Neural Mechanisms Underlying the Modulation of Auditory Sensory Gating by Different Forms of Attention

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Abstract

Prepulse inhibition (PPI) is a measurement model of auditory sensory gating that reflects the early information selection function of the auditory system. Although the primary neural circuit of PPI is located in the brainstem, research has demonstrated that PPI can be top-down modulated by attention. However, existing studies have not distinguished the specific modulatory effects of different attentional types (feature attention and spatial attention) on PPI, and neurophysiological investigations have concentrated on auditory cortical regions, leaving subcortical mechanisms largely unexplored. Building upon previous research findings and leveraging the dual-pathway model of auditory information processing, this study employs behavioral measurements, electroencephalography (EEG), and brain imaging techniques to elucidate the hierarchical neural expression within the auditory system of neural activities underlying feature and spatial attentional modulation of PPI. This includes 1) establishing a unified behavioral model of feature and spatial attention modulating PPI to examine the similarities and differences in temporal dynamics between the two attentional modulations; 2) investigating the brainstem dissociation mechanisms underlying the two types of attentional modulation of PPI, specifically the differential contributions of pre-pulse stimulus envelope and fine-structure component processing to attentional modulation of PPI; and 3) characterizing the differences in key brain regions and brain networks involved in the two types of attentional modulation of PPI.

Full Text

Neural Mechanisms Underlying the Modulation of Auditory Sensory Gating by Different Attentional Forms

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Abstract: Prepulse inhibition (PPI) serves as a measurement model for auditory sensory gating, reflecting the early information selection function of the auditory system. Although the primary neural circuits of PPI are located in the brainstem, research has demonstrated that PPI can be top-down modulated by attention. However, previous studies have not distinguished the specific modulation of different attentional forms (feature-based attention and spatial attention) on PPI, and neurophysiological investigations have focused primarily on auditory cortical regions, leaving subcortical mechanisms largely unexplored. Building upon previous findings and guided by the dual-pathway model of auditory information processing, this project will employ behavioral measurements, electroencephalography (EEG), and brain imaging techniques to reveal the hierarchical neural representations of feature-based and spatial attentional modulation of PPI within the auditory system. Specifically, the research will: 1) establish a unified behavioral model of feature-based and spatial attentional modulation of PPI to examine similarities and differences in the temporal dynamics of these two attentional modulations; 2) investigate the brainstem dissociation mechanisms underlying attentional modulation of PPI, focusing on differential roles of envelope and fine-structure processing of prepulse stimuli in attentional modulation; and 3) identify differences in key brain regions and neural networks between feature-based and spatial attentional modulation of PPI.

Keywords: attention; auditory sensory gating; prepulse inhibition; dual-pathway model

1. Problem Statement

Auditory information processing represents one of the most fundamental and essential cognitive functions of the human brain. However, the auditory system’ s information processing capacity is limited when confronted with massive auditory input. This necessitates an information selection mechanism that concentrates limited neural resources on important auditory signals for prioritized processing. The brain achieves this selection of relevant auditory information through two distinct mechanisms: an attention mechanism located in the forebrain and an auditory sensory gating mechanism located in the brainstem. Auditory sensory gating reflects the brain’ s early processing capacity for auditory stimuli, specifically inhibiting irrelevant sensory input to ensure that higher-order cognitive processes (such as memory, thinking, and decisionmaking) are not overwhelmed by sensory overload (Csomor et al., 2014; Jones et al., 2016). Researchers generally agree that sensory gating reflects early information selection, operates as an automatic processing mechanism, and involves neural circuits primarily located in the brainstem (Davis & Gendelman, 1977; Li et al., 2009). In contrast, attentional selection of information reflects higher-order cognitive processes and involves mainly cortical regions (Chen et al., 2014; Fritz et al., 2007). Attention has long been a central topic in psychology and cognitive neuroscience and can be categorized into feature-based, spatial, and object-based attention. Importantly, attention and sensory gating are not independent processes; both human and animal studies have demonstrated top-down attentional modulation of auditory sensory gating (Du et al., 2009, 2010, 2011b; Hazlett et al., 2003, 2007; Lei et al., 2014; Li et al., 2009).

Prepulse inhibition (PPI) of the startle reflex is a widely recognized measurement model of auditory sensory gating shared by humans and animals. PPI refers to the inhibition of a startle response when a weak sensory stimulus (the prepulse) precedes the startling stimulus by 30-500 ms. Although the main neural circuits of PPI are located in the brainstem (see review by Davis, 2006) and reflect early selective information processing, previous research has shown that PPI can be top-down modulated by higher-order cognitive processes such as attention (Li et al., 2009; Du & Li, 2011). This attentional modulation of PPI has been demonstrated in both rats (Du et al., 2009, 2010, 2011; Lei et al., 2014) and human subjects (Lei et al., 2018; Yang et al., 2017). However, existing studies have only examined the behavioral manifestation of a single attentional form on PPI modulation, without distinguishing the specific top-down modulation of different attentional forms (such as spatial attention versus feature-based attention) on PPI. Moreover, neurophysiological studies of attentional modulation of PPI have concentrated on auditory cortical regions, with no research to date investigating the subcortical mechanisms of human attentional modulation of PPI. Can both forms of attention be examined within a single behavioral paradigm? What are the neural manifestations of this attentional PPI modulation across auditory cortex, brainstem, and higher-order cognitive networks?

Previous animal and human studies have confirmed that visual information is processed along two separate pathways in the cerebral cortex: an occipitotemporal or ventral pathway responsible for visual object recognition (the "what" pathway), and an occipitoparietal or dorsal pathway that processes spatial relationships between objects and guides movements toward them (the "where" pathway) (de Haan & Cowey, 2011; Goodale & Milner, 1992). Recent research indicates that human auditory information processing also involves two separate pathways: a "what" pathway responsible for auditory pattern recognition and a "where" pathway that processes spatial information of auditory objects, constituting the dual-pathway model for auditory processing (Arnott, Binns, Grady, & Alain, 2004; Romanski et al., 1999; Wang et al., 2008; Zündorf, Lewald, & Karnath, 2016). Importantly, this dual-pathway processing of "what" and "where" information exists not only at the cortical level but also subcortically (Smith et al., 2002; Luo et al., 2017). Based on these findings, the present research proposal aims to demonstrate through a series of behavioral, EEG, and brain imaging studies that feature-based and spatial attentional modulation of PPI conforms to the dual-pathway model of auditory information processing. Specifically, the neural representations of feature-based and spatial attentional modulation of PPI across auditory brainstem, auditory cortex, and higher-order cognitive networks will also involve separate "what" and "where" pathways.

2.1 The Startle Reflex and Prepulse Inhibition (PPI)

The startle reflex is a whole-body reflexive response to intense stimuli shared by humans and animals (Landis & Hunt, 1939), characterized by short latency, strong stimulus summation, and a wide dynamic response range. For example, a sudden impact to the head activates auditory, vestibular, and trigeminal sensory systems, eliciting a strong whole-body startle response. This defensive mechanism evolved as a protective response to head impacts (Yeomans et al., 2002). The neural circuit of the startle reflex is relatively simple: external stimuli project via the cochlear nucleus, trigeminal nucleus, and vestibular nucleus fibers to the caudal pontine reticular nucleus (PnC), where giant cells send projections to cranial nerve motor nuclei and spinal motor or premotor neurons (see review by Yeomans et al., 2002). The startle reflex can be modulated by emotion and learning; threatening stimuli (fear-inducing film clips for humans or stimuli paired with foot shock for animals) enhance startle responses, whereas neutral or sad film clips do not affect startle (Röskam & Koch, 2006). Conversely, reward stimuli or threat-reducing stimuli (pleasant images for humans or reward-related stimuli for rats) can attenuate startle responses (Filion et al., 1998). Currently, the startle reflex is widely used in clinical psychiatry to investigate various emotional states including fear, anxiety, sensitivity, and homeostasis (Rajji & Mulsant, 2008).

Although the startle reflex is a rapid self-protective behavior crucial for survival, it can also interfere with ongoing cognitive and behavioral activities. To adapt to complex environments, the central nervous system has evolved a gating mechanism that inhibits the startle reflex. As illustrated in Figure 1 [Figure 1: see original paper], when a weak sensory stimulus (the prepulse) precedes the startling stimulus by 30-500 ms, the prepulse inhibits the subsequent startle response despite being too weak to elicit a startle reflex itself. This inhibitory effect is termed prepulse inhibition (PPI).

Current research suggests that the neural circuits of PPI are primarily located in the subcortical brainstem. Anatomical studies have confirmed that PPI neural circuits reside in the brainstem, including the inferior colliculus (IC), deeper and intermediate layers of the superior colliculus, and the pedunculopontine tegmental nucleus (PPTg) (Swerdlow et al., 2001; Swerdlow et al., 2008). However, despite the primary location of PPI circuits in the brainstem, PPI circuits maintain extensive connections with sensory cortex, motor systems, and limbic systems, enabling complex modulatory influences. For instance, animal studies have shown that PPI is modulated by the cortico-striato-pallido-thalamic

(CSPT) circuitry (Swerdlow et al., 2001). Brain imaging studies in healthy humans have also confirmed that PPI involves multiple brain regions including the frontal lobe, striatum, hippocampus, insula, anterior cingulate cortex, and thalamus (Campbell et al., 2007; Hazlett et al., 2001; Kumari et al., 2008). Thus, the complex neural network underlying PPI extends from the brainstem through the thalamus to multiple higher cortical regions, providing a biological basis for top-down modulation of PPI by higher cognitive processes.

2.2 Top-Down Attentional Modulation of PPI and Its Neural Mechanisms

Current evidence from animal behavior, human behavioral measurements, and partial neuroscientific data indicates that attention can top-down modulate PPI.

2.2.1 Feature-Based Selective Attention Modulation of PPI

Both human and animal studies have found that feature-based selective attention can enhance PPI (Blumenthal et al., 2015; Dawson et al., 1993; Dawson et al., 2000; Hazlett et al., 2003; Hazlett et al., 2007; Poje & Filion, 2017). Human studies typically employ an "attention-to-prepulse" paradigm in which two pure tones of different frequencies are presented as prepulse stimuli: a standard tone lasting 5 s and a probe tone lasting 8 s. Participants are instructed to silently count the number of probe tones of one frequency while ignoring the other frequency (Hazlett et al., 2003; Hazlett et al., 2007). Research has shown that PPI under attention-to-prepulse conditions is greater than under ignore conditions, demonstrating that attention to prepulse features enhances PPI (Hazlett et al., 2003; Hazlett et al., 2007; Poje & Filion, 2017). Hazlett and colleagues further investigated the neural mechanisms of feature-based attentional modulation of PPI, finding that attention-to-prepulse conditions produced greater BOLD signal activation in the anterior and dorsomedial thalamic nuclei compared to ignore conditions, suggesting thalamic involvement in the neural circuitry of feature-based attentional modulation of PPI (Hazlett et al., 2001). Additionally, animal studies have shown that fear conditioning of a prepulse sound (e.g., a 1300 Hz complex tone) can imbue that sound with ecological significance and capture the rat' s attention, thereby selectively enhancing PPI elicited by that specific sound (Du et al., 2009; Du et al., 2010). Further research has demonstrated that emotional attentional modulation of PPI exhibits stimulus-specificity, with selective emotional attention to prepulse stimuli of a particular feature (e.g., 1300 Hz but not 2300 Hz complex tones) enhancing PPI (Du et al., 2010, 2011).

However, the paradigms used in previous feature-based attentional modulation studies of PPI are not without limitations. In typical PPI paradigms, prepulse stimuli last 20-200 ms, whereas in Hazlett and colleagues' experiments, prepulse durations were 5 s or even 8 s. Research from Luo Huan' s team has demonstrated that human attention exhibits rhythmic oscillations over time (Song et al., 2014; Wang & Luo, 2017), making it impossible for participants to continuously maintain attention on a particular frequency for such extended periods. Consequently, even ignored pure tones receive some attentional resources. Furthermore, in fMRI experiments using these paradigms, the long prepulse durations (5-8 s) combined with the inherent lag of BOLD signals may reflect sensory processing of the prepulse rather than sensory gating per se. This raises an important research question: If prepulse stimuli are presented using traditional PPI parameters (20-200 ms), and participants are instructed to attend to one type of prepulse while ignoring another, does feature-based selective attention still enhance PPI, and what are the corresponding neural mechanisms?

2.2.2 Spatial Selective Attention Modulation of PPI

Spatial selective attention can also enhance PPI (Lei et al., 2014; Lei et al., 2018; Wu et al., 2016b). In noisy auditory environments, listeners hear both direct sound from a source and multiple delayed reflections. When the delay between direct and reflected sound is sufficiently short (approximately 1-10 ms, depending on sound type), the delayed reflection is captured by the leading direct sound (Li et al., 2005), and listeners perceive a single fused sound image originating from the leading source—an auditory object (Litovsky et al., 1999). This phenomenon is known as the precedence effect, which has been observed in humans and experimental animals including rats, cats, and owls (Lei et al., 2014; Lei et al., 2018; Wu et al., 2016a).

Under laboratory conditions, the precedence effect can be used to create perceptual spatial separation or coincidence of irrelevant sound signals, thereby modulating spatial selective attention. As illustrated in Figure 2 [Figure 2: see original paper], when two loudspeakers on the left and right both play two different sounds (A and B) (Figure 2a), if sound A is presented 3 ms earlier from the left speaker while sound B is presented 3 ms earlier from the right speaker, the two A sounds will subjectively fuse with a perceived location at the left speaker. Similarly, the two B sounds will fuse with a perceived location at the right speaker, resulting in perceptual spatial separation of the A and B sound images (Figure 2b). Conversely, if both sounds A and B are presented 3 ms earlier from the left speaker, the two sound images will be perceived as spatially coincident (Figure 2c). Since both sounds originate from the same two speakers, there is no objective separation and thus no change in signal-to-noise ratio. When the loudspeaker positions are symmetric relative to the listener, this perceptual separation also does not affect the perceived density of the sound images. Perceptual spatial separation based on the precedence effect reflects the integration of auditory object feature processing and spatial attribute processing in the auditory cognitive system. This perceptual spatial separation allows listeners to ignore one sound image while selectively enhancing spatial attention to another (Li et al., 2009).

Perceptual spatial separation between signal and masker stimuli can facilitate spatial selective attention on the target signal, thereby improving speech recognition performance (Freyman et al., 2004, 2008; Wu et al., 2016a; Wu et al., 2005; Zheng et al., 2016). Brain imaging results indicate that perceptual spatial separation under masking conditions enhances auditory speech recognition by activating the superior parietal lobule within the auditory attention network (Zheng et al., 2016). EEG studies have found that perceptual spatial separation enhances selective attention to target stimuli, specifically increasing the cortical evoked potential N1P2 component (Lei et al., 2018; Zhang et al., 2014). Animal behavioral studies have shown that perceptual spatial separation can enhance PPI (Du et al., 2011b; Lei et al., 2014). In rat experiments, perceptual spatial separation enhances spatial selective attention and increases PPI (Du et al., 2009, 2010; Lei et al., 2014), with the PPI enhancement dependent on excitatory glutamate transmission in the posterior parietal cortex (Du et al., 2011). These results have been replicated in multiple experiments (Lei et al., 2014; Wu et al., 2016). Our recent research has adapted animal PPI paradigms for human subjects and found that perceptual spatial separation also enhances PPI in humans (Lei et al., 2018; Yang et al., 2017).

PPI is recognized as an endophenotype of schizophrenia. Since Braff et al. (1978) first reported significantly reduced PPI in schizophrenia patients—a finding repeatedly validated in subsequent studies—attentional deficits have also been established as an endophenotype of schizophrenia. A longitudinal study showed that individuals at high risk for developing schizophrenia spectrum disorders exhibited attentional deficits before any clinical symptoms emerged (Smith & Cornblatt, 2005). Thus, attention represents another schizophrenia endophenotype closely related to PPI (Javitt et al., 2015). Both attention and PPI serve as mechanisms for selecting important information and inhibiting irrelevant interference, and both can serve as endophenotypes for early identification and screening of schizophrenia. However, research on their relationship remains limited. Hazlett et al. (2007) found that in schizophrenia patients, both baseline PPI and attentional modulation of PPI were impaired, but only the deficit in attentional modulation of PPI correlated significantly with schizophrenia-specific symptom severity. In animal models of schizophrenia using early social isolation, isolation rearing only attenuated PPI in adulthood but completely eliminated both fear conditioning-induced enhancement and perceptual separation-induced enhancement of PPI (Du et al., 2009; Du et al., 2010). Therefore, deficits in attentional modulation of PPI are more closely related to schizophrenia, making research on the cognitive and neural mechanisms of attentional modulation of PPI crucial for understanding schizophrenia pathophysiology and exploring new endophenotypic markers.

Despite substantial progress in behavioral research on feature-based and spatial attentional modulation of PPI, few studies have comprehensively examined both forms of attention together. Furthermore, research on the neural mechanisms of attentional modulation of PPI remains in its early stages, with cortical and subcortical mechanisms still unclear. Limited studies have addressed cortical mechanisms. For example, brain imaging research has found that BOLD signal enhancement in the anterior and dorsomedial thalamic nuclei correlates with feature-based attentional modulation of PPI (Hazlett et al., 2001). Perceptual spatial separation facilitating speech recognition under masking conditions activates the superior parietal lobule within the auditory attention network (Zheng et al., 2016). Our recent EEG research has found that perceptual spatial separation enhances PPI and strengthens neural representation of prepulse stimuli, manifested as enhanced cortical evoked potentials N1/P2. Importantly, the PPI enhancement induced by perceptual spatial separation positively correlates with the N1 component enhancement but not with P2 enhancement (Lei et al., 2018). The N1 component likely reflects auditory cortical activity in temporal regions including Heschl' s gyrus and the superior temporal plane (STP), while P2 reflects non-modality-specific higher cortical activity primarily localized to association cortex. This further suggests that perceptual spatial separation enhances PPI by strengthening early cortical evoked potentials (N1) to prepulse stimuli, thereby enhancing spatial selective attention to the prepulse and consequently increasing PPI (Lei et al., 2018).

These studies suggest that feature-based and spatial selective attention modulation of PPI involve different neural circuits. However, current research has not addressed the common or specific modulation of PPI by feature-based and spatial selective attention, and the similarities and differences in neural mechanisms remain unclear.

2.2.3 Subcortical Mechanisms of Attentional Modulation of PPI and Frequency-Following Responses (FFRs)

As previously mentioned, previous neurophysiological studies of attentional modulation of PPI have focused primarily on cortical mechanisms, while subcortical mechanisms remain unclear. Current research indicates that PPI neural circuits are mainly located in the subcortical brainstem. Anatomical studies have confirmed that PPI neural circuits reside in the brainstem, including the inferior colliculus (IC), deeper and intermediate layers of the superior colliculus, and the pedunculopontine tegmental nucleus (PPTg). However, how these subcortical brainstem structures participate in feature-based and spatial selective attentional modulation of PPI remains unknown.

Frequency-following responses (FFRs) are neural population activities originating from the auditory brainstem that reflect precise phase-locking of neurons to low- and mid-frequency auditory stimuli (Chandrasekaran & Kraus, 2010; Du et al., 2011a; Kraus et al., 2017; Marsh et al., 1970). Scalp-recorded FFRs in humans can reflect phase-locking to sounds up to 1.5 kHz (Glaser et al., 1976), while intracranial electrophysiological recordings in animals can reflect phase-locking up to 4 kHz (Ping et al., 2008). FFRs reflect auditory brainstem activity, which serves as a critical relay pathway for binaural information transmission to the brain while also receiving modulation from numerous descending cortical networks. Therefore, brainstem neural activity reflects the interaction between sensory information processing and higher-order cognition, making it an ideal region for studying top-down attentional modulation of bottom-up PPI.

In human subjects, FFRs can reflect neural population processing of key components of complex sound stimuli (Coffey et al., 2017). Unlike traditional auditory brainstem responses (ABRs) that typically use clicks or pure tones, FFRs can be recorded in response to auditory stimuli ranging from simple pure tones (Chimento & Schreiner, 1990; Galbraith, 1994) to complex speech stimuli (Aiken & Picton, 2008; Akhoun et al., 2008; Krishnan et al., 2004; Russo et al., 2004; Song et al., 2008) and music (Musacchia et al., 2007). FFR studies have also shown that responses to target signals can be modulated by attention (Galbraith et al., 2003; Hairston et al., 2013; Lehmann & Schönwiesner, 2014), short-term training (Skoe & Kraus, 2012; Song et al., 2008; Song et al., 2012), and long-term experience (Chandrasekaran & Kraus, 2010; Musacchia et al., 2007). Previous reports have shown that spatial selective attention to target sounds can enhance inferior colliculus FFRs (Du et al., 2011a; Wilson & Krishnan, 2005), reflecting subcortical mechanisms of spatial attentional enhancement of target signal representation.

Importantly, through appropriate signal processing methods (Hilbert transform), FFR information can be decomposed into phase-locked responses to rapidly changing temporal fine structure and more slowly varying envelope structure (Aiken & Picton, 2008; Ananthakrishnan et al., 2015; Luo et al., 2017; Wang & Li, 2017). According to the dual-pathway model of auditory information processing, "what" and "where" pathway processing already exists subcortically (Arnott et al., 2004; Wang et al., 2008). Smith et al. (2002) proposed that fine structure processing may be more involved in sound localization, while envelope processing may be more related to sound object and semantic information, forming the acoustic basis for spatial (where) and content (what) circuits in auditory cortex, respectively. This "fine structure-envelope double dissociation hypothesis," proposed in 2002, provides a specific description of the dual-pathway model at the subcortical level. Therefore, FFRs serve not only as an important tool for investigating midbrain mechanisms of attentional modulation of PPI but also can reflect differential roles of envelope and fine structure in feature-based versus spatial attentional modulation of PPI. This raises an intriguing research question: Does the inferior colliculus play an important role in the neural circuits of attentional modulation of PPI? Do feature-based and spatial selective attentional modulation of PPI correspond respectively to envelope and fine structure processing in FFRs?

3. Research Proposal

This project will systematically investigate the modulatory effects of feature-based and spatial selective attention on PPI and their neural mechanisms across multiple levels of the auditory system using auditory behavioral measurements, scalp EEG, and functional magnetic resonance imaging (fMRI). First, we will establish a unified behavioral paradigm for feature-based and spatial attentional modulation of PPI. Using EEG, we will examine temporal dynamic differences in attentional modulation of PPI at the cortical level while investigating brainstem dissociation mechanisms at the subcortical level, focusing on differential roles of envelope and fine-structure components of prepulse stimuli. Finally, using fMRI, we will examine similarities and differences in key brain regions and neural networks activated by feature-based versus spatial attentional modulation of PPI. Specifically, we plan to conduct three lines of research (Figure 3 [Figure 3: see original paper]).

3.1 Temporal Dynamics of Different Attentional Forms in Modulating PPI

As previously described, both feature-based and spatial attention can modulate PPI. EEG technology, with its millisecond-level temporal resolution, is an ideal tool for investigating the temporal dynamic processing mechanisms of these two attentional modulations. In the "attention-to-prepulse" paradigm, attending to a particular prepulse feature (e.g., a 400 Hz pure tone versus an 800 Hz pure tone) enhances PPI (Hazlett et al., 2003, 2007). EEG studies have found that when PPI occurs, prepulse-evoked components P50 (50-75 ms) and N1 (75-150 ms) show significant changes, while the P30 (10-40 ms) component remains unchanged (Simons & Perlstein, 1996). Researchers currently believe that P30 reflects transient detection of the prepulse, while P50 reflects sensory processing of the prepulse, with P30 reflecting rapid medial lemniscal pathway activity and P50 reflecting slower lateral lemniscal activity. These results support the "processing-protection" theory of PPI (Graham, 1975). Similarly, previous studies have found that PPI is associated with enhancement of early auditory processing components P50 and N1, while later components P2 and N2 remain unchanged (Simons & Perlstein, 1996). These findings suggest that processing of prepulse features is reflected primarily in early processing components, particularly P50 and N1, while later components P2 and N2 are unaffected.

Additionally, as previously mentioned, in spatial attention modulation paradigms, perceptual spatial separation between prepulse stimuli and background noise can enhance spatial selective attention to the prepulse, thereby increasing PPI. Our ERP study (Lei et al., 2018) found that perceptual spatial separation enhances PPI while strengthening neural representation of prepulse stimuli, manifested as enhanced cortical evoked potentials N1/P2. Importantly, PPI enhancement induced by perceptual spatial separation positively correlates with N1 component enhancement but not with P2 enhancement. The N1 component reflects auditory cortical activity in temporal regions including Heschl' s gyrus and the superior temporal plane (STP) (Näätänen et al., 1987), while P2 reflects non-modality-specific higher cortical activity primarily localized to association cortex (Crowley et al., 2004). Another brain lesion study found that patients with inferior parietal lobule (IPL) damage showed significantly reduced N1 responses to auditory stimuli but unaffected P2 responses. Since IPL is an important brain region for auditory spatial selective attention, these results indicate that the N1 component is closely related to auditory spatial selective attention (Woods et al., 1993). However, previous

ERP studies have used only simple white noise as prepulse stimuli and have not examined more complex narrowband noise or vowel stimuli, thus failing to investigate later auditory components such as N2. It can be hypothesized that processing of spatial information in prepulse stimuli is reflected primarily in relatively later processing components, particularly N1 and N2, while early components such as P50 may remain unaffected.

Furthermore, in speech perception research, Du et al. comprehensively examined the roles of frequency cues and spatial cues in speech segregation, finding that participants could use both types of cues to improve target speech recognition, with behavioral improvements showing linear additive effects. Subsequent MEG research revealed that both frequency and spatial cues enhanced the N1 component (peaking at 110 ms) of auditory evoked magnetic fields (AEFs) to target speech, with linear additive characteristics—meaning that the N1 enhancement when both cues were present together was essentially equal to the sum of N1 enhancements when each cue was presented separately. Therefore, we hypothesize that both feature-based and spatial selective attentional modulation of PPI may affect the auditory cortical evoked N1 component, with the two attentional forms exerting independent effects on PPI modulation that show linear additive relationships in their impact on the N1 component.

According to the dual-pathway model of auditory information processing, the spatial (where) and content (what) circuits in auditory cortex process auditory information at different speeds (Arnott et al., 2004; Wang et al., 2008). Therefore, different attentional forms may modulate PPI with distinct temporal dynamics. However, previous results and our own work have not definitively demonstrated this, primarily because each study measured only feature-based or spatial attentional modulation of PPI separately, without assessing both within the same participants and the same study. Therefore, in Study 1, we will use behavioral measurements and EEG to establish a unified paradigm for feature-based and spatial attentional modulation of PPI and examine similarities and differences in their temporal dynamics. We hypothesize that: 1) feature-based and spatial attentional modulation of PPI exhibit different temporal characteristics, with feature-based attentional modulation occurring in early processing stages, reflecting rapid processing of stimulus features and specifically correlating with early EEG components such as P50; 2) spatial attentional modulation of PPI occurs in relatively later processing stages, reflecting slower processing of spatial cues and specifically correlating with later EEG components such as N2; and 3) both feature-based and spatial attentional modulation of PPI are associated with the N1 component, which is closely related to auditory cortex activity, with the two attentional forms exerting independent effects on N1 enhancement that show linear additive relationships.

3.2 Brainstem Dissociation Mechanisms of Feature-Based and Spatial Selective Attentional Modulation of PPI

As previously described, frequency-following responses (FFRs) are neural population activities originating from the auditory brainstem that reflect precise phase-locking of neurons to low- and mid-frequency auditory stimuli (Chandrasekaran & Kraus, 2010; Du et al., 2011a; Kraus et al., 2017; Marsh et al., 1970). Scalp electrophysiological recording of FFRs in human subjects is now well-established (Kraus et al., 2017). FFRs reflect auditory brainstem activity, which serves as a critical relay for binaural information transmission to the brain while receiving modulation from numerous descending cortical networks. Therefore, brainstem neural activity reflects the interaction between sensory information processing and higher-order cognition, making it an ideal region for studying top-down attentional modulation of bottom-up PPI.

FFRs can reflect neural population processing of key components of complex sound stimuli (Coffey et al., 2017). More importantly, through appropriate signal processing methods (Hilbert transform), FFR information can be decomposed into phase-locked responses to rapidly changing temporal fine structure and more slowly varying envelope structure (Aiken & Picton, 2008; Ananthakrishnan et al., 2015; Luo et al., 2017; Wang & Li, 2017). Previous studies have confirmed that these two components (fine structure and envelope) can be recorded and measured in the central nervous system. For example, auditory evoked responses in animal auditory nerve and inferior colliculus can accurately represent both envelope and fine structure components (Luo et al., 2017). Additionally, human FFRs can also be decomposed into envelope and fine structure components (Aiken et al., 2008). This provides a feasible recording method for investigating the brainstem dissociation mechanisms of feature-based and spatial attentional modulation of PPI, allowing separate recording of envelope and fine structure components of neural responses to target sounds.

In 2002, Smith et al. proposed the "fine structure-envelope double dissociation" hypothesis, suggesting that fine structure is primarily involved in spatial localization of speech signals while envelope components mainly carry semantic information, forming the acoustic basis for spatial (where) and content (what) circuits in auditory cortex, respectively. This hypothesis elegantly corresponds to the classic "where" and "what" dual-pathway model of the auditory system and is therefore considered a specific manifestation of the dual-pathway model at the auditory brainstem level (Smith et al., 2002; Luo et al., 2017). Previous reports have shown that spatial selective attention to target sounds can enhance inferior colliculus FFRs (Du et al., 2011a; Du et al., 2012; Wilson & Krishnan, 2005), and recent animal neurophysiological research has further confirmed that spatial cue processing of simultaneously presented sounds in the brainstem is related to fine structure components recorded in FFRs (Luo et al., 2017). Since envelope structure primarily contributes to content recognition (Ding et al., 2016, 2017) and forms the acoustic basis for the content (what) circuit, we hypothesize that feature-based attentional modulation of PPI may be related to enhanced brainstem envelope representation of target signals. Conversely, since fine structure information primarily contributes to sound localization (Luo et al., 2017) and forms the acoustic basis for the spatial (where) circuit, we hypothesize that spatial attentional modulation of PPI may be related to enhanced brainstem fine structure representation of target signals. Thus, feature-based and spatial attentional enhancement of PPI may show dissociation at the brainstem neural level.

Additionally, the correspondence between brainstem and cortical mechanisms of attentional modulation of PPI warrants investigation. Central representation of auditory sensory signals exhibits hierarchical changes in coding strategies: brainstem neural coding shows high redundancy, while auditory cortical coding demonstrates sparse coding strategies (Ding et al., 2016, 2017). Consequently, high-frequency fine structure temporal representation is greatly reduced in auditory cortex compared to brainstem, while envelope temporal representation remains prominent. Ding et al. found that auditory cortex can record envelope components reflecting speech syllable rhythms in delta and theta bands using EEG and MEG (Ding et al., 2016, 2017). By recording both brainstem FFRs and cortical evoked potentials (EEG) in the same subjects, we can examine the correspondence between subcortical and cortical mechanisms of the two attentional modulations of PPI. Previous research has found that inferior colliculus and auditory cortex show very similar representation of narrowband noise envelope information, and under attentional conditions, both show enhanced synchronous activity in the gamma band (50-100 Hz) (Luo, 2017). Therefore, we predict that feature-based attentional modulation of PPI will enhance envelope representation of sound signals in the auditory brainstem, with further enhancement of envelope representation observed at the cortical level, and that the electrophysiological signals recorded under attentional conditions will show enhanced gamma band response synchrony.

Therefore, in Study 2, we will use EEG to record human brainstem frequency-following responses (FFRs) within the unified paradigm for feature-based and spatial attentional modulation of PPI established in Study 1, to investigate the brainstem dissociation mechanisms of feature-based and spatial attentional modulation of PPI. We hypothesize that feature-based and spatial attentional modulation of PPI will show dissociated effects at the brainstem level: 1) feature-based attentional modulation of PPI will be associated with enhanced brainstem envelope representation of prepulse stimuli; and 2) spatial attentional modulation of PPI will be associated with enhanced brainstem fine structure representation of prepulse stimuli. Integrating findings from Studies 1 and 2, we propose the following hypotheses regarding the relationship between cortical and subcortical responses in attentional modulation of PPI: 3) feature-based and spatial attention separately modulate envelope and fine structure representations of prepulse stimuli in the brainstem, providing initial attentional modulation of PPI at the subcortical level. Feature-based attentional modulation of PPI will enhance envelope structure of sound signals in the auditory brainstem, with further enhancement of envelope representation at the cortical level, and the electrophysiological signals recorded under attentional conditions will show enhanced gamma band response synchrony.

3.3 Key Brain Regions and Neural Networks in Feature-Based and Spatial Selective Attentional Modulation of PPI

According to the dual-pathway model of auditory information processing, neural representations of feature-based and spatial attentional modulation of PPI differ not only in processing speed but also in brain activation patterns. Previous neuroimaging research has found that during attention-to-prepulse feature conditions, BOLD signal activation in the anterior and dorsomedial thalamic nuclei is greater than during ignore conditions, suggesting thalamic involvement in the neural circuitry of feature-based attentional modulation of PPI (Hazlett et al., 2001). Schizophrenia patient studies have shown that during attention-to-prepulse feature conditions, healthy subjects activate the frontal-striatal-thalamic (FST) circuit including dorsolateral prefrontal cortex, striatum, and dorsomedial thalamus, whereas schizophrenia patients show reduced activation in FST circuit regions (Hazlett et al., 2008). Animal neuropharmacological studies have found that fear conditioning of a particular prepulse frequency can selectively enhance PPI elicited by that frequency (Du et al., 2011), with this fear conditioning-induced PPI enhancement showing stimulus specificity and depending on excitatory glutamate transmission in the amygdala and primary auditory cortex (Du et al., 2011). These results suggest that feature-based attentional modulation of PPI may involve brain regions including the thalamus, primary auditory cortex, striatum, and frontal lobe—key regions in the auditory "what" ventral pathway.

Meanwhile, both human and animal behavioral studies have confirmed that perceptual spatial separation can modulate PPI (Lei et al., 2014, 2018). At the neural level, fMRI studies of perceptual spatial separation facilitating speech recognition have found that perceptual spatial separation between target speech and masking speech significantly activates brain regions including the superior parietal lobule, precuneus, inferior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and caudate nucleus (Wu et al., 2016; Zheng et al., 2016). This indicates that perceptual spatial separation facilitating speech recognition involves activity in multiple brain network circuits beyond the auditory system, including frontal, parietal, cingulate, and basal ganglia regions. Animal studies have also found that perceptual spatial separation can enhance PPI (Lei et al., 2014), with this enhancement closely related to excitatory glutamate transmission in the posterior parietal cortex (Du et al., 2011). Therefore, we can hypothesize that the precuneus, inferior parietal lobule, and the dorsal pathway (where pathway) in which they reside may constitute important neural substrates for using perceptual spatial separation cues to enhance PPI.

Therefore, in Study 3, we will use brain imaging techniques within the unified paradigm for feature-based and spatial attentional modulation of PPI established in Study 1 to investigate key brain regions and neural networks involved in feature-based and spatial attentional modulation of PPI. We hypothesize that: 1) feature-based and spatial attentional modulation of PPI involve different key brain regions, with feature-based attentional modulation involving brain regions in the auditory "what" pathway including auditory thalamus, primary auditory cortex, striatum, and superior temporal gyrus; 2) spatial attentional modulation of PPI involves brain regions in the auditory "where" pathway including primary auditory cortex, precuneus, and inferior parietal lobule; and 3) despite being different forms of attentional modulation, both may involve activation of some common brain regions due to partial overlap between the neural networks of the auditory dual-pathway model, such as primary auditory cortex (which serves as a central hub for auditory processing in both attentional forms), frontal lobe activity (as both feature and spatial attention networks show common activation in higher cortical regions like dorsolateral prefrontal cortex), and inhibitory function-related regions such as the caudate nucleus (since attentional modulation of PPI involves both enhancement of target signal processing and inhibition of interfering information).

4. Theoretical Framework

When humans and animals face complex information input, they utilize sensory gating systems to suppress irrelevant sensory stimuli while ensuring deep processing of important sensory information (Du et al., 2011; Yeomans et al., 2002). When an intense sensory stimulus suddenly appears, humans and animals exhibit a strong whole-body reflex called the startle reflex, representing the first level of information processing. The startle reflex is crucial for survival, enabling rapid responses to threatening stimuli. However, startle reflexes can also interfere with ongoing behavioral and cognitive activities. To ensure execution of important behaviors and cognitive processes, the central system has evolved a gating mechanism that inhibits the startle reflex: prepulse inhibition, representing the second level of information processing that reflects modulation of the startle reflex. Although PPI, as a pre-attentive gating process, has neural circuits located in the brainstem, it maintains extensive connections with sensory cortex, association cortex, motor systems, and limbic systems, enabling top-down attentional modulation (Li et al., 2009).

This study hypothesizes that spatial attention and feature-based attention can enhance PPI, representing the third level of sensory gating information processing that reflects modulation of PPI (Du & Li, 2011). According to the dual-pathway model of auditory information processing, spatial and feature attentional modulation of PPI have different neural substrates. This research will establish a unified behavioral model of feature-based and spatial attentional modulation of PPI to examine similarities and differences in processing speed and activation patterns across auditory brainstem, auditory cortex, and higher-order cortex. Instructing participants to attend to stimuli of a particular frequency while ignoring others is a common paradigm for auditory feature-based attention, while the perceptual spatial separation paradigm based on the precedence effect effectively elicits spatial selective attention to target stimuli. Combining frequency-specific attention with the perceptual spatial separation paradigm allows behavioral measurement of combined and separate effects of feature-based and spatial attentional modulation of PPI. This new behavioral model provides an important foundation for further investigation of the neural mechanisms underlying selective attentional enhancement of PPI.

Integrating previous findings with our theoretical hypotheses, attentional modulation of PPI exhibits hierarchical representations in the auditory system. Auditory system information processing is hierarchical, and central representation of auditory sensory signals shows hierarchical changes in coding strategies: brainstem neural coding demonstrates high precision and redundancy, while auditory cortical coding shows sparse coding strategies. The brainstem can precisely represent both fine structure and envelope components of auditory signals, whereas high-frequency fine structure representation is greatly reduced in auditory cortex compared to brainstem, though envelope representation remains prominent. First, at the brainstem level, feature-based attentional modulation of PPI may be related to enhanced brainstem envelope representation of target signals, while spatial attentional modulation may be related to enhanced brainstem fine structure representation. Fine structure is primarily involved in spatial localization of speech signals, while envelope components mainly carry semantic information. At the auditory brainstem level, feature-based and spatial attentional enhancement of PPI show dissociated neural representations, supporting the dual-pathway model of auditory processing. Second, at the auditory cortical level, feature-based and spatial selective attentional modulation of PPI show different temporal dynamic characteristics, with feature-based modulation occurring in early processing stages reflecting rapid feature processing, while spatial modulation occurs in later stages reflecting slower spatial cue processing. EEG research will further examine the dissociation in processing speed of the dual-pathway model from a temporal dynamics perspective. Finally, at the higher cortical level, feature-based attentional modulation of PPI involves brain regions in the auditory "what" pathway, while spatial attentional modulation involves brain regions in the "where" pathway. Brain imaging research will further confirm different activation patterns for the two attentional modulations of PPI, validating the dual-pathway model at the cortical level.

Additionally, feature-based and spatial attentional modulation of prepulse inhibition share common principles. Although the brain' s processing of prepulse feature and spatial location attention depends on separate "what" and "where" pathways, the neural networks for feature-based and spatial attention partially overlap, and both forms of attentional modulation involve some common brain regions. Previous animal studies have found that primary auditory cortex plays important roles in both spatial attentional and emotional attentional modulation of PPI (Du et al., 2011). The deeper layers of the superior colliculus (DpSC) in the PPI brainstem circuit also participate in both spatial and emotional attentional modulation of PPI, possibly working through both top-down modulation from forebrain and bottom-up modulation of midbrain prepulse signal representation (Ding et al., 2019). Recent animal research indicates that the medial agranular cortex (AGm) in rats also contributes to attentional enhancement of PPI, with AGm projecting to dorsomedial striatum, then to the substantia nigra pars reticulata in the brainstem, thereby implementing attentional modulation of PPI (Meng et al., 2020). Therefore, we propose that primary auditory cortex, superior colliculus, and secondary motor cortex (corresponding to the rat AGm region) are commonly activated across different attentional modulations of PPI.

Finally, this research has clinical applications. The cognitive deficits observed in schizophrenia patients may be related to early information processing disturbances (Javitt & Sweet, 2015; Jones et al., 2016), and abnormal sensory gating and its higher-order cognitive modulation are considered important pathophysiological bases of schizophrenia. Therefore, investigating the cognitive and neural mechanisms of attentional modulation of sensory gating is important for understanding schizophrenia pathophysiology, exploring potential biomarkers, and assisting early objective diagnosis and intervention (Lei, Tian, Wang, & Li, 2017). This research also has industrial applications. Speech recognition has long been an important topic in artificial intelligence. While many algorithms can recognize speech signals well in quiet conditions, computers are far inferior to the human brain in noisy environments. Investigating how the brain's sensory gating process is top-down modulated by different attentional forms in noisy environments may provide insights for developing computer speech recognition technology.

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