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SEX SPECIFIC EVENT-RELATED POTENTIAL (ERP) CORRELATES OF DEPRESSION IN SCHIZOPHRENIA

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SUMMARY

Background: *Depressive symptoms in schizophrenia are common, more so in women, but associated neurobiological mechanisms are poorly understood. The current study investigated sex differences in the relationship between depression and brain function, as measured using event-related potentials (ERPs), in people with schizophrenia.*

Subjects and methods: *Fourteen men and 14 women with schizophrenia, matched on age of illness onset and illness duration, were assessed for depression using the Calgary Depression Scale. ERP amplitudes were measured during an auditory oddball task in response to target (P3b, anterior N100) and novel (P3a, posterior N100) stimuli.*

Results: *Depression was significantly positively associated with early perceptual processing in response to novels in men (parietal N100 amplitude), and with a later processing stage (parietal P3b) in women. No association was found for anterior P3a.*

Conclusions: *Results suggest that temporally distinct pathophysiological mechanisms are involved in depression in men compared to women, at least in the context of schizophrenia.*

Key words: *schizophrenia - depressive symptoms - sex differences - event-related potentials - novelty processing - target detection*

Abbreviations: *ERPs=Event-related potentials; CPZEQ=chlorpromazine equivalence; HPA=hypothalamic-pituitary-adrenal; MDD=major depressive disorder*

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INTRODUCTION

Depressive symptoms occur in approximately 60% of patients during the course of schizophrenia, often with major implications for well-being, general functioning and suicide (Marengo et al. 2000, Zisook et al. 1999, Schennach-Wolff et al. 2011). Depression in schizophrenia has been associated with a later age of onset (Kohler et al. 1998a), poor performance on several cognitive tasks (e.g. attention, working memory and psychomotor ability; Halari et al. 2006, Holthausen et al. 1999, Kohler et al. 1998a), and subjectively reported greater effort during task performance, suggesting less efficient processing (Holthausen et al. 1999). Men generally have fewer depressive symptoms than women, along with an earlier age of onset and poorer prognoses (Abel et al. 2010). Furthermore, certain psychiatric vulnerability genes show a sex-specific relationship with depressive symptoms, at least in the general population (Strohmaier et al. 2013). Sex might also mediate the relationship between depression and cognition in schizophrenia (Kohler et al. 1998a). However, it is unclear whether this latter notion is supported by direct measures of brain function. Nevertheless, neuroimaging studies support the presence of sex-related neuropathological processes involving networks implicated in emotion regulation (Gur et al. 2004, Cohen et al. 2013) that could impact on the presentation of depression in psychiatric populations, including schizophrenia.

Event-related potentials (ERPs) have been used to index neural responses during cognitive and affective processes in major depression (Bruder et al. 2009, Kemp et al. 2009, Sumich et al. 2008) and schizophrenia (Sumich et al. 2008, 2013), and/are sensitive to sex of the participant (Sumich et al. 2012, Sumich et al. 2006b). ERPs may therefore be particularly useful in understanding sex differences in the neurobiological underpinnings of depression in schizophrenia. ERP components, such as N100 and P300, index temporally contiguous information processing stages that respond differentially to stimulus properties and task demands (Polich & Criado 2006, Luck 2005, Friedman et al. 2001). For example, N100 primarily responds to manipulation of the physical properties of a stimulus (Luck 2005). This composite waveform comprises several subcomponents - with generators in the frontal, parietal and superior temporal cortices - that likely rely on thalamic relay to these regions and reflect cognitive processes such as feature encoding and integration. A medial frontal N100 has also been found to increase with tonic increases in conscious effort during performance on an auditory oddball task, in which participants respond to target stimuli presented among a train of physically deviant standard stimuli (Mulert et al. 2007). N100 to novel stimuli, in comparison, has

additional sources in the inferior parietal cortex (Woods et al. 1993). P300 reflects several processes involved in attention orientation, contextual; updating/closure and response modulation (Luck 2005, Polich & Criado 2006, Friedman et al. 2001, Sumich et al. 2008). Novel stimuli evoke an anteriorly distributed, stimulus-driven P300 response (P3a) associated with the orienting reflex, whilst effortful responses to target stimuli elicit a posteriorly distributed P3b (Luck 2005, Polich & Criado 2006, Friedman et al. 2001).

ERP abnormalities have been associated with affective problems in several psychiatric and non-psychiatric populations, with some indication of bidirectional effects that may depend on task-demands and sex (Sumich et al. 2006b, Shagass & Roemer 1992). For example, N100 amplitude is higher in mild unipolar depression, but lower in severe depression, compared to non-depressed individuals (Shagass & Roemer 1992). High N100 amplitude in response to novel stimuli has also been observed in children with high trait anxiety (Hogan et al. 2007). Several studies report lower P300 amplitude in major depressive disorder, particularly in the right hemisphere (Kaustio et al. 2002, Kemp et al. 2009) and following novel stimuli (Bruder et al. 2009), suggesting involvement of P3a (Volpe et al. 2007). In comparison, high P300 amplitude was reported in subclinical depression (Sumich et al. 2006b). This study reported effects at temporoparietal sites that were most evident in women, suggesting a sex-dependent positive association between P3b and subclinical depression.

P300 and N100 amplitudes are reduced in schizophrenia early in the illness course (Sumich et al. 2006a). In line with involvement of P3a in depression, Mathalon et al. (2000) report an inverse association between depressive symptoms and P300 following noise bursts in male veterans with schizophrenia. However, associations between P300 and depression in women with schizophrenia remain unclear. Sex differences for P300 (i.e. lower amplitude in male patients) appear to be preserved in schizophrenia (Sumich et al. 2013). However, there is some indication that this may depend on subcomponent. That is, male patients show a greater right parietal deficit and female patients show greater frontal deficits (Turetsky et al. 1998). Whether such findings are explained by a difference in depression between the two sexes is unclear. We previously reported sex differences in the association between another ERP component, the anterior N200, and excitement symptoms in schizophrenia (Sumich et al. 2013). We have also reported sex-dependent ERP (including N100 and P300) correlates of schizotypy (Sumich et al. 2008b).

The aim of the current study was to test associations between N100 and P300 measures and depression. Here we hypothesised that (a) depression would be inversely associated with frontal P300 amplitude in response to novel stimuli (P3a; Mathalon et al. 2000), but positively associated with parietal P300 in response to targets (P3b; Sumich et al. 2008) and (b) as with Sumich et al. 2008, associations with parietal P3b may be more evident in women. Associations with N100 amplitude were explored with no specific hypothesis in the absence of previous direct data on this topic.

SUBJECTS AND METHODS

Subjects

All participants were right handed. Twenty-eight in- and out-patients from in and around London were recruited, including 14 men matched as closely as possible to 14 women on age in years (men mean=43.29, sd=12.50; women mean=44.43, sd=9.65), years of formal education (men mean=11.64, sd=4.25; women mean=10.79, sd=1.93), age of onset (men mean=23.21, sd=4.77; women mean=24.14, sd=6.77) and illness duration (men mean=20.07, sd=14.01; women mean=20.29, sd=9.09). Data on anterior N200 and P300 in relation to excitement symptoms from this sample are reported elsewhere (Sumich et al. 2013). Patients with a history of illicit substance abuse or dependence, learning disability, or medical condition that may affect brain structure or function other than schizophrenia were excluded. A structured clinical interview administered by trained psychiatrists confirmed a diagnosis of schizophrenia based on DSM-IV Axis 1 disorders (SCID 1) (First et al. 1996) and included the Calgary Depression Scale for schizophrenia to assess depression (Addington et al. 1990).

The study procedures were approved by the Joint Institute of Psychiatry and South London and Maudlsey NHS Trust research ethics committee. All participants provided written informed consent after the study procedures had been explained to them.

ERP Assessment

All subjects refrained from smoking before task performance (>1 hour). They sat alert and still with eyes open and fixed on a focal point.

Stimuli were presented binaurally through insert ear plugs. Stimuli comprised 40 target tones (1000Hz), 160 nontarget (2000Hz) tones (duration=200ms; 10ms rise/fall) and 40 novel, environmental sounds (100-300 ms duration; average =200ms) presented quasi randomly. Two targets or two novels did not occur in a row. Stimulus intensity was set at 65dB. Subjects responded to targets with a button press using their right thumb as fast and as accurately as possible.

A Nihon Kohden model EEG-4321F/G amplifier and NeuroScan Acquire 4.0 software were used to record EEG from 15 electrodes (10-20 system), referenced to linked earlobes with a forehead ground (Impedance<5kΩ; sampling rate =1000Hz). Vertical eye-movements (EOGv) were recorded from above and below the left eye. Horizontal eye-movements (EOGh) were recorded from bipolar electrodes placed near the outer canthi of each eye.

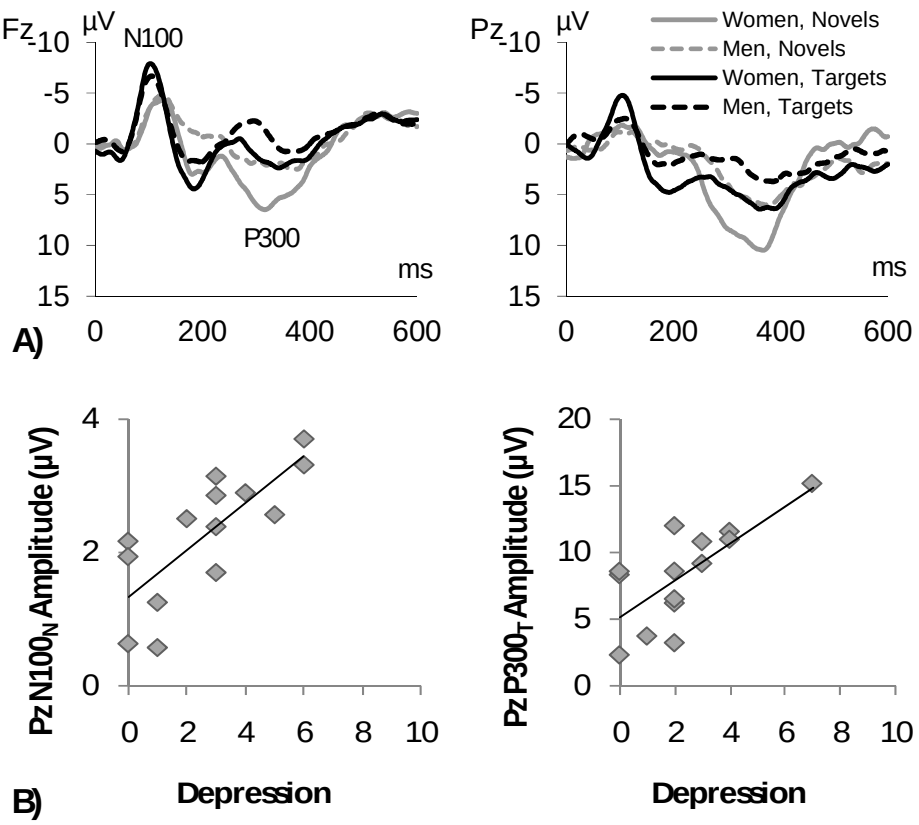

Figure 1. Panel A: Event-related potential waveforms in response to novel and target stimuli at frontal (Fz) and parietal (Pz) electrode sites in men and women; Panel B: Scatter plots of parietal N100 (additive inverse) in response to novels (N) in men and P300 in response to targets in women

NeuroScan Edit 4.2 was used to apply a bandpass filter (0.015-40 Hz) offline. Ocular artefact reduction (Semlitsch et al. 1986) was performed using EOGv. Following a linear detrend on EOGh for the entire sweep, epochs with EOGh activity outside –60 to +60μV were rejected. Epochs (-100-800ms post-stimulus) that contained excessive movement artefact were rejected. Averaged ERPs included at least 30 trials. N100 was defined as the most negative peak occurring 70-170ms post-stimulus, and was measured at Fz to targets and Pz to novels (given purported parietal sources). Because N100 is measured as a negative deflection, the additive inverse of its amplitude was used in statistical analysis. P3a was defined as the most positive peak occurring 250-500ms post-stimulus at Fz in response to novels. P3b was defined as the most positive peak occurring 250-500ms post-stimulus at Pz in response to targets. Baseline-peak amplitudes were measured (Figure 1).

Statistical analysis

All statistical analyses were performed using SPSS 19.0. Multivariate analysis of variance (MANOVA) with Wilk's Llambda were used to test for sex differences in age of onset, illness duration and depression. Similar, separate, analyses were used to test for sex differences in P3a, P3b, frontal N1 to targets and parietal N1 to novels. Pearson's correlation was used to test the association between ERPs and depression in men and women. A Hochberg correction was applied for multiple comparisons. Fisher's Z transformation was used to confirm significant differences in rho values.

RESULTS

There were no sex differences in depression score (men mean=2.64, sd=2.10; women mean=2.29, sd=1.90). As previously reported (Sumich et al. 2013), due to matching, men and women did not significantly differ in age, education, age of onset or illness duration. Figure 1a shows ERP waveforms for men and women (top panel) and figure 1b shows scatter plots of significant correlations. Women had significantly higher P300 amplitudes (P3a mean=8.70, sd=4.74; P3b mean=8.35, sd=3.66) than men (P3a mean=3.87, sd=2.83; P3b mean=5.20, sd=4.22) (MANOVA main effect of *sex* $F(4, 23)=4.06$, $p=.012$, $\eta^2=.414$ univariate ANOVA for P3a $F(1, 26)=10.73$, $p=.003$, $\eta^2=.292$; P3b $F(1, 26)=4.46$, $p=.044$, $\eta^2=.146$). N100 amplitudes did not significantly differ between women (N100 to targets mean=-8.64, sd=2.76; N100 to novels mean=-3.41, sd=2.22) and men (N100 to targets mean=-7.31, sd=2.83; N100 to novels -2.25, sd=0.96). Positive correlations were found between depression and parietal

N100 amplitude in men (r=.77, p=.008$_{\text{Hochberg corrected}}$), and between depression and P3b amplitude in women (r=.72, p=.028 $_{\text{Hochberg corrected}}$). Fisher's Z transformation showed significant sex differences in these associations (parietal N100 z=3.36, p=.008; P3b z=-2.01, p=.044). There was no significant correlation between P3a or frontal N100 amplitude and depression in either group.

DISCUSSION

The current study investigated sex-differences in ERP correlates of depression in schizophrenia. As previously reported in this cohort (Sumich et al. 2013), women had higher P300 amplitudes than men. This is in line with sex differences previously shown for healthy controls (Nagy et al. 2003, Golgeli et al. 1999), suggesting preservation of these differences. Furthermore, in the current study, effect sizes for P3a were twice that for P3b. Several organisational and activational effects of sex hormones, including interaction with dopamine function and the disease process, might underlie such sex differences in P300 amplitude (Sumich et al. 2012). Differences between men and women were not apparent for N100 amplitude. In contrast to a previous study of male war veterans with schizophrenia (Mathalon et al. 2000), P3a was not associated with depression. It is possible that schizophrenia in war veterans is characterised by a history of psychological trauma and thus specific neurobiological dysfunctions, such as more prominent volume reduction in medial temporal regions (Hoy et al. 2012, Mondelli et al. 2011), which are implicated in P300 generation (Polich & Criado 2006). Inconsistent findings might also be due to the use of novel stimuli in the current study in comparison to the noise bursts used by Mathalon and colleagues to elicit P3a. Rather, sex-dependent positive associations were identified between depression and P3b in women, and between depression and parietal N100 in men. Such findings may reflect increased, yet inefficient, effort in the context of depression, as has been previously suggested (Holthausen et al. 1999). However, several alternative explanations also exist.

Whilst P300 is generally reduced in schizophrenia (Sumich et al. 2008, 2006a, Turetsky et al. 1998), higher P300 amplitude has been reported in relation to anxiety and subclinical depression (Sumich et al. 2006b, Shagass & Roemer 1992, Karch et al. 2007, 2008, Clark et al. 1996). The parietal topography and prominence in women of the current results for P3b are in line with the study of subclinical depression (Sumich et al. 2006b). Structural studies in schizophrenia show similar findings, in that depression has been associated with greater volume of temporal regions (Kohler et al. 1998b) despite the volume of these regions being generally lower in patients compared to controls (Sumich et al. 2002). Given neural generators for the P300 exist in the temporal lobes, such differences in brain structure and function might underlie the currently reported association between depression and P300. However, this hypothesis should be confirmed in future multimodal studies, and several other mechanisms might also be implicated. For example, the novelty N100 and target-elicited P300 share similar sources in the inferior parietal cortex (Woods et al. 1993, Bocquillon et al. 2011). Whilst this region is often implicated in depression, there are mixed findings with regard to whether it is hyper- or hypo-activated (Delaveau et al. 2011, Kim et al. 2009). Hyperactivation of IPC in depression is usually associated with stimuli of negative valence (Delaveau et al. 2011). It is possible that, in the context of schizophrenia, simple tones and environmental noises adopt a negative/threatening valence. IPC is also part of the default network found hyperactivated in depression. However, several other sources, such as posterior cingulate gyrus (Cohen et al. 2013) and limbic regions (Gur et al. 2004), might also contribute to the current findings. In future studies, it will be important to dissociate the contribution of anxiety from those of depression on the activation of these networks. Interactions might also be seen for other factors such as alcohol (Karch et al. 2008) and/or substance use.

Others have reported lower P300 amplitude in MDD, but this is more evident over the right hemisphere and in response to novel stimuli (Kaustio et al. 2002, Kemp et al. 2009, Bruder et al. 2009). Inconsistency between these findings and the current study may in part reflect involvement of several temporally overlapping pathophysiological processes in depression that load differentially onto the processing of novel and target stimuli, but might also vary as a function of illness severity (Shagass & Roemer 1992), diagnosis (Cooke et al. 2005, Coryell & Tsuang 1992) and sex (Armitage & Hoffmann 2001, Thurston-Snoha & Lewine 2010). For example, MDD, psychotic depression and schizophrenia with depression may differ in several psychological and pathophysiological factors, such as involvement of insight into illness (Cooke et al. 2005, Mintz et al. 2003) and dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) (Coryell & Tsuang 1992). That is, depression in schizophrenia has been found to correlate positively with illness insight (Cooke et al. 2005, Mintz et al. 2003) which in turn has been associated with centroparietal P300 amplitude (Pallanti et al. 1999). Thus, interaction with intact insight could provide an alternative explanation of the current association between P3b amplitude and depression in women and should be further investigated. Anxiety has also been associated with better performance and outcome in women, but not men with schizophrenia (Thurston-Snoha & Lewine 2010).

High amplitude N100 and P300 might also reflect a hypervigilant and/or threat response, involving HPA hyperactivation and catecholaminergic systems. In

partial support of this idea, subchronic hydrocortisone administration increases P300 and N100 amplitudes (Posener et al. 2000, Ashton et al. 2000, Born et al. 1988). Depression in the context of psychosis has been associated with HPA-axis dysregulation, and markedly elevated postdexamethasone cortisol levels, compared to nonpsychotic depression (Coryell & Tsuang 1992). Dexamethasone nonsupression has been found to be prognostic of good insight and outcome (Coryell & Tsuang 1992). However, confirmation of an underpinning HPA mechanism will require further investigation that includes other indices of HPA function, such as cortisol assays, together with ERP and clinical measures.

CONCLUSIONS

Whilst sample size in the current study is small, limiting investigation of laterality effects and warranting replication in a larger group, the current study offers important information on possible pathophysiological mechanisms underlying sex differences in depression in schizophrenia. Results suggest that depression in men is more associated with an early sensory-perceptual stage during novelty processing, whilst in women later target-related mechanisms are implicated. Whether these neurobiological differences relate to sex-differences in the phenomenology of depression in schizophrenia should be the focus of future research. In any case, the current study highlights the importance of taking sex and depression into account in investigations of brain function in this heterogeneous illness.

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