional processes, distinguishing it from startle PPI, which does not necessitate such processes. However, until this thesis, research had not assessed these requirements across different sensory modalities to determine their generality. Furthermore, direct manipulations of attention and other related higher-order processes, potentially contributing to the PPIPSI phenomenon, had not been investigated.

5.1 SOA & prepulse intensity

Expanding on the foundational concepts of PPIPSI, this section examines its sensitivity to experimental parameters like stimulus intensity and SOA, and how it differs from startle PPI. While initial conceptualisations posited a relationship between PPIPSI and startle PPI in which PPIPSI is a byproduct of startle PPI, subsequent studies have reported findings which oppose this simple explanation. For instance, PPIPSI has been observed even in the absence of startle PPI (Swerdlow et al., 2005), and other studies have evidenced that it correlates

more strongly with startle PPI magnitude than probability (Neuman et al., 2004). PPIPSI's responsiveness to stimulus intensities sub-optimal for eliciting startle, as noted by Cohen et al. (1981) and Peak (1939), also challenges the notion of its complete dependency on startle PPI. Historically, PPIPSI has been assessed as an auxiliary finding in startle PPI studies, using parameters best suited for eliciting startle PPI. This has likely contributed to ideas that PPIPSI is dependent on startle PPI. Though limited, more recent experiments by Swerdlow et al. (1999; 2005; 2007) have focussed on PPIPSI whilst simultaneously recording startle PPI. Swerdlow et al. (2005) tested a range of high intensities (both prepulse and pulse) and SOAs (10, 20, 30, 60 and 120 ms). Their findings revealed that while both phenomena were optimally elicited by higher intensity stimuli (80 dB prepulse and 105 dB pulse); differences emerged in their correlation patterns and time-course of activation. For example, a strong positive correlation ($r > .72$) was observed during their 'interval' session, yet their 'intensity' session revealed no correlation. As discussed in the General Introduction, this lack of correlation in their 'intensity session' may be attributed to a ceiling effect. The experiment focused on manipulating higher intensity prepulses, which may have limited the variability in PPI responses, thus resulting in a lack of association with PPIPSI (Swerdlow et al., 2005). Regardless, this lack of correlation suggests some dissociation between startle PPI and PPIPSIs underlying mechanisms. Furthermore, PPIPSI's activation time-course diverged from that of startle PPI, being significant only at longer SOAs (Swerdlow et al., 2005). Specifically, PPI was observed from 30 ms+ SOAs, but PPIPSI was non-significant until 60 ms and maximal at 120 ms SOAs (Swerdlow et al., 2005). This variability in correlation, and differences in time-course support the idea that startle PPI and PPIPSI share some, but not all underlying mechanisms. Moreover, PPIPSI's reliance on longer SOAs is consistent with proposals that it involves higher-level (e.g., attention) processes that startle PPI does not (Swerdlow et al., 2005).

In chapter 2, we sought to determine the optimal SOA and prepulse intensity parameters for electrotactile PPIPSI. We tested SOAs of 0 (no gap), 42, 82, 122, 162 and 202 ms (experiment 1) and 202, 302, 402, 502, 60 ms (experiment 2), as well as prepulse intensities of 1×, 2×, and 3× perceptual threshold (experiment 3). Consistent with Swerdlow et al. (2005) we predicted that PPIPSI would be more pronounced (optimal) at longer (e.g. 120 ms+) SOAs and using higher prepulse intensities. In experiment 1, we identified that as

SOA increases so does the proportion of PPIPSI trials observed. PPIPSI increased gradually until it was significantly above chance at SOAs over 160 ms. This indicates that, like acoustic PPIPSI (Swerdlow et al., 2005), electrotactile PPIPSI is observed in ranges amenable to attentional processes. Considering the findings that PPIPSI was most pronounced at the two longest SOAs we measured, experiment 2 was designed to investigate whether this trend of increasing PPIPSI with longer SOAs continues beyond the 200 ms mark. This was based on our hypothesis that extended durations between the prepulse and pulse onset facilitate more effective engagement of attentional processes, resulting in greater reporting of PPIPSI. The aim was to identify the SOA range where electrotactile PPIPSI is maximal, which we defined as the interval which produces the most 'with prepulse' trials reported as less intense.

In experiment 2, our analysis showed that all SOAs durations (200 – 600) resulted in above chance levels of PPIPSI, with no significant difference between SOAs. These findings suggest that after a large enough gap (200 ms), the mechanisms of PPIPSI are relatively stable for hundreds of milliseconds (up to 600 ms). The findings are consistent with the latencies post stimulus onset that attentional processes are believed to start taking effect (~120 ms; Dawson et al., 1993), providing further indication that PPIPSI is influenced by attentional processes. It is possible that PPIPSI remains stable for hundreds of milliseconds due to an overlap between stimulus-driven and goal-directed forms of attention. Stimulus-driven attention is a largely automatic process which is captured by stimulus properties and is engaged rapidly (~80 – 120 ms) post-stimulus onset. Conversely, goal-directed attention is more effortful and sustained, taking longer post-stimulus onset to be engaged (~300 – 700 ms; Ling & Carrasco, 2006; Muller & Rabbitt, 1989; Nakayama & Mackeben, 1989). Thus, sustained PPIPSI across 200 – 600 ms SOAs, might suggest a transition from an automatic, stimulus-driven form of attention at shorter SOAs to a more controlled, goal-driven form of attention at longer SOAs. In experiment 3, using a SOA of 200 ms, we found that a prepulse intensity of 2× perceptual threshold produced the greatest proportion of PPIPSI trials. The results show that the relationship between PPIPSI and prepulse intensity are non-linear, an increase in PPIPSI with increased prepulse intensity from 1× to 2× perceptual threshold, followed by a reduction in PPIPSI in the 3× perceptual threshold condition was observed. These findings are consistent with prepulse intensity effects in acoustic PPIPSI (Swerdlow et

al., 1999; Swerdlow et al., 2007). Overall, the series of experiments demonstrates that the parameters that elicit the greatest proportion of electrotactile PPIPSI are a 2x perceptual threshold prepulse with an SOA of 200 ms. The chapter 2 findings provide converging evidence with Swerdlow et al. (2005), suggesting that PPIPSI requires higher-order processes, like attention, which startle PPI does not. It appears that an attentional shift, even if driven indirectly by the prepulse, towards the pulse is required to observe PPIPSI, and that the time-gap of about 200 ms is needed to sufficiently engage these processes.

Although the results of chapter 2 suggest that attentional processes are engaged during PPIPSI, attention was not manipulated directly. That is, while time-course data and task requirements (explicit instruction that participants attend to the pulse) provide preliminary evidence of higher order processes contributing to perceptual gating, such processes have not been directly manipulated. As such, chapter 3 and 4 investigated evidence of PPIPSIs relationship with attention and other higher-level processes.

5.2 Processes contributing to gating of conscious perception (PPIPSI)

Building on the findings of chapter 2, the experiments presented in chapter 3 used the optimal PPIPSI parameters to investigate the possible relationship between PPIPSI and cortical PPI (the net neural response of the cortical system at the N1-P2 timeframe; ~50–250 ms) in both electrotactile (experiment 4) and acoustic (experiment 5) modalities. We demonstrated that in both modalities, the more effectively the prepulse inhibits the N1-P2 response (cortical PPI), the greater the probability that participants perceive the 'pulse-alone' more intense (demonstrating PPIPSI). Our findings are consistent with previous evidence that the N1-P2 complex is associated with processes of encoding stimulus characteristics such as intensity (Annic et al., 2014; Garcia-Larrea et al., 1992; Mulert et al., 2005; Paiva et al., 2016; Rosburg et al., 2008). Moreover, the findings of this chapter suggest that the processes occurring during the N1-P2 timeframe (particularly their gating by a prepulse) contribute to a higher probability of participants' being consciously aware that gating has occurred. Our findings also provide converging evidence for the independent observations of Swerdlow et al. (2007) and Kedzior et al. (2007), who noted that PPIPSI and N1-P2 gating share similar magnitude reductions and temporal sensitivities.

In experiment 5, attentional load was manipulated to investigate its effects on PPIPSI and cortical PPI. Here we found that attentional load affects PPIPSI but failed to detect a significant change in cortical PPI. Gating of conscious perception (PPIPSI) was observed significantly less under high attentional load compared to the low attentional load condition. PPIPSI's reduction under high attentional load provides evidence for the involvement of attention in gating of conscious perception, supporting the time-course findings of chapter 2 as well as other studies using acoustic stimuli (Swerdlow et al., 2005; Swerdlow et al., 2007). The finding that cortical PPI was unaffected by attentional load is consistent with Näätänen et al's (2011) model of auditory processing and conscious perception (adapted in Figure 5.1). This model proposes that the N1 acts as a transient detector—a neural mechanism that responds to brief changes in sensory input, such as the onset or offset of a stimulus—and a feature detector (e.g., intensity), which in itself is largely unaffected by and non-representative of attentional processing (Näätänen & Winkler, 1999). That is, a stimulus will elicit an N1-P2 response even if unattended or not entering conscious perception. Though reduced in magnitude, N1-P2 responses in sleeping participants support this conceptualisation (Lightfoot, 2016). However, while acting as a transients and feature detector, N1 sends an attentional call that directs attention to the stimulus representation (in sensory memory) when sufficiently activated, bringing it into conscious perception (Näätänen et al., 2011).

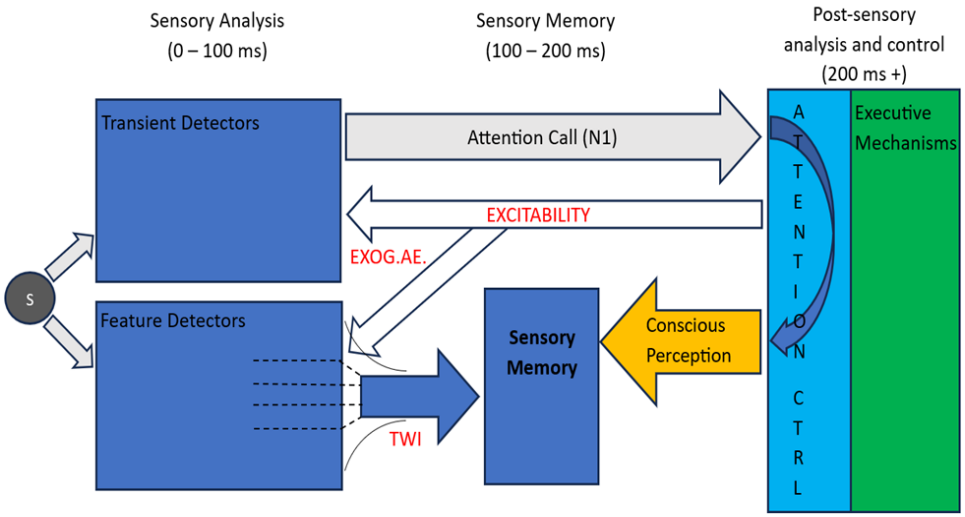


Figure 5.1. *Adapted and simplified version of Näätänen et al. (2011) auditory processing and conscious perception model. Note. S = Stimulus, EXOG.AE. = exogenous attention effects, TWI = temporal window of integration.*

Our findings support this model by showing that N1-P2 magnitude is unaffected by attentional load, whereas PPIPSI is. This suggests that the early cortical processes are precursors to conscious perception, but whether a stimulus' features are consciously perceived is mediated by attention being direct to the relevant sensory channels. Thus, when attentional resources are too low, the prepulse may still inhibit the N1-P2 response to the pulse, but the lack of attentional resources results in reduced conscious perception of the gated pulse in sensory memory.

5.2.1 Allocating attention

The findings of chapter 3 demonstrate the involvement of attention in the gating of conscious perception (PPIPSI) and provide new insights as to where attention may be directed. During PPIPSI experiments, participants are explicitly instructed to attend to the pulse (with/without prepulse). This means that attending to a stimulus of interest is required to make an accurate judgement of it. The finding that increased attentional load impairs PPIPSI (experiment 5) supports the notion that attention is directed towards the pulse. However, the relationship between PPIPSI and cortical PPI also suggests that directing attention internally, towards relevant sensory channels is important for conscious perception. Coupled with the time-course findings of chapter 2, and acoustic experiments by Swerdlow et al. (2005), we propose that PPIPSI may be less observed at SOAs as brief as those which startle PPI is seen because more time is required to direct attention (even if driven indirectly by the prepulse) to monitor inputs to the cortex. Note that although participants likely attend to the sensory channel throughout the entire trial, it is difficult to maintain a high level of attention when the exact timing of the stimuli is random (see Bendixen et al., 2009). Therefore, in addition to inhibiting the input to the cortex, the prepulse might serve as a cue, recruiting additional resources to monitor sensory channels.

Attention can be goal-directed (top-down; intentional and focussed on task relevant signals) or stimulus-driven (bottom-up; automatically captured by stimuli's salient properties; Annic et al., 2014). As opposed to the prepulse being a cue that consciously drives attention towards processing of the pulse, it likely captures attention automatically which is then used to process the pulse. The prepulse is of perceptible intensity, brief in rise time and duration, and typically presented at an SOA which makes it distinct from the pulse, but no explicit instruction is given to attend to it - characteristics most consistent with

conditions eliciting stimulus-driven attention. It is also possible that the type of attention engaged is dependent on the chosen SOA. PPIPSI using shorter SOA is more consistent with the time-course of stimulus-driven attention (rapid ~80 – 120 ms post cue-onset). Conversely, longer SOAs (such as those seen in chapter 2 experiment 2) may engage goal-directed attention, which appears at longer latencies (~300 ms) and can be sustained in a task-focussed manner (Ling & Carrasco, 2006; Muller & Rabbitt, 1989; Nakayama & Mackeben, 1989). Therefore, particularly when short SOAs are used, the automatic attention captured by the prepulse may increase activity in relevant sensory areas, resulting in a greater capacity to process the pulse (Hillyard et al., 1973; Näätänen et al., 2011; Posner, 1980). This suggests that the prepulse in PPIPSI acts like the cue in cue-target reaction time studies. In these paradigms, the similarities (location and frequency) between the cue and target facilitate selective attention, resulting in faster reactions (Mondor & Breau, 1999). This model is consistent with Brunia's (1993) proposal that motor and attention processes use similar mechanisms. More precisely, because motor responses cannot be held in a high state of preparation for long periods (100–300 ms; Alegria, 1975; Müller-Gethmann et al., 2003), responses are maximally prepared when a warning signal is presented around 200 ms before the imperative stimulus to act. In PPIPSI, the participants similarly cannot stay in a high state of attention to perceive the pulse, because the timing of pulse presentation is uncertain. Thus, the prepulse recruits additional attentional resources used to monitor inputs to the cortex. The longer gap (SOA) required to observe PPIPSI may reflect the necessary time-course of attention reactively shifting from the prepulse towards pulse processing. That is, the prepulses utility as a cue is dependent on there being enough time to process it and to reallocate attention from the prepulse to the pulse – at shorter SOAs there is insufficient time for the brain to fully exploit the cueing aspect and reallocate attentional resources. This may also be conceptualised through Näätänen et al.'s (2011) model, where the prepulse elicits an N1 (attention call) which increases the attentional resources available for conscious perception to direct towards processing the subsequent pulse (see Figure 5.1).

The preceding chapters have underscored the important role attention has in consciously perceiving that the pulse intensity has been inhibited by the prepulse. Furthermore, by evidencing that attention to the pulse and relevant cortical channels is

central to PPIPSI, the findings outline a new process by which PPIPSI may be influenced. Specifically, the unpredictability of the pulse poses a substantial challenge for the efficiency of allocating attention. The prepulse appears to mitigate this challenge by provisionally boosting attention towards the pulse, albeit in a reactive manner due to its own unpredictable onset. From these findings, we postulate that PPIPSI's increase with longer SOAs may be attributable to the limited nature of attentional resources and the necessity that they take time to reallocate. Building upon these insights, the final chapter focusses on temporal predictability (reduced uncertainty) influences gating of conscious perception.

5.3 Temporal predictability

As detailed in the previous section, cognitive functions, including motor responses and selective attention to a target are improved when preceded by a 'warning' stimulus or cue (Alegria, 1975; Nobre & van Ede, 2018). This enhancement is widely agreed to result from the limited nature of cognitive resources; the cue, by reducing uncertainty, provides crucial information leading to more efficient allocation of these resources (Nobre & van Ede, 2018). In chapter 4, we focussed specifically on the temporal information provided by cues and whether they influence the SOA PPIPSI is observed at. Temporal predictability was manipulated by a clock-like visual stimulus that gradually filled over a duration of 3 seconds, with its completion synchronised with pulse onset, representing the high predictability condition. In contrast, the low predictability condition featured a stationary visual stimulus (green circle) that provided minimal information about the timing of pulse presentation. Two SOAs were tested, one shorter than what the literature indicates optimal (90 ms; optimal = 120 ms, Swerdlow et al., 2005), and one longer (150 ms). EEG was also recorded to assess the relationship between cortical PPI and PPIPSI under different experimental settings.

The results presented in chapter 4 reveal that at both SOAs, high temporal predictability increases the observation of PPIPSI. This effect is likely due to temporal predictability facilitating a voluntary shift of attention (Nobre & van Ede, 2018). Put another way, temporal predictability facilitates a proactive shift or pre-allocation of attention to the pulse and its relevant sensory channels, which increases the likelihood this information will reach conscious perception. The current findings align PPIPSI with the broader literature in

which temporal predictability has been shown to improve numerous cognitive processes. Though preliminary, the findings that a 3s visual stimulus timed with the pulse onset improves the observation of PPIPSI draws parallels with findings from McInnes et al. (2021). When a movement is being prepared, suppression of corticospinal excitability occurs, known as preparatory suppression (Hasbroucq et al., 1997; McInnes et al., 2021). McInnes et al. (2021) found that preparatory suppression is not observed under time constraints which limit movement preparation (~350 ms) but emerges at longer intervals (700 – 1400 ms). Consequently, they propose that like voluntary shifts of attention, preparatory suppression is a form of inhibition that protects motor responses from disruption by external stimuli but requires time to develop (McInnes et al., 2021). In comparison to the stimulus-driven attention captured by the prepulse, the clock with its lengthier time likely captures more controlled, goal-directed attention (Ling & Carrasco, 2006; Muller & Rabbitt, 1989; Nakayama & Mackeben, 1989). As such, this 3s lead-interval likely facilitates a more efficient allocation of attentional resources. In essence, when the timing of the pulse is more predictable, attention can be reserved for or pre-allocated towards the pulse and its relevant sensory channels in advance. This pre-allocation of attention makes the brain more efficient at accessing the sensory information that subserves PPIPSI, resulting in increased observations of PPIPSI at shorter SOAs. The findings of this chapter extend support for Brunia's (1993) proposal that motor and attention processes use similar mechanisms. Stronger evidence of a consistency between these findings and those of McInnes et al. (2021) would come from testing whether the clock is less effective at shorter lead-intervals, if this was the case it would suggest that pre-allocating or proactive attentional shifts also require time to sufficiently develop.

5.4 Conceptual model of PPIPSI

The findings of this thesis lay the groundwork for a working model of how gating of conscious perception occurs in PPIPSI, emphasising the interplay between attention, cortical activity, and the temporal dynamics of stimulus presentation. Central to the model is our proposal that attention plays a dual role in the allocation of resources towards a target stimulus (here, the pulse) and its relevant processing channels, influencing what is consciously perceived.

When a stimulus such as the pulse (🔊) is presented, it elicits a change in cortical activity (e.g., N1-P2 response = blue line; Figure 5.2). In chapters 4 and 5, we demonstrate a link between N1-P2 amplitude and PPIPSI, revealing that the more effectively the cortical response to the pulse is modulated by the prepulse, the higher the probability that participants will perceive the pulse preceded by a prepulse as less intense. This observation aligns with Näätänen et al. (2011) who suggest that cortical activity during the N1-P2 time window plays a crucial role in stimulus perception through directed attention. This cortical response is transient, it rises and declines rapidly, occurring approximately 100 – 200 ms post-stimulus. We propose that for the prepulses inhibitory effect to reach conscious perception, attention must be sufficiently focussed towards relevant processing channels during this time-window.

Particularly in conditions when the pulse-onset is unpredictable, the prepulse serves as a cue, initiating a useful, though inherently less efficient reactive shift in attention towards relevant sensory channels. The utility of this cueing is reliant on there being sufficient time to re-allocate attention, supported by the chapter 2 findings, and Swerdlow et al. (2005) which evidence the importance of longer SOAs. These extended intervals provide crucial time for attention to be redirected, allowing the information processed during the transient N1-P2 window to contribute to conscious perception. Moreover, the inefficiency of reactively directing attention (exemplified by the lower attention level in the unpredictable condition at the N1-P2 time-window; intercept between red line and vertical dotted line; Figure 5.2), highlights why information processed during the N1-P2 window, despite being informative of sensory processing, may not always successfully contribute to conscious perception in such settings. Conversely, predictable conditions allow for earlier and more efficient attention allocation (Nobre & van Ede, 2018), as depicted by the attention levels being higher and peaking earlier for the green line in Figure 5.2. This pre-allocation and reservation enhances resource allocation during the critical N1-P2 window, increasing the probability that the contained stimulus information will reach conscious perception, even at shorter SOAs (chapter 5). The model thus delineates a dual mechanism: in unpredictable scenarios, longer SOAs compensate for the reactive and less efficient attentional shift necessitated by the prepulse cue, while in predictable conditions, the pre-allocation of attention provides more immediate and effective perceptual access to gated

sensory information. By outlining the interplay between cortical activity, attention, and temporal predictability, the model provides a deeper understanding of the higher-level processes contributing PPIPSI, highlighting attention's key role in modulating sensory perception within this paradigm.

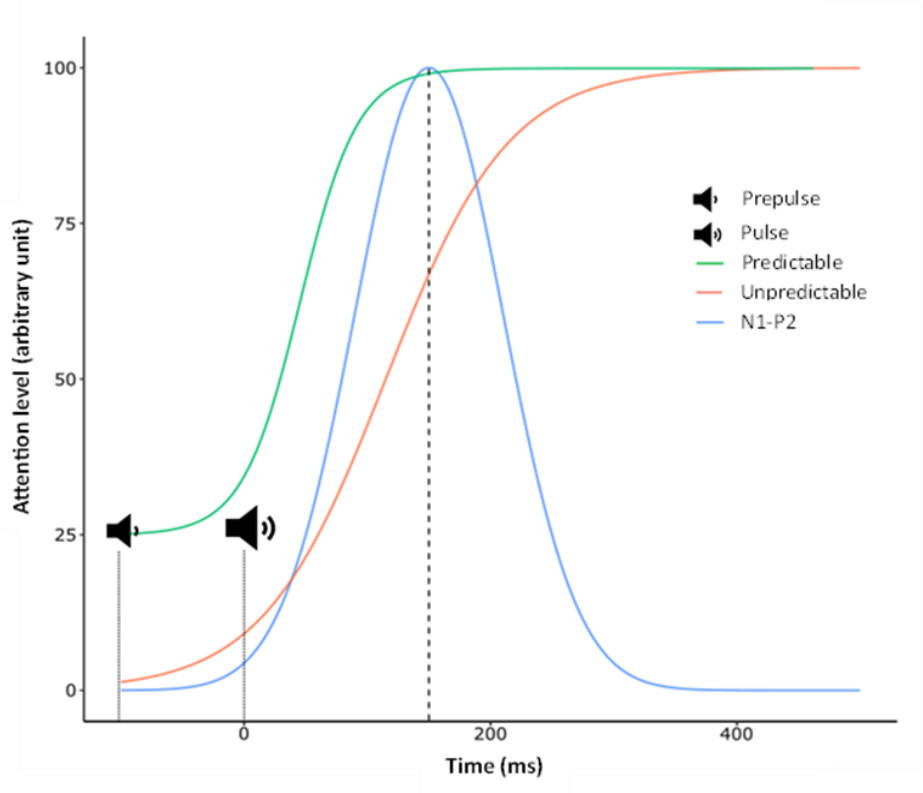


Figure 5.2. *Model of the interaction between attention and temporal predictability in the observation of PPIPSI. This figure illustrates the dual roles of attention in PPIPSI under varying temporal predictabilities. In both conditions, the prepulse acts as a stimulus-driven attentional cue, depicted by the uptick in attention level post prepulse onset. In the unpredictable condition (red line), the prepulse is more reliant on reactively shifting attention towards relevant sensory channels (e.g. N1-P2 – blue line). This reliance requires extended SOAs for attention to be sufficiently allocated, as shown by a more gradual increase in attention level, and later peak. Conversely, in the predictable condition (green line), attention is pre-allocated and/or efficiently preserved, starting at a higher level, increasing more rapidly, and peaking sooner. These dynamics enhance the processing of pulse-stimulus information during the critical N1-P2 window (approximately 100 – 200 ms post-stimulus), increasing the likelihood participants will consciously perceive the inhibitory effect of the prepulse.*

5.5 Link between 'lower' and 'higher' level gating

The association found between PPIPSI, and cortical PPI suggests that the inhibition caused by the prepulse is driven by lower-level (pre-perceptual) mechanisms. Consistent with Näätänen and Winkler's (1999) model of stimulus processing, given that cortical PPI is unaffected by attentional load, we propose that the inhibited pulse representation can later enter conscious perception by attention being directed towards relevant processing channels (see Figure 5.1). Temporal predictability is typically associated with enhanced perceptual discrimination (visual: Fernandez et al., 2019; auditory: Jones, 1976; Jones et al., 2002) and reduced interference from distractors (Gresch et al., 2021; van Ede et al., 2018). Thus, if PPIPSI was a mere perceptual level error, we would expect temporal predictability to reduce, rather than amplify its effect. Combined, these findings suggest a pathway where startle PPI and PPIPSI share a lower-level gating mechanism but diverge as PPIPSIs also engages attentional and self-monitoring processes mediated by (higher-level) brain areas.

In cross-mammalian models of startle PPI, the prepulse inhibitory pathway implicates the inferior colliculus (IC) and superior colliculus (SC), which receive input from the specific stimulus modality receptors. The IC and/or SC (depending on prepulse modality) then project prepulse information to the pedunculopontine tegmental nucleus (PPTg), which sends inhibitory projections to the caudal pontine reticular neurons (PnC), dampening activation levels of the spinal motor neurons (Azzopardi et al., 2018; Fendt et al., 2001). PPIPSI likely shares these lower-level pathways for the prepulse, but after engaging the PPTg, the prepulse pathway extends projections to the prefrontal cortex (PFC) and medial prefrontal cortex (mPFC). These areas are instrumental in focusing attentional resources on the sensory cortex(es) and sensory memory (Vazey et al., 2018), thus influencing how the sensory characteristics of the stimulus, such as its intensity, are accessed and processed. Crucially, for the modulated stimulus features to enter conscious awareness, the mPFC and PFC must activate a perceptual mechanism. This activation allows the attended stimulus representation to be brought from the sensory cortex(es)/memory to conscious perception, echoing Näätänen et al.'s (2011) premise that attention steered by higher cognitive processes is essential for conscious perception. Moreover, these frontal regions' involvement in PPIPSI is consistent with the longer time-course (SOA) at which PPIPSI emerges. To reach these frontal areas, the prepulse must enter the ear (or other modality

neurons), pass through numerous sub-cortical and midbrain areas, reach the frontal and prefrontal cortices, create neural changes which recruit attention and direct this towards relevant processing channels allowing the gated pulse stimulus representation to be perceived. Thus, it is logical that this added physiological distance travelled would correspond with an increase in the time-course at which perceivable gating effects occur. Figure 5.3 presents a visual representation of the hypothetical startle PPI and PPIPSI mechanisms discussed above.

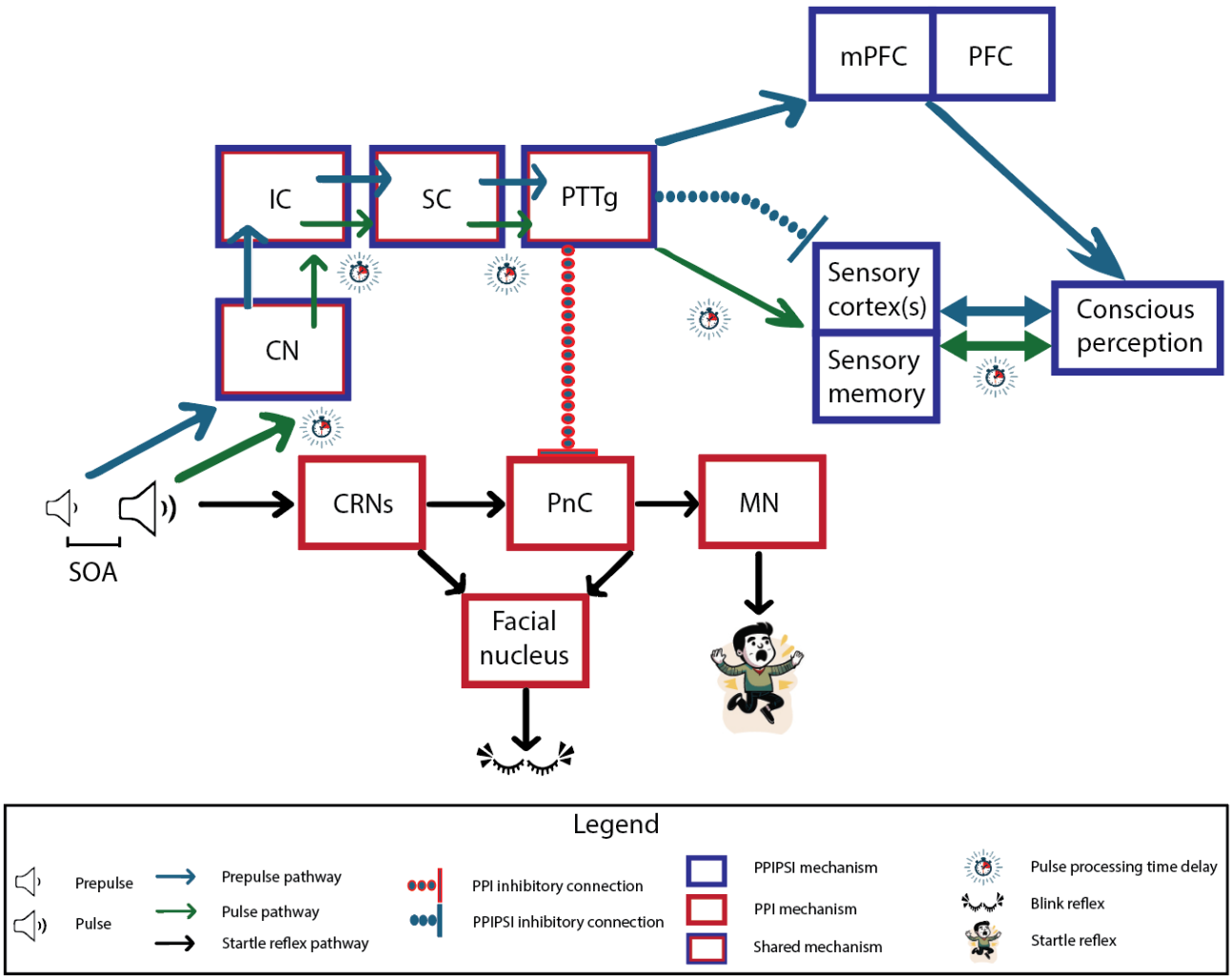


Figure 5.3. *Hypothetical circuit of startle PPI and PPIPSI.*

Figure 5.3 represents the neural circuitry involved in modulating the startle reflex (PPI) and perceived intensity (PPIPSI). The prepulse inhibition (PPI) pathway is represented with red outlines, indicating how a prepulse can reduce both the blink reflex and startle reflex. This pathway involves auditory signals from the cochlear nucleus (CN) that inhibit the startle

circuit at the pontine reticular nucleus (PnC) through its connections with the inferior and superior colliculi and the pedunculopontine tegmentum (PTTg). The blue outlines represent the PPIPSI pathway, where the prepulse activates the prefrontal cortex (PFC) and medial prefrontal cortex (mPFC), affecting higher order cognitive functions such as attention and conscious perception. This activation modulates the capacity of an individual to perceive changes in the amplitude of the signal reaching cortical areas of the brain: cortical PPI. The components with both red and blue outlines represent shared neural mechanisms of both pathways before they diverge. ***Note.*** *The pulse pathway (green arrows) follows the same sensory processing channels as the prepulse but with notable distinctions. The pulse is presented following a specific time delay (SOA), hence traversing the neural circuit subsequently to the prepulse, indicated by the clock icon. This latency ensures that the pulse is processed after the attention-directing effects of the prepulse (blue arrows) have been established. Thus, in addition to the prepulse facilitating an attentional shift towards the pulse and its sensory channels, the pulse information reaches the sensory cortex(es)/memory after the prepulse activates an inhibitory projection from the PTTg (blue dotted closed arrow). This hypothetical inhibitory projection may explain why the pulse information accessed from the sensory cortex(es)/memory is reduced when preceded by the prepulse.*

5.6 Potential clinical relevance

Along with mechanistic insights gained from the experiments reported here, the findings of this thesis provide potential directions and applications for populations characterised by impaired sensory gating. Clinical presentations including Schizophrenia, anxiety, panic disorder (PD; Ludewig et al., 2002; Naegeli et al., 2018), PTSD, obsessive-compulsive disorder, and Tourette's Syndrome (Braff et al., 2001; Braff et al., 1978; Geyer, 2006) are known to have reduced startle PPI compared to non-clinical control groups. In Schizophrenia, impaired sensory gating has been implicated in common symptoms of thought flooding and hallucinations (Braff et al., 1978). However, most of what we know about sensory gating in these populations comes from measuring startle PPI, and little evidence exists to support the assumption that PPI directly assesses processes associated with individuals' subjective perception of sensory information (Swerdlow et al., 1995; Swerdlow et al., 2005). Attentional dysfunctions are widely held to be key attributes of Schizophrenia (Braff, 1993). However, startle PPI procedures and mechanisms, unless

specifically manipulated, are independent from attentional control. That is, PPI usually follows a passive design (no instructions to participants) and requires little attention or higher-order processing, as it can be elicited in infants (Graham et al., 1981), sleeping adults (Silverstein et al., 1980) and decorticated rats (Ison et al., 1991). Therefore, making inferences about clinical presentations characterised by attentional dysfunctions from a motor response largely independent of attentional processes is likely suboptimal for extending our knowledge (Swerdlow et al., 2005). The current thesis' findings provide evidence that PPIPSI may provide a more direct measure of attentional and perceptual processes in such clinical populations. We showed that attentional resources are central to consciously perceiving that gating has occurred. Thus, if clinical populations were found to display reduced PPIPSI, it may give greater insights into processes associated with the perceptual experience of these populations and where the source(s) of their experience lies.

Initial accounts conceptualised sensory gating in conditions like Schizophrenia as containing blocks or irregularities in early information processing stages, which result in "downstream" effects on higher-level processes like cognition, attention, and social functioning (Braff, 1993; Saccuzzo et al., 1974). Under such conceptualisations, startle PPI alone may be sufficient for inferring symptom presentations. However, PPI deficits are not associated with performance in numerous neuropsychological tests (Swerdlow et al., 1995) and the association between reduced PPI in schizophrenia and symptom measures is debated in the literature (for review see, Swerdlow et al., 2001; Swerdlow et al., 2005). Theories and evidence align best with models where both early sensory processing and attentional dysfunctions contribute to symptom presentations (Braff, 1993; Cohen & Servan-Schreiber, 1992). Our findings in the current experiments are consistent with theories of startle PPI and PPIPSI in which their brain substrates are overlapping but non-identical (Swerdlow et al., 2001; Swerdlow et al., 2005). As such, experiments with clinical populations (e.g. Schizophrenia) may benefit from testing startle PPI and PPIPSI simultaneously, because they are complementary. Attentional load, and temporal predictabilities' influence on PPIPSI suggest that PPIPSI may be more suitable for investigating attentional and internal representation dysfunctions in such clinical populations than startle PPI. While startle PPI is more suitable for understanding early sensory processing deficits. By combining, greater insight about the aetiology of conditions

might be found. For example, specific presentations may exhibit greater PPI deficits than PPIPSI, and vice versa, which might assist differentiating at which level a specific set of symptoms arise as opposed to another.

5.7 Future research directions

The present thesis aimed to further advance our understanding of the gating of conscious perception (PPIPSI) and the processes which contribute to it. The findings and proposed model provide both new conceptualisations for existing models, and future ways of investigating the neural and cognitive mechanisms underlying sensory gating.

The finding that temporal predictability also increases the observation of PPIPSI at shorter SOAs (chapter 4) suggests that resources and processing speeds are important for consciously perceiving that gating has occurred. This likens PPIPSI to the attentional blink (AB) phenomenon, where identifying the second of two targets within a stimulus sequence is impaired by identification of the first (Horvath & Burgyan, 2011; Raymond et al., 1992; Willems & Martens, 2016). Furthermore, individuals with a shorter or no attentional blink, meaning they require less time between the first and second stimulus have been found to have higher levels of executive working memory and faster processing speeds (Willems & Martens, 2016). It is evidenced that these individuals typically have greater attentional control (less affected by distractors), and update representations in working memory faster (Martens et al., 2006; Troche & Rammsayer, 2013). Thus, an interesting step forward would be investigating if individual differences, such as high/low executive working memory capacity and processing speed influence the SOA at which PPIPSI is observed. If, as previous research suggests temporal predictability assists the preservation and pre-allocation of attentional resources (Nobre & van Ede, 2018), my proposed model hypothesises that like what is seen with AB, individuals with heightened executive working memory and/or processing speeds may perceive PPIPSI at shorter SOAs.

Identifying whether, like AB, higher executive working memory and processing speed are associated with greater PPIPSI at shorter SOAs would shed new insights onto the relationship between sensory gating and cognitive functions. This may be explored through a two-part experiment beginning with standardised cognitive tasks evaluating each participant's executive working memory and processing speed, followed by a PPIPSI session

with varying SOAs. Neuroimaging techniques could also be used to investigate the neural correlates of executive working memory and processing speed in relation to sensory gating mechanisms. This would provide a more comprehensive understanding of how cognitive capacities, particularly those related to attentional control and information processing, modulate the perception of sensory inputs. Such an approach could also provide new insights into the neural underpinnings of PPIPSI and contribute to broader theories of sensory perception and consciousness. Ultimately, this research has implications for understanding individual differences, both clinical and non-clinical, in sensory processing and their potential links to broader cognitive and neural mechanisms.

Building on the similarities between PPIPSI and AB and given the impact of executive working memory and processing speed on AB, it would be worthwhile to investigate whether attentional control training, such as meditation, can influence PPIPSI and how it does so. Studies have shown that extensive meditation training can lead to a reduced AB (van Leeuwen et al., 2009; Slagter et al., 2007). Slagter et al. (2007) indicate that long-term meditators have an enhanced ability to allocate attentional resources to the first and second target stimuli more evenly, meaning fewer resources are used in processing the first stimulus, or that long-term meditation training results in more efficient processing of the first stimulus. This suggests that meditation may improve cognitive functions such as sustained attention and inhibitory control, which are critical in sensory gating processes.

While direct evidence linking meditation to improvements in inhibitory control specific to PPIPSI is yet to be investigated, a number of studies have demonstrated that meditation is linked with enhanced inhibitory control in the Stroop Task and Stop-signal task (Ron-Grajales et al., 2021), response inhibition tasks (Sahdra et al., 2011), and improved behavioural markers of impulsive responding (Pozuelos et al., 2019). Additionally, meditation and mindfulness have been associated with improved attention and reduced attentional impulsivity in both non-clinical populations (Jha et al., 2007) and individuals with ADHD (Zylowska et al., 2008). Notably, there is also conflicting evidence that meditation does not reduce impulsivity on the go/no-go task or Barratt Impulsiveness Scale (Korponay et al., 2019). This highlights the need for further research to explore these potential effects in the context of PPIPSI, as meditation may improve PPIPSI through shared underlying processes such as inhibitory control and attention. Future studies could clarify these

relationships and determine the extent to which meditation can enhance sensory gating mechanisms, further elucidating the underlying processes that are involved.

Similarly, the findings from Chapters 3 and 4 suggest that allocating attentional resources to the pulse and its processing channels is central to perceiving the inhibitory effects of the prepulse in PPIPSI. Consequently, a longitudinal study involving participants' engagement in structured meditation practices known to enhance attentional control, followed by assessments of their PPIPSI responses at varying SOAs, would provide valuable insights. Such meditation-based attentional training could potentially refine cognitive functions like attentional control and processing speed, leading to more efficient gating of conscious perception in the context of PPIPSI.

Moreover, this research may provide insight into the possible distinction between the prepulse being the activator of a gating mechanism and a cue guiding attention towards the pulse, as proposed in the current thesis. If the prepulse activates dual processes that result in PPIPSI, enhanced attentional control and/or processing speed may differentially affect these processes. EEG or neuroimaging techniques may be incorporated to elucidate possible cortical adaptations underlying the observed changes in sensory gating and cognitive processing. This line of research holds significant promise not only in advancing our understanding of the neural and cognitive mechanisms of sensory gating but also in exploring meditation as a potential therapeutic tool for clinical populations with deficits or declining sensory processing, attentional, or inhibitory control. Such research may be particularly informative about attentional and inhibitory control as we age (Rey-Mermet & Gade, 2017).

The model proposed in Chapter 4, and above in Section 5.4 (Figure 5.2), also provides new methods of testing attention's role in PPIPSI and sensory gating more broadly. For example, Miller et al. (2021) presented a revised model of startle PPI in which startle magnitude is modulated by two overarching factors, startle scaling and sound scaling. In their model, startle scaling refers to how the startle response is affected by the presence of the prepulse, or how much the motor response is altered by being preceded by a prepulse. On the other hand, sound scaling pertains to how the presence of the prepulse alters the perceived intensity of the startle stimulus, and by altering this, affects the startle response (Miller et al., 2021). They propose that when the prepulse reduces the perceived intensity of

the startle sound, the startle response magnitude is also inhibited. The introduction of a sound scaling aspect extends the conventional model, in which PPI is merely a reduction in the physical startle response magnitude, to present a more nuanced element where cognitive and perceptual processes also influence the motor response. My findings and model complement Miller et al. (2021) by highlighting that attention has a dual role in affecting perception, or as they refer to it: sound scaling. This adds a layer of complexity by suggesting that the reduction in perceived intensity of the startle stimulus, as facilitated by the prepulse (sound scaling), is significantly influenced by how attention is directed and modulated by the prepulse. Such an influence is not considered in Miller et al.'s (2021) model in its present form. In conclusion, the attention-mediated model of PPIPSI presented here enriches the framework set out by Miller et al. (2021), inviting further investigation into the cognitive and perceptual dimensions of sensory gating. The model not only accounts for the reduced motor response because of the prepulse (startle scaling) but also proposes that the attentional state at the time of the prepulse is pivotal to the perceived intensity of the pulse (sound scaling). By suggesting that directed attention modulates the perceptual processing of sensory events, it generates novel hypotheses regarding the interaction of attentional states with sensory gating phenomena. For instance, it hypothesises that an individual’s attentional control capacity may predict the effectiveness of observing PPIPSI. The model suggests that greater attentional control should be associated with greater reports of PPIPSI at shorter SOAs because these individuals can control attention's limited resources and allocate or even pre-allocate them more efficiently, thus requiring less time between the prepulse and pulse. A future study may test this by incorporating attentional control paradigms with PPIPSI, such as comparing the time-course (SOAs) at which participants with varying levels of attentional control perceive PPIPSI. Thus, this work not only extends existing models but also introduces novel research avenues that could advance our knowledge of the neural and cognitive mechanisms underlying sensory gating.

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