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Clarifying the functional process represented by P50 suppression

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ABSTRACT

P50 suppression refers to the amplitude-reduction of the P50 event related potential to the second (S2) relative to the first (S1) of identical auditory stimuli presented 500 ms apart. Theory suggests that refractory periods (RPs) and/or inhibitory inputs (II) underlie P50 suppression. The present study manipulated interval between stimulus pairs (IPI: 2, 8 s) and direction of participants' attention (Attention, Non-Attention) in order to determine which theory best explains P50 suppression. The rationale is that: 1/ RP and II predict opposite effects of manipulating the functionality of the mechanism responsible for S2P50 suppression (e.g. reducing function would increase S2P50 according to the II and decrease S2P50 according to the RP hypothesis); 2/ IPI2 (relative to IPI8) will *reduce functionality* of the mechanism responsible for S2P50 suppression, as it results in less recovery of (and a greater challenge to) that mechanism — RP would thus predict reduced S2P50, whereas II would predict enhanced S2P50 amplitude; and 3/ where the mechanism responsible for S2P50 suppression is challenged (i.e. at IPI2, due to insufficient recovery), Attention (relative to Non-Attention) will *enhance functionality* of this mechanism — RP would thus predict increased S2P50, whereas II would predict reduced S2P50 amplitude. In the Non-Attention paradigm, reducing IPI from 8 to 2 s tended to *increase* S2P50 amplitude (and consequently impaired P50 suppression), and in the 2 s IPI paradigm, directing attention towards the stimuli *reduced* S2P50 amplitude (and improved P50 suppression), with both effects supporting the II hypothesis only.

1. Introduction

Presenting two identical auditory stimuli (S1 and S2) separated by 500 ms elicits a P50 event-related potential (ERP)—a positive deflection in the electroencephalogram (EEG)—approximately 50 ms after each stimulus. The P50 amplitude elicited by S2 is usually smaller relative to the S1 P50 amplitude. This reduction is termed "P50 suppression" (Siegel et al., 1984) and is quantified primarily using two derived ERP measures: the P50 Difference (S1 − S2) and the P50 Ratio (S2/S1).

Theory suggests that two processes may account for P50 suppression: a refractory period (RP) (Jerger et al., 1992) and/or an inhibitory input (II) process (Freedman et al., 1996). The RP hypothesis posits (Siegel et al., 1984) that after responding to an auditory stimulus, the neuronal population generating the P50 response (thought to be in the auditory cortex; ACx) (Godey et al., 2001; Korzyukov et al., 2007; Liégeois-Chauvel et al., 1994; Weisser et al., 2001; Yvert et al., 2001) is temporarily exhausted. Following this, it gradually recovers, and P50 amplitudes depend on the recovery status of this neuronal population. Thus, under the RP hypothesis, S2P50 is reduced relative to S1P50 because at the arrival of S2 (500 ms after S1), the ACx neuronal population has not recovered fully, whereas at the arrival of S1 (≈8 s after the previous S2), it has recovered to a greater extent, perhaps fully (Zouridakis and Boutros, 1992).

According to the II hypothesis, the ACx neuronal population generating the P50 response also engages inhibitory inputs which, in a feedback loop with these ACx neurons, act to inhibit the responding of ACx to the subsequent arrival of an identical auditory stimulus. These inhibitory inputs were originally thought to originate in the CA3 hippocampal region (Freedman et al., 1996; Hershman et al., 1995) however there is also evidence implicating frontal lobe (Knight et al., 1999) and reticular activating system (Erwin and Buchwald, 1986) involvement in this purported inhibitory process. The II process is thought to be long lasting (>500 ms; (Miller and Freedman, 1995)). Thus, since they are still active when S2 is presented (500 ms after S1) these inhibitory inputs serve to reduce the ACx P50 response to S2.

P50 suppression is important in schizophrenia (Bramon et al., 2004; Chang et al., 2011; de Wilde et al., 2007; Heinrichs, 2004; Patterson et al., 2008) and across the schizophrenia spectrum (Croft et al., 2001, 2004). It has been argued to be an endophenotype for schizophrenia (Thaker, 2008) however failures to find P50 suppression impairments in schizophrenia (Greenwood et al., 2012; Light et al., 2012) have called this assertion into question. The lack of clarity as to the functional relevance of P50 suppression may contribute to this uncertainty, as it is difficult to control for confounds in schizophrenia research without such

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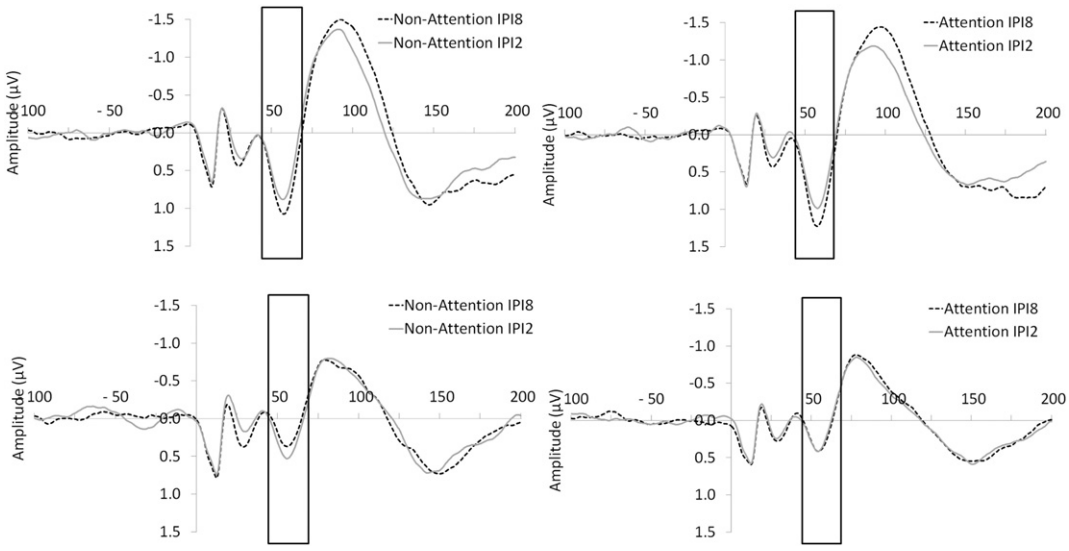

Fig. 1. ERPs elicited in the Non-Attention (left) and Attention (right) conditions at IPI8 (dotted black line) and IPI2 (solid gray line). P50 ERPs to S1 (top) and S2 (bottom) are boxed. Stimulus onset is at 0 ms. Positive is plotted downwards.

knowledge. The logic underpinning these hypotheses can be used to help determine their adequacy, and thus their relation to schizophrenia:

If, as per the RP hypothesis, the ACx is temporarily exhausted after responding to an auditory stimulus and gradually recovers from this, then presenting auditory stimuli at incrementally greater intervals should produce a commensurate increase in P50 amplitudes as recovery increases. The results of such studies suggest that P50 amplitude (and thus the ACx response generating it) fully recovers 3000 ms after responding to a prior stimulus (Dalecki et al., 2011), but shorter intervals (250–1000 ms) are insufficient for full recovery (Dalecki et al., 2011; Dolu et al., 2001). So if recovery of the ACx *alone* accounts for P50 suppression, then reducing the time in between stimulus pairs (inter-pair interval; IPI) from the standard 8 s to <3 s should reduce S1P50 (due to less recovery), but as S2 always occurs 500 ms after S1, S2P50 should be either unaffected (if S1 exhausts the P50 generator and S2P50 is thus generated from a minimal neural reserve regardless of the IPI preceding S1) or reduced (if it is generated from a proportion of the reduced neural reserve). On the other hand, if P50 suppression is due to ACx activating inhibitory inputs, then reducing the time in between stimulus pairs from the standard 8 s to <3 s would result in either the ACx itself being insufficiently activated (as indexed by reduced S1P50) to adequately engage inhibitory inputs, or reduction of the inhibitory resource (due to insufficient time for full recovery of the inhibitory inputs). Both of these possibilities would result in *increased* S2P50 (in the 2 s relative to 8 s IPI condition). Thus the present study will manipulate the interval between stimulus pairs in order to determine which theory best explains P50 suppression, with similar or smaller S2P50s in the 2 s (relative to 8 s) condition supporting the refractory period hypothesis, and larger S2P50s in the 2 s condition supporting the inhibition hypothesis.

Another way to address this issue is via the manipulation of attention. As set out above, the RP hypothesis postulates that ACx recovery status underlies P50 suppression. Thus, if RP accounts for P50 suppression and attention enhances the ACx response, then directing attention towards stimuli should enhance both S1 and S2 P50s. On the other hand, as II posits inhibitory input involvement (and ACx as the trigger for this inhibitory input) in P50 suppression, attention could enhance neither, one, or both of these. If attention enhances the *ACx response only*, then directing attention towards the stimuli should enhance both S1 and S2P50s (although, if the enhanced S1 response subsequently engaged more inhibitory inputs then the S2P50 ACx increase may be countered by greater inhibition and thus results in no change in S2P50). If attention enhances the *inhibitory inputs only*, then directing attention towards auditory stimuli should not affect S1P50 (as inhibitory inputs are not active at the time of S1 presentation), and should reduce S2P50 (due to attentional enhancement of inhibitory action on S2). Finally if attention enhances both the ACx response *and* inhibitory inputs, directing attention to auditory stimuli should enhance S1P50 (due to attentional enhancement of the ACx response) and reduce S2P50 (due to greater ACx engagement of inhibitory inputs and/or attention enhancing inhibitory inputs directly). Thus the present study also manipulated the direction of attention in the 2 s IPI condition (where the mechanisms for each hypothesis are challenged) in order to determine which theory best explains P50 suppression, with larger S2P50s in the Attention condition (relative to Non-Attention) supporting the recovery hypothesis, and similar or smaller S2P50s supporting the inhibition hypothesis.

The question of attention effects on P50 is particularly relevant to schizophrenia, as patients are known to have attentional impairments. That is, if attention modulates either the ACx response or inhibitory inputs, this raises the possibility that group differences may arise due merely to the well-described attentional differences between the groups (Braff, 1993), rather than because of specific differences in ACx response and/or inhibitory processing.

Few studies have examined the effects of directing attention *towards* and *away from* auditory stimuli on P50 measures. Some studies have compared the standard 'passive' P50 paradigm with one where attention is directed toward auditory stimuli (Rosburg et al., 2009; Yee et al., 2010). However, this comparison is problematic as it is difficult to determine where attention is directed under 'passive' conditions. That is, despite not being given specific instructions to attend to the stimuli, it is possible that participants may do so regardless, thus removing the difference between this and an 'attention' condition. Only two studies have compared P50 across conditions where attention is directed toward and away from auditory stimuli (Gjini et al., 2011; Kho et al., 2003). Neither of these studies found differences in P50 across these conditions. However, as they used only a long IPI (≈8 s), they do not answer the question of whether attention effects are present at shorter IPIs where refractory and/or inhibitory mechanisms are challenged. The present study will address this.

The present study aimed to clarify which theory (RP or II) best explains P50 suppression by manipulating IPI and attention, within the P50 auditory paired-stimulus paradigm, and testing the hypotheses that: 1/ Reducing the functionality of the mechanism responsible for P50 suppression, by reducing IPI from 8 s to 2 s, will affect S2P50 amplitude (with a reduction in amplitude consistent with RP and an increase