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The relevance of attention in schizophrenia P50 paired stimulus studies

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HIGHLIGHTS

- Attention (versus non-attention) increases P50 suppression (P50 difference) and attention effects differ between schizophrenia (SCZ) and healthy controls (CON).
- When attention is directed, there are no P50 group differences between SCZ and CON.
- The SCZ–CON P50 difference reported in the literature may relate to uncontrolled attention, not impaired suppression.

ABSTRACT

Objective: P50 suppression refers to the P50 ERP amplitude-reduction to the second (S2) relative to the first (S1) of identical brief auditory stimuli (SOA = 500 ms). Its reduction in schizophrenia is argued to represent impaired inhibitory input (II) mechanisms. Enhancing attention enhances II functionality (*reducing* S2P50 amplitude and increasing P50 difference) in healthy subjects. We determined whether the effect of attention on P50 suppression differs between schizophrenia patients (SCZ) and controls (CON) and thus is a confound in P50 schizophrenia research.
Methods: We manipulated the direction of attention (attention, non-attention) in 21 SCZ and 18 CON in the P50 suppression task.
Results: Directing attention towards stimulus pairs (versus non-attention) increased P50 suppression (P50 difference). This effect differed between groups, with attention increasing S1P50, *reducing* S2P50 and increasing P50 suppression (P50 difference and reducing P50 ratio) in CON only. No group differences were found for P50 difference or ratio.
Conclusions: Attention is a confound in schizophrenia P50 research and thus should be carefully controlled. When attention was controlled, P50 group differences were not found.
Significance: The SCZ–CON P50 difference reported in the literature may be related to uncontrolled attention (and not impaired P50 suppression *per se*).

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 using the P50 difference (S1–S2) and P50 ratio (S2/S1) metrics.

P50 suppression is thought to reflect the operation of a neuronal circuit consisting of the P50 generator (thought to be in auditory cortex: ACx; Liégeois-Chauvel et al., 1994; Godey et al., 2001; Weisser et al., 2001; Yvert et al., 2001; Korzyukov et al., 2007) which, once activated by S1, in turn activates inhibitory inputs that suppress the ACx response to the subsequent arrival of an identical stimulus, S2 (Freedman et al., 1996). These inhibitory inputs are thought to be active for >500 ms (Miller and Freedman, 1995), and so as they are still active when S2 is presented (500 ms after S1), the inhibitory inputs reduce the magnitude of the ACx

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response to S2. The inhibitory inputs were originally thought to be hippocampal (Hershman et al., 1995; Freedman et al., 1996), however subsequent evidence also suggests the involvement of other areas, including frontal cortex (Knight et al., 1999; Korzyukov et al., 2007; Ehlis et al., 2009) and reticular activating system (Erwin and Buchwald, 1986).

The P50 suppression impairment reported in schizophrenia (Bramon et al., 2004; Chang et al., 2011) is thus assumed to reflect an inhibitory input impairment and argued to be an endophenotype for schizophrenia (Thaker, 2008). However, failures to find impaired P50 suppression in schizophrenia (Greenwood et al., 2012; Light et al., 2012) have called this view into question.

Importantly, the methodology employed across P50 studies varies substantially (de Wilde et al., 2007b). These variations explain some of the variability in results (Patterson et al., 2008) and suggest the possibility that different neural functions are being assessed across studies. One of these methodological differences relates to how attention is controlled; most commonly, a participant's attention is not controlled (e.g., participants are not given instructions pertaining to the stimuli; (Tregellas et al., 2007), or simply instructed to fixate a cross and relax during stimulus presentation; (Hazlett et al., 2015)), however it may also be directed away (Mazhari et al., 2011), or towards the task stimuli (Johannesen et al., 2005). Thus it is important to know whether attention is relevant to P50 suppression, as it may be that the variable P50 suppression findings in schizophrenia are due to a combination of the well-characterised attention deficit in the disorder, and the task dependent variability of attentional demands.

Indeed, we have previously demonstrated (Dalecki et al., 2015) that attention is important for P50 suppression. In that study we challenged the mechanisms underlying P50 suppression by reducing the interval between stimulus pairs (IPI; inter-pair interval) from the standard 8–2 s (thus not allowing the mechanism underlying P50 suppression to recover fully (Zouridakis and Boutros, 1992; Dolu et al., 2001; Dalecki et al., 2011). Under these conditions, enhancing attention *reduced* S2P50 amplitude and increased P50 suppression (and also increased the P50 difference). Thus attention can enhance P50 suppression in healthy subjects, and it is not only pre-attentive inhibitory inputs that are captured in the P50 paired-stimulus task. This attentional effect may be relevant to schizophrenia, a population in which attentional impairments are well established (Braff, 1993). Specifically, schizophrenia patients and healthy controls may differently apply attention to paired stimuli in the P50 paradigm. Where attention is relatively enhanced (such as in healthy controls relative to schizophrenia patients), this may result in enhanced P50 suppression in controls and apparent P50 suppression failure in schizophrenia patients. Thus, since schizophrenia patients have impaired attention, the attention-related enhancement of P50 suppression in controls (Dalecki et al., 2015) may explain the "P50 suppression" difference often reported in schizophrenia (Adler et al., 1982).

Consistent with this, evidence within the schizophrenia memory literature has shown that while schizophrenia patients have impaired recognition in memory tasks relative to controls (Paul et al., 2005), these group differences may reduce or disappear when patients are given a strategy for directing their attention (Ragland et al., 2003). This suggests the possibility that under 'normal' circumstances (i.e., in the absence of any task instructions) groups may be differentially applying attention and that this may in part underlie group differences in outcome measures. Further, given that attention is relevant to P50, it is possible that patients and controls allocate attention differently during 'normal' P50 tasks: for example, in tasks where participants are simply asked to 'listen to' the stimuli (Grunwald et al., 2003; de Wilde et al., 2007a). Although ostensibly controlling for attention, these commonly used instructions do not require that attention is actually directed towards stimuli for successful completion of the task, nor do they allow for measurement of where attention has been directed. Nevertheless, if controls are better at following these attentional instructions, then they (but not patients) will have an attentional-related improvement of P50 suppression whereas patients, who are not as good at allocating attention, do not get this improvement of P50 suppression.

The present study will compare the effect of attention on P50 suppression between schizophrenia patients and healthy controls in order to determine whether attention is a confound in schizophrenia P50 research. The present P50 paradigm, in the non-attention condition, instructs participants to ignore the auditory stimuli while they watch a concurrently playing silent movie. In the attention condition, it instructs participants to attend to the auditory stimuli and to respond to infrequently occurring target pairs (where one stimulus in the pair is louder than the other). In order to adequately perform this attention task, attention must be directed to the auditory stimuli and thus is different from 'attention' conditions of studies where participants are simply asked to 'listen to' auditory stimuli. Further, as it provides strategies for directing attention to the participants, through the combination of an attentional task and simple instructions (i.e., 'press the button to the loud stimuli'), the present paradigm may act to remove or reduce attentional differences between SCZ and CON (as has been shown to occur in the schizophrenia memory literature, e.g., Ragland et al. (2003)).

2. Methods

2.1. Participants

Twenty-one patients and 18 healthy controls participated in the study (Table 1). To be eligible for inclusion in the study, patients had to be aged between 18 and 55, have a diagnosis of schizophrenia ($n = 16$) or schizoaffective disorder ($n = 5$) (SCZ) (American Psychiatric Association, 2000), be on a stable dose and type of antipsychotic medication (no change over the 4 weeks prior to inclusion in the study), not taking clozapine and not pregnant or breastfeeding. Patients were recruited through the Alfred Hospital Outpatient Clinic, the Monash Alfred Psychiatry Research Centre participant database, advertisements placed at community mental health organisations and via referral through psychiatrists (with whom the researchers made contact to inform about the study). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was conducted to assess patients' current clinical symptoms. The MINI International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998) was administered in order to confirm the diagnosis in the SCZ sample. Healthy controls (CON) were recruited via word of mouth and advertisements placed around community noticeboards. The MINI screen was conducted with CON to screen

Table 1
Demographic characteristics of the sample.

	SCZ	CON
Age (years)	*M* = 37.90; SD = 8.26	*M* = 37.17; SD = 8.82
Gender	9 male; 12 female	9 male; 9 female
Education (years)	13.86 (SD = 3.10)	18.11 (SD = 3.51)
Handedness	20 right; 1 left	17 right; 1 left
PANSS scores		
Total (range)	73 (52–93)	*n/a*
Positive (range)	17 (9–28)	*n/a*
Negative (range)	17 (9–28)	*n/a*
General (range)	38 (28–51)	*n/a*