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Neurophysiological correlates of excitement in schizophrenia

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ABSTRACT

Objective: The excitement cluster (excitement, hostility, uncooperativeness and impulsivity) may contribute to the risk of violent behaviour, treatment non-adherence, likelihood of discharge and substance use in psychosis. Evidence suggests involvement of frontal executive mechanisms that may show sex differences in their association with symptom severity. The current study tests the association between excitement and the frontal N200 and P300 components of the auditory event-related potential in schizophrenia as a function of sex.
Method: Fourteen men and 14 women with schizophrenia (mean illness duration = 20 years) completed a novelty oddball and clinical interview.
Results: Men showed higher midline N200 and lower novelty P300 amplitude than women. They had more pronounced differences between midline and lateral N200 amplitude, and did not show the same Novel > Target effect for right frontal P300 as did women. Right frontal N200 amplitude to target stimuli was positively associated with excitement in women and inversely associated with excitement in men. Novelty P300 amplitude was inversely associated with excitement, particularly in women and over the right hemisphere.
Conclusion: Results suggest that mechanisms underpinning frontal N200 and P300 subcomponents are differentially involved in excitement depending on sex. Understanding these individual differences may have implications for developing personalised treatment.

1. Introduction

The excitement cluster (e.g. excitement, hostility, uncooperativeness and impulsivity derived from the Positive and Negative Syndrome Scale; PANSS; Kay et al., 1987) manifests as an independent group of symptoms in schizophrenia, which together with Positive, Negative, Disorganisation and Emotional distress form a five factor model of this heterogeneous illness (van der Gaag et al., 2006), and contributes to risk of violent behaviour, treatment non-adherence, likelihood of discharge and substance use (Colasanti et al., 2010; Kaladjian et al., 2011; Schiffer et al., 2010; Yang et al., 2012). Understanding neurobiological mechanisms underpinning excitement may have implications for understanding and treating such behaviours. For example, identification of intermediary, biological treatment targets can in turn facilitate the development of novel therapeutic compounds and facilitate personalised interventions (Kantrowitz and Javitt, 2010). This is particularly important for illnesses like schizophrenia that show large individual differences in aetiology and symptom presentation, for example those observed between men and women (Gur et al., 2004; Mendrek and Stip, 2011).

The composition of the excitement cluster suggests disruption to fronto-temporal and thalamo-cortical executive systems, involved in modulating affect, cognition and behaviour. Networks involving the medial temporal, thalamus, anterior cingulate (ACC), dorsolateral prefrontal, right inferior frontal and orbito-frontal (OFC) are implicated and have been identified in relation to impulsivity (Kaladjian et al., 2011; Schiffer et al., 2010) and/or violent behaviour (Barkataki et al., 2008; Kumari et al., 2009). Nishimura et al. (2011) report increased frontal activation, as measured using near infrared spectroscopy during response suppression in a visual Go/NoGo task, with more severe excitement symptoms in people with schizophrenia. This is in line with a neuroimaging study that found a positive correlation between right ventrolateral frontal activation and impulsivity (Kaladjian et al., 2011), despite this area being generally underactivated in schizophrenia (Kaladjian et al., 2007; Rubia et al., 2001). Right frontal regions have also been implicated in aggression and impulsivity in schizophrenia by studies of white matter (Hoptman et al., 2002). In comparison, impulsivity in adolescents has been associated with underactivation of the right inferior frontal cortex (Whelan et al., 2012). Atypical frontal electroencephalographic (EEG) lateralization

Abbreviations: PANSS, Positive and Negative Syndrome Scale; ACC, Anterior cingulate; OFC, orbito-frontal; EEG, Electroencephalographic; ADHD, Attention deficit hyperactivity disorder; ERP, Event-related potential; EOGv, Vertical electrooculogram; EOGh, Horizontal electrooculogram.

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has been seen in relation to hostility and violent behaviour (Czobor and Volavka, 1993). Other authors implicate temporoparietal asymmetry. For example, conceptual overlap exists between excitement and active syndrome which has been associated with hyperarousal and a bias in responding to words compared to faces (Gruzelier, 2003).

Some executive mechanisms, such as the orbitoprefrontal-amygdala network, show dramatic sex differences in the way they are affected by the presence of psychosis (Gur et al., 2004), and could underpin sex differences in response to medication (Mendrek and Stip, 2011). Sex differences in brain function may also contribute to differences in the presentation of hostility (higher in women, Gur et al., 2004) and violent behaviour (higher in men; Biancosino et al., 2009; Soyka et al., 2007), and would be expected to confound links with symptom severity, as is the case for negative symptoms (Gur et al., 2004). Networks involving dorsal ACC and inferior frontal gyrus also show sex differences in their association with response inhibition and impulse control in relation to attention deficit hyperactivity disorder (ADHD) symptoms (Elton et al., 2013) and in individuals with a family history of alcoholism (Devito et al., 2013). Thus sex may well modulate the association between fronto-temporal function and excitement in schizophrenia.

Event-related potential (ERP) components index temporally contiguous information processing stages (Luck, 2005) that respond differentially to task demands, such as those involved in processing target – compared to background, novel, distractor, or affect laden – stimuli (Friedman et al., 2001). The auditory N200 is a negative deflection in the ERP that is evoked in response to identification and categorisation of target stimuli and reaches a peak at approximately 200 ms. It also responds to novelty and stimuli with emotional valence. N200 is a composite waveform that comprises several subcomponents that vary slightly in scalp distribution and time of occurrence (latency). These subcomponents putatively reflect several fronto-temporal and fronto-parietal mechanisms with functional significance to excitement, including autonomic alerting, discrimination, behavioural/conflict monitoring, template matching and cognitive control (Crottaz-Herbette and Menon, 2006; Kopp et al., 2006; Patel and Azzam, 2005; Van Veen and Carter, 2002). N200 amplitude declines initially during childhood, concurrent to development of affective and behavioural control (Buss et al., 2011; Sumich et al., 2012a,b), but increases at medial frontal sites during adolescence (Davies et al., 2004).

N200 amplitude reduction in schizophrenia seems to be more consistent over the frontal sites, at least in those with an established illness (Doege et al., 2010; O'Donnell et al., 2004). Some studies report relative preservation of posterior N200 (Doege et al., 2010), more diffuse N200 topography (Rentrop et al., 2011) and loss of the normal target > non-target bias (Brown et al., 2002), whilst others report no difference between patients and controls (Sumich et al., 2008; Weisbrod et al., 2000). Sensation seeking in schizophrenia has been positively associated with the amplitude of a negative deflection occurring at 300 ms post stimulus (N300) that might reflect later N200 subcomponents (Guillem et al., 2005). We previously reported a positive association between right frontal N200 and negative symptoms in men with recent onset psychosis (Sumich et al., 2006). Given sex differences in the association between the OFC:amygdala ratio and symptoms (e.g. correlation has opposite direction for men compared to women; Gur et al., 2004), sex may impact on links between N200 and symptom severity. Indeed sex differences are seen in the relationship between N200 and goal directed behaviour in the general population, thought to reflect OFC-medial temporal activity (Proverbio et al., 2010).

The P300 is a positive deflection that follows the N200, occurring around 300 ms post stimulus, and reflects several processes involved in attention orientation, contextual-updating/-closure and response modulation (Friedman et al., 2001; Luck, 2005, Polich and Criado, 2006). Distinct P300 subcomponents are evoked in response to the presentation of novelty (P3a) and following effortful response to target stimuli (P3b). Reduced auditory P300 amplitude is one of the most robust electrophysiological findings in schizophrenia (Turetsky et al., 2009), and is seen for both P3b as well as P3a. The latter was reported in medication naïve participants, and was particularly evident at right frontal sites (Mondragón-Maya et al., 2013). Whilst low left temporoparietal P300/P3b amplitude has been observed in relation to the active syndrome in schizophrenia (Gruzelier et al., 1999), the relationship between frontal P300 and excitement in schizophrenia is unclear. Nevertheless, frontal/P3a amplitude has been associated with impulsive, deviant and antisocial behaviour (Justus et al., 2001) and intermittent explosive disorder (Koelsch, 2009), suggesting it may index frontotemporal mechanisms that underpin excitement-type traits.

The current study investigates sex differences in anterior N200 and P300 amplitudes, following target and novel stimuli. If sex differences are preserved in schizophrenia, then men should have higher N200, but lower P300 amplitudes than women. Furthermore, the association between ERPs and excitement symptoms is tested. Specifically, it is expected that more severe excitement symptoms would be associated with low frontal N200 and P300 amplitude. However, these associations may be subject to sex differences.

2. Method

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

2.1. Participants

Twenty eight out-patients were recruited from in and around London. Fourteen men (n = 9 paranoid, n = 1 undifferentiated, n = 3 residual, n = 1 schizoaffective) were matched as closely as possible to 14 women (n = 8 paranoid, n = 1 undifferentiated, n = 4 residual, n = 1 schizoaffective) on age, education, age of onset, illness duration (please

Table 1
Means and standard deviations (sd) for demographic and clinical variables in men and women with schizophrenia.

	Possible	Men (n = 14)		Women (n = 14)		Sex differences (F statistics[b])		
	Range	Mean	Sd	Mean	Sd	F	p	η^2
Age	n.a.	43.29	12.50	44.43	9.65	.07	.79	.003
Education	0–18+	11.64	4.25	10.79	1.93	.47	.50	.018
Age of onset	n.a.	23.21	4.77	24.14	6.77	.18	.68	.007
Illness duration	n.a.	20.07	14.01	20.29	9.09	.002	.96	<.001
Cigarettes[a]	n.a.	20.00	9.65	20.54	11.13	.016	.90	.001
FTQ		5.92	2.47	4.55	2.38	1.83	.19	.08
EXC[c]	*0–28*	*9.71*	*3.77*	*6.57*	*2.38*	*6.96*	*.014*	*.21*
Total PANSS	*0–140*	*83.30*	*24.31*	*67.79*	*17.03*	*3.82*	*.06*	*.13*

EXC = Excitement; PANSS = Positive and Negative Syndrome Scale; FTQ = Score on Fagerström Tolerance Questionnaire
Italics = significant difference between men and women.
[a] Self-reported number of cigarettes smoked each day.
[b] Univariate Analyses of Variance.
[c] Significantly higher scores in men $p < .05$.