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Evidence for a differential contribution of early perceptual and late cognitive processes during encoding to episodic memory impairment in schizophrenia

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Abstract

Objectives: Schizophrenia is characterised by significant episodic memory impairment that is thought to be related to problems with encoding, however the neuro-functional mechanisms underlying these deficits are not well understood. The present study used a subsequent recognition memory paradigm and event-related potentials (ERPs) to investigate temporal aspects of episodic memory encoding deficits in schizophrenia.

Methods: Electroencephalographic data was recorded in 24 patients and 19 healthy controls whilst participants categorised single words as pleasant/unpleasant. ERPs were generated to subsequently recognised versus unrecognised words on the basis of a forced-choice recognition memory task. Subsequent memory effects were examined with the late positive component (LPP). Group differences in N1, P2, N400 and LPP were examined for words correctly recognised.

Results: Patients performed more poorly than controls on the recognition task. During encoding patients had significantly reduced N400 and LPP amplitudes than controls. LPP amplitude correlated with task performance however amplitudes did not differ between patients and controls as a function of subsequent memory. No significant differences in N1 or P2 amplitude or latency were observed.

Conclusions: The present results indicate that early sensory processes are intact and dysfunctional higher order cognitive processes during encoding are contributing to episodic memory impairments in schizophrenia.

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Title Page

Title Evidence for a differential contribution of early perceptual and late cognitive processes during encoding to episodic memory impairment in schizophrenia

Short Title: ERPs and encoding in schizophrenia

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Abstract

Objectives: Schizophrenia is characterised by significant episodic memory impairment that is thought to be related to problems with encoding, however the neuro-functional mechanisms underlying these deficits are not well understood. The present study used a subsequent recognition memory paradigm and event-related potentials (ERPs) to investigate temporal aspects of episodic memory encoding deficits in schizophrenia. *Methods:* Electroencephalographic (EEG) data was recorded in 24 patients and 19 healthy controls whilst participants categorised single words as pleasant/unpleasant. ERPs were generated to subsequently recognised versus unrecognised words on the basis of a forced-choice recognition memory task. Subsequent memory effects were examined with the late positive component (LPP). Group differences in N1, P2, N400 and LPP were examined for words correctly recognised. *Results:* Patients performed more poorly than controls on the recognition task. During encoding patients had significantly reduced N400 and LPP amplitudes than controls. LPP amplitude correlated with task performance however amplitudes did not differ between patients and controls as a function of subsequent memory. No significant differences in N1 or P2 amplitude or latency were observed. *Conclusions:* The present results indicate that early sensory processes are intact and dysfunctional higher order cognitive processes during encoding are contributing to episodic memory impairments in schizophrenia.

Key words: Event-related potentials, episodic memory, encoding, schizophrenia

Introduction

It is well established that people with schizophrenia demonstrate pronounced deficits in cognitive processing, with these deficits considered a key feature of the illness (for review see Reichenberg, 2010). Memory performance is significantly impaired in schizophrenia (Aleman et al., 1999; Dickinson et al., 2007; Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998) particularly with respect to declarative memory (for a review see Cirillo & Seidman, 2003). Declarative memory includes episodic memory (i.e. the ability to consciously recollect information about past events and experiences), and semantic memory (i.e. memory of meaning and concept-related knowledge). Among several cognitive domains that are affected in schizophrenia, episodic memory impairments have shown some of the largest effect sizes (e.g. $d=-1.23$, Schaefer et al., 2013) and do not appear to be related to demographic or clinical variables such as age, medication, symptom severity or illness duration (Aleman et al., 1999; Keefe et al., 2006), with a similar profile of episodic memory impairments observed in both unmedicated first episode patients (Saykin et al., 1994) and previously-treated patients with chronic illness (for review see Rund, 1998). Finally, while episodic memory impairments have been shown to be a strong predictor of functional outcome and quality of life (Green, 1996) they do not respond well to either typical or atypical antipsychotic medications, despite improvements in psychotic symptoms (Blyler, 2000; Harvey, 2009). In order to develop new treatments targeting the improvement of memory dysfunction, it is important to further understand the neural bases of episodic memory deficits in schizophrenia.

Episodic memory involves encoding, storage and retrieval processes (Tulving, 1984). The extent to which episodic memory deficits in schizophrenia relate to these different stages

of processing remains unclear, however a comprehensive review of the neuropsychological literature concluded that deficits in recall are most likely the result of impairments in the initial acquisition of the learned material (encoding) rather than difficulties with storage or retrieval (Cirillo & Seidman, 2003), and recent behavioural research supports this conclusion. For example impairments at retrieval have been attributed to early encoding processes such as refreshing (Grillon et al., 2010), patients are less likely to spontaneously employ efficient or elaborate strategies for organising information at encoding (for review see Barch, 2005), and evidence suggests that deeper encoding leads to better recognition performance in schizophrenia (Paul et al., 2005). Furthermore, evidence from working memory studies suggests a specific contribution at the encoding stage to behavioural deficits (e.g. Javitt et al., 2007). These findings are consistent with the electroencephalographic (EEG) literature, where event-related potential (ERP) components associated with early perceptual and later cognitive processes that occur during encoding, have been shown to be particularly important for successful working memory in schizophrenia (Dias et al., 2011; Haenschel et al., 2007; Kayser et al., 2006; Zhao et al., 2011). Finally, the encoding hypothesis has received further support from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies that have reliably shown aberrant patterns of encoding-related brain activity in patients with schizophrenia (Achim & Lepage, 2005; Barch et al., 2002; Hazlett et al., 2000; Hofer et al., 2003; Jessen et al., 2003; Ragland et al., 2001) that improved when individuals were provided with item-specific processing strategies, such as making a semantic judgement about each item (Bonner-Jackson et al., 2008; Ranganath et al., 2008).

EEG with its high temporal resolution is well-suited to investigating the rapid changes in brain activity that underlie encoding-related episodic memory deficits in schizophrenia, with different components of the ERP reflecting distinct stages of cortical processing. However no

electrophysiological studies of episodic memory deficits in schizophrenia have specifically investigated ERP correlates of encoding, and have instead focused on retrieval mechanisms (eg. Guillem et al., 2001; Kayser et al., 1999; Kayser et al., 2001; Kayser et al., 2010; Kim et al., 2004; Tendolkar et al., 2002). In order to provide greater clarity as to the encoding deficit in schizophrenia, the present study used a subsequent memory paradigm in conjunction with ERP measures, to determine the relative contributions of different stages of information processing to this deficit. Subsequent memory paradigms have often been used in the study of memory formation in healthy participants to segregate neural processes underlying successful encoding (for review see Paller & Wagner, 2002). To this end, measures of brain activity (such as EEG, fMRI and PET) are recorded while participants study a number of items. These measures are then sorted on the basis of whether the items are correctly recalled or recognised in a subsequent memory test. Furthermore, by only looking at ERPs to words that are subsequently encoded successfully (i.e. words correctly recognised), this method provides an opportunity to assess whether, or at what stage, the processes that reflect successful encoding are different in schizophrenia.

The present study investigated the contribution of early perceptual and attention processes (indexed by N1 and P2), compared to later semantic (N400) and elaborative (LPP) memory processes during episodic memory encoding. N1 and P2 (negative and positive ERP components, elicited approximately 100ms and 200ms after word onset, respectively) are modulated by attention to visual stimuli (Hackley et al., 1990; Hillyard et al., 1998). Furthermore P2 may index feature detection and other early perceptual processes during item encoding (Dunn et al., 1998). The visual N400 is a negative going ERP deflection elicited between 300 and 500ms following word onset that is modulated by both repetition as well as the way in which a stimulus relates to its preceding context. It is thought to index language processing and other semantic memory mechanisms (for review see Kutas & Federmeier,

2011), and has been shown to be abnormal in patients for both implicit semantic memory (eg. repetition priming - for review see Kumar & Debruille, 2004) and explicit memory paradigms (e.g. those involving recognition memory tasks; Guillem et al., 2001; Kim et al., 2004). LPP, part of the family of late positive components including P3 and the late positive complex (LPC), involves a slow sustained positivity beginning approximately 400-500ms post-stimulus, is believed to index stimulus evaluation and consolidation (Kissler et al., 2006), and is often examined in the context of subsequent memory (Friedman & Johnson, 2000). In schizophrenia, reductions in late positive potentials, particularly P3, have been reported (for review see Ford, 1999).

The aim of the present study was to determine the integrity of early and late neural functions during the successful episodic memory encoding of words in schizophrenia. Due to a lack of previous episodic encoding-related ERP literature in this population it is difficult to draw a clear hypothesis as to the expected differences between ERP components, however based on Kayser et al. (2006) it is predicted that compared to healthy controls, patients with schizophrenia will show reductions in later ERP components (LPP in particular) reflecting deficits in higher cognitive processing during encoding that contribute to episodic memory impairment, while earlier ERP components will remain intact.

Methods

Participants

Twenty-eight patients with schizophrenia (n=24) or schizoaffective disorder (n=4) and 19 age- and gender-matched (at the group level) healthy controls were recruited for this study. Patients were recruited through outpatient clinics of the Alfred Hospital, the Monash Alfred

Psychiatry Research Centre participant database, and from the general community (Wollongong and Melbourne). Patients were clinically stable with no current hospitalisation and no change to medication for at least 4 weeks prior to inclusion in the study. Current clinical symptoms were assessed using the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990). Participants were screened for comorbid Axis-I diagnoses including current substance abuse or dependence, and diagnosis was confirmed, using the MINI International Neuropsychiatric Inventory (MINI; Sheehan et al., 1998). The Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) was used to estimate premorbid IQ. All patients were receiving antipsychotic medication at the time of testing (risperidone 5; olanzapine 5; aripiprazole 4; quetiapine 2; paliperidone 2; amisulpride 2; ziprasidone 1; zuclopenthixol 4; flupenthixol 1; haloperidol 1; chlorpromazine 1). Healthy controls were recruited from the general community and were screened for Axis I psychiatric disorders using the MINI screen. Participants were excluded on the basis of history of serious head injury or neurological conditions. All participants had normal or corrected to normal vision. For clinical and demographic information see Table 1. Four patients did not complete the subsequent recognition task of the EEG testing protocol, resulting in a final sample size of 24 in the patient group. All participants provided written informed consent and the protocol was approved by the Alfred Hospital, Monash University, and University of Wollongong Human Research Ethics Committees.

[Insert Table 1 here]

Paradigm

Study items were 400 nouns selected from the Medical Research Council Psycholinguistic Database (http://www.psych.rl.ac.uk/MRC_Psych_Db.html). Words were presented visually on a computer screen in capital letters with white font on a black background. Stimuli were presented via Neuroscan STIM2 software (Compumedics, Melbourne, Australia). During the encoding phase 200 words were presented one at a time for 1200ms each, where participants were instructed to decide 'Is the word pleasant?', by pressing the 'yes' or 'no' response on a button box, and were given up to 2000ms for a response (self-paced). Stimuli were divided into two blocks of 100 words with a 30 second rest between blocks. Following completion of a separate EEG testing paradigm unrelated to this study, the recognition phase occurred 45 minutes after the initial word presentation. In the recognition stage a forced-choice paradigm was used. Each of the 200 old words was presented simultaneously with a new word matched for length and frequency of use, with presentation side of the old word counterbalanced within participant. Each word pair was presented for 1200ms, with up to 2000ms allowed for a response (self-paced). Participants responded via a button box by choosing the word on the left or right of the screen as the word that they recognised from the encoding stage. The range of the horizontal visual angle was 0.8° to 2.7° visual arc (for shortest and longest words respectively). The monitor had a refresh rate of 60Hz and was set to 50/50 brightness.

ERP Recording

Data Acquisition and ERP analysis

Continuous EEG data were acquired during the encoding stage using a Neuroscan 64-channel Quick Cap with Ag/AgCl electrodes, using NeuroScan Acquire Software with SynAmps 2 amplifier (Compumedics, Melbourne Australia), from 19 channels (FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 and O2), digitised at 250 Hz. Electrodes were referenced to the point midway between Cz and CPz, and grounded midway between Fz and FPz. Eye movements were recorded with electrodes placed above and below the left eye, and on the outer canthi of the eyes, with electrode impedances below 20k Ω at the start of recording. Scan 4.3 (Compumedics, Melbourne Australia) was used to analyse the EEG data offline: data were visually inspected and periods contaminated by non-cerebral artefact rejected, EOG correction performed (Semlitsch et al., 1986), data were re-referenced to digitally linked mastoids, band pass filtered 0.1-30Hz (24dB/octave roll-off), separated into 1200 millisecond epochs (-200 to 1000ms), and for each participant epochs at encoding were then averaged on the basis of whether a word was subsequently correctly recognised or not. During the recognition test, words for which no response was recorded were not included in the analysis. Based on previous literature, analyses were limited to three frontal (F3/Fz/F4), three central (C3/Cz/C4), three parietal (P3/Pz/P4) and two occipital (O1/O2) electrodes, where signal to noise ratio of relevant components are largest (e.g. Paller et al., 1988). Latency intervals were decided based on methods used in previous studies (e.g. Dunn et al., 1998; Paller et al., 1988; Zhao et al., 2011) and were confirmed by visual inspection of the individual and grand-average ERP waveforms (see Figure 2). N1 and P2 peak amplitude and latencies were obtained via an automatic peak detection algorithm, relative to baseline, with the following latency intervals: 50-160ms (N1) and 80-235ms (P2). N1 peak latency and amplitude were calculated at occipital sites as the average of O1 and O2 electrodes, and at parietal sites as the average of P3, Pz and P4 electrodes. P2 peak amplitude and latency were calculated at mid-line sites (Fz/Cz/Pz) separately. For P2 peak detection, in cases where a

double peak was present, the positive peak immediately following N1 was selected. N400 was defined as the mean amplitude between 320-450ms and calculated at three mid-line electrodes (Fz/Cz/Pz). Based on previous literature (Paller et al., 1987; Paller et al., 1988) and visual inspection of the waveforms (see Figure 3) LPP was defined as the mean amplitude 450-750ms post stimulus presentation. Analyses were conducted with mean frontal (F3/Fz/F4), mean central (C3/Cz/C4) and mean parietal (P3/Pz/P4) amplitudes. Participants with fewer than 15 accepted trials for not-recognised items were excluded, resulting in a final sample size of 37 (20 schizophrenia; 17 controls). For the included participants, the mean (SD) of accepted epochs for recognised items was 114.4 (29.1) for the patient group and 144.9 (21.8) for the control group. The mean (SD) of accepted epochs for not recognised items was 51.8 (20.5) for patients and 38.6 (13.3) for controls.

Statistical Analysis

Independent samples t-tests for continuous variables and chi-square tests for categorical variables were performed to investigate group differences in demographic characteristics and behavioural measures (subsequent recognition accuracy and response latency). Between-group differences in N1 amplitude and latency were examined separately using mixed design analysis of variance (ANOVA) with factors sagittality (occipital/parietal) and group (control/schizophrenia). P2 (amplitude and latency) and N400 (mean amplitude) were examined using mixed design ANOVA with factors sagittality (frontal/central/parietal) and group (control/schizophrenia). For the subsequent memory analysis LPP was examined using a mixed design ANOVA with factors recognition (recognised/not recognised), sagittality (frontal/central/parietal) and group (control/schizophrenia). Post hoc independent samples t-tests were performed to investigate significant interactions and Bonferroni

correction was applied to control for Type I error, with adjusted p-values reported where appropriate. Cohen's d for t-tests and partial-eta squared (η^2_p) for ANOVA are reported as measures of effect size for significant between-group differences (Lakens, 2013). As a secondary analysis to adjust for differences in education level and WTAR scores, where the assumptions of analysis of covariance (ANCOVA) were met for each variable, ANCOVA was conducted on those variables where group differences were observed, such that years of education (for behavioural data, P2 and LPP amplitude) and WTAR scores (for N400 amplitude) were included as covariates

Pearson correlations were calculated between recognition accuracy and ERP measures that were significantly differentiated between the groups. Further correlations were carried out between these ERP measures and demographic/clinical variables (age, education, duration of illness, PANSS total and subscale scores, CDSS total scores, and WTAR standardised scores). Correlations were conducted with the mean amplitude and latency of midline electrodes (Fz/Cz/Pz) for P2, mean amplitude (Cz/Pz) for N400, and the mean amplitude (frontal/central/parietal) for LPP. These analyses were treated as exploratory and so adjustment for Type I error was not used.

Results

Demographic

Demographic data and clinical characteristics are shown in Table 1. The groups did not differ on age [$p=0.98$] or gender [$p=0.86$], however controls were more educated [$t(1,41)=4.32$, $p<0.001$], and had higher WTAR scores [$t(1,41)=2.55$, $p=0.02$] than those with schizophrenia.

There was a trend for smoking status to differ between the groups with a larger proportion of smokers in the patient group compared to healthy controls [$\chi^2=2.97$, $p=0.08$].

Behavioural

Figure 1 shows the mean response times and accuracy for each group. Patients tended to be slower [$t(1,41)=-1.87$, $p=0.069$, $d=0.59$] and they performed less accurately [$t(1,41)=2.73$, $p=0.009$, $d=0.86$] than controls on the recognition task.

[Insert figure 1 here]

Electrophysiological

Means and standard deviations for each group of electrodes for each component can be seen in Table 2.

[Insert Table 2 here]

N1

Amplitude: N1 peak amplitudes did not differ between the groups [$p=0.280$], nor was an interaction with sagittality found [$p=0.465$]. *Latency:* N1 latencies did not differ between groups [$p=0.350$], nor was an interaction with sagittality found [$p>0.166$].

P2

Amplitude: P2 peak amplitude was larger for controls than patients [$F(1,41)=6.83$, $p=0.012$, $\eta^2_p=0.143$], however this effect did not interact with sagittality [$p=0.26$]. *Latency:* P2 peak latencies were later for patients than controls at trend level [$F(1,41)=3.87$, $p=0.056$, $\eta^2_p=0.086$], but this effect did not interact with sagittality [$p=0.73$].

N400

Amplitude: N400 amplitudes were larger for controls than patients [$F(1,41)=4.10$, $p=0.049$, $\eta^2_p=0.091$], with this effect interacting with sagittality [$F(2,82)=3.43$, $p=0.037$, $\eta^2_p=0.077$]. Post hoc analyses revealed that patients' N400 amplitudes were smaller at Cz [$t(1,41)=-2.73$, $p_{adj}=0.027$, $\eta^2_p=0.154$] and Pz [trend level; $t(1,41)=-2.43$, $p_{adj}=0.060$, $\eta^2_p=0.125$], but not Fz [$p_{adj}>1.0$].

[Insert figure 2 here]

LPP and subsequent memory effects

LPP mean amplitude was larger for words subsequently recognised than not recognised [$F(1,35)=4.58$, $p=0.039$, $\eta^2_p=0.116$] but this did not interact with group, sagittality, or group by sagittality [all $p>0.1$]. LPP amplitude was larger in controls than patients [$F(1,35)=8.36$, $p=0.007$, $\eta^2_p=0.193$] but this did not interact with sagittality [$p=0.76$].

[Insert figure 3 here]

[Insert figure 4 here]

Confounding variables

After adjusting for years of education, a significant difference between the groups remained for recognition performance [$F(1,40)=5.05$, $p=0.024$, $\eta^2_p=0.121$], but differences in response latency were no longer significant ($p=0.107$). For ERP data, after adjusting for years of education, differences between the groups were no longer significant for P2 peak amplitude ($p=0.156$), though a significant difference between the groups remained for mean LPP amplitude [$F(1,34)=4.35$, $p=0.045$, $\eta^2_p=0.114$]. After adjusting for WTAR scores, significant between-group differences in mean N400 amplitude were observed at Cz [$F(1,40)=4.30$, $p=0.045$, $\eta^2_p=0.97$], Pz [$F(1,40)=4.45$, $p=0.041$, $\eta^2_p=0.10$], and P3 [*trend-level*: $F(1,40)=3.42$, $p=0.072$, $\eta^2_p=0.08$] ..

Correlations between ERP indices and recognition accuracy

Overall, there was a trend for recognition accuracy to correlate with mean P2 peak amplitude (*trend level*; $r=.288$, $p=0.061$) and mean LPP amplitude (*trend level*; $r=.300$, $p=0.051$), but not N400 amplitude. When the groups were examined separately no significant correlations were found between accuracy and either P2 peak or N400 amplitude in either group. For LPP however, in controls a correlation was found between mean LPP amplitude and recognition performance (*trend level*; $r=-.433$, $p=.064$) indicating that smaller LPP amplitude was

associated with better performance in that group. In patients a correlation was found between mean LPP amplitude (*trend level*; $r=.379$, $p=.068$) indicating that larger LPP amplitude was associated with better recognition memory performance in that group.

Correlations between ERP indices and demographic and clinical variables

In controls no significant correlations were found between any ERP indices and demographic variables. For patients there were no significant correlations between demographic or clinical variables and either P2 peak amplitude or N400 mean amplitude, whereas there was a significant correlation between LPP mean amplitude and WTAR scores ($r=.431$, $p=0.045$). No other relations with LPP were found in the patient group.

Discussion

This study used a subsequent memory task to investigate ERP correlates of successful episodic memory encoding to determine the temporal nature of an episodic memory encoding deficit in schizophrenia. Patients tended to be slower and accuracy was significantly reduced compared to controls on the subsequent memory task, with several electrophysiological encoding differences observed between the groups. First, patients and controls did not differ in terms of N1 peak amplitude or latency. Second, P2 peak amplitudes were smaller in patients relative to healthy controls, though this difference became non-significant after controlling for education. Third, the schizophrenia group had significantly reduced mean N400 and LPP amplitudes than controls, and finally, LPP amplitude correlated with recognition accuracy.

That group differences were not found in the N1 time window indicates that the underlying neuronal substrate for early visual processing is relatively intact in this sample. In the working memory literature several previous studies have investigated early ERP components during encoding in schizophrenia. For example, Zhao et al. (2011) investigated working memory encoding processes in schizophrenia with a modified Sternberg task that used digits as stimuli, finding smaller N1 amplitudes in patients compared to controls. Likewise, the AX-CPT paradigm was used to investigate the relationship between sensory deficits and working memory in schizophrenia, finding reduced N1 amplitudes in the patient group during encoding that contributed significantly to behavioural performance (Dias et al., 2011). On the contrary, only slight reductions in N1 amplitude were reported during the encoding stage of a working memory task that used words as stimuli (Kayser et al., 2006), and N1 differences between schizophrenia and controls in that study failed to reach statistical significance. Taken together with the present study, the discrepancies in N1 findings suggest that the subprocesses underlying encoding may differ according to the type of stimuli used, with more complex stimuli such as words less sensitive to early sensory processes.

For memory generally, a number of studies using simple target detection tasks and continuous recognition paradigms have found reductions in visual N1 amplitudes in schizophrenia (Bruder et al., 1998; Butler & Javitt, 2005; Butler et al., 2007; Kayser et al., 2009; Kayser et al., 2012; Kim et al., 2004; Neuhaus et al., 2011; Yeap et al., 2006). Reduced N1 amplitudes have been associated with dysfunction in parvocellular pathways and reflect ventral stream processing (for review see Butler & Javitt, 2005). Therefore a failure to detect abnormal N1 amplitude in the current study suggests that poorer recognition performance and abnormalities in later ERP components in the patient group cannot be attributed to deficits in early ventral stream processing during the encoding of words into episodic memory. While some anatomical and neurophysiological evidence does indicate early visual processing

deficits in schizophrenia, it has been suggested that magnocellular and parvocellular pathways are differentially affected (Butler & Javitt, 2005), and current findings support earlier evidence that the initial stages of ventral stream processing are relatively preserved in schizophrenia (Foxy et al., 2001).

Compared to controls patients had smaller P2 peaks indicating a deficit in the allocation of attentional resources during encoding, and thus support the findings of Zhao et al. (2011). However, given that accounting for education status reduced the statistical significance of this finding, whether the P2 difference was related to the disorder or to education more directly cannot be determined here. As a result, these P2 findings should be treated more cautiously and will not be elaborated in this discussion. (Dunn et al., 1998; Luck & Hillyard, 1994).

No previous reports have specifically investigated N400 during encoding, however in the recognition memory literature abnormalities have been observed, with one study demonstrating reduced modulation of an N400-like component during recognition for faces (Guillem et al., 2001), but not words (Kayser et al., 1999; Kim et al., 2004). There is evidence that these abnormalities are seen only when the task requires semantic categorisation (Grillon et al., 1991; Matsuoka et al., 1999), such as the task used by Guillem et al. (2001) and the present study. Therefore our finding of reduced central and parietal N400 amplitude in patients compared to controls may reflect a generalised dysfunction in semantic processing or a dysfunction in the allocation of resources to these processes (Andrews et al., 1993) during the encoding of words.

LPP amplitude for recognised words was more positive than for not recognised words, and though the effect was only small it was still reliable. Previously, smaller subsequent memory effects have been observed for recognition compared to free recall (Paller et al.,

1988). It has been suggested that these smaller effects may be accounted for when factors such as guessing influence recognition performance, and that using recall to test retrieval can be more sensitive to the differences between words that are successfully encoded or not (Paller et al., 1988). Hence had a recall task been used in the current study larger ERP differences at encoding may have been observed for subsequently correctly recalled compared to not recalled items. However, small sample size and insufficient number of trials for the ‘not recognised’ condition is a likely explanation for the lack of observed between-group difference for the subsequent memory effect. In general an average of 20-30 trials per condition is an acceptable number for an ERP average, and typically large, slow components such as the LPP require fewer trials than earlier components (Woodman, 2010), however several participants performed particularly well on the subsequent recognition task resulting in too few trials (fewer than 20 epochs) in the ‘not recognised’ condition to be included in the analysis. Several participants (n=3) had between 15 and 20 trials available for an average ‘not recognised’ ERP. As a trade-off between further reducing the sample size, 15 was set as the minimum criterion for inclusion in the analysis. Furthermore it has been suggested that the increased signal to noise ratio that results from fewer included trials can be mitigated by measuring the mean amplitude of a specified time window rather than peak amplitude (Picton et al., 2000), as is the case with examination of the LPP component for the subsequent memory analysis. However it is important to note this as a limitation of the study, though one that is specific to the subsequent memory findings.

The finding of smaller LPP amplitudes measured in the 450-750ms range in patients compared to controls in the present study is consistent with previous working memory literature examining late positive potentials during encoding. For example, Kayser et al. (2006) found reduced amplitude of a positive component around 400ms, while another study found reductions in a P370 component but no difference in P3a and P570 components

(Haenschel et al., 2007). On the other hand, P300 amplitudes in patients compared to controls have also been found to be increased relative to controls in during working memory encoding (Zhao et al., 2011). Divergent outcomes from this research may merely be due to methodological considerations, with substantial differences in task, stimuli (words vs abstract shapes), and symptom severity and duration of illness (chronic, inpatient vs early onset) across the studies. Late positive potentials are thought to index late cognitive and elaborative encoding processes such as stimulus evaluation and consolidation. Significant reductions in LPP amplitude were observed for patients in the current study suggesting a deficit in the elaborative evaluation of stimuli. Furthermore, LPP correlated (though only marginally significantly) with subsequent recognition, suggesting that this component may be of particular importance to effective episodic memory performance, and taken together with the findings from working memory, this late cognitive process during encoding may make a particularly significant contribution to memory impairment observed in schizophrenia. However, it should be noted that LPP also correlated significantly with WTAR scores suggesting an association between premorbid IQ and this stage of processing during encoding, but only for patients. The correlations reported in this study are mostly trend-level, nor corrected for multiple comparisons. Furthermore, lack of findings of any further associations between ERPs and clinical variables of interest may simply be due to a small sample size that has resulted in an underpowered study, and we are therefore limited in the conclusions that can be drawn from these associations.

There are several other limitations of the present investigation that should be considered. First, the recognition task used did not distinguish remember/know responses. ‘Remember’ judgements involve conscious recollection of the actual encoding event whereas ‘know’ judgements rely on feelings of familiarity, and there is evidence that ERPs differ when sorted on the basis of the two different responses (Friedman & Johnson, 2000). While the intention

was to not over-complicate the task for the patient group, source memory probes in the present study would have enabled sorting of ERPs on the basis of conscious recollection of item-specific encoding and therefore may have provided a more accurate representation of episodic encoding processes. Second, the reduced rate of subsequent recognition in the schizophrenia group generates a possible confound as a result of patients only remembering items that are particularly memorable and such factors may influence the neural correlates of encoding. For example emotional stimuli are more memorable than neutral stimuli and it has been reported that a number of ERP components vary with positive or negative words compared to neutral words (for review see Citron, 2012). In schizophrenia, reduced modulation of LPP for pleasant (relative to neutral) stimuli has been reported while earlier ERP components remained intact (Horan et al., 2010), suggesting a disruption of evaluative processing of pleasant stimuli associated with the disorder. Given that the orienting task during encoding in the present study utilises pleasant/unpleasant categorisation it is difficult to determine the extent to which an effect of elaborative encoding associated with emotional processing had on the ERP components observed here.

A further limitation relates to antipsychotic use. Antipsychotic medications can influence many aspects of brain function. For example, typical antipsychotics have been associated with adverse effects on cognitive functioning (Blyler, 2000), while atypical antipsychotics have been associated with improvements in episodic and semantic memory dysfunction in schizophrenia (Sumiyoshi et al., 2006; Sumiyoshi et al., 2001), and worsening of some cognitive dysfunctions such as working memory (Reilly et al., 2007). Additionally, changes in quantitative EEG topography have been associated with atypical antipsychotic use (Joutsiniemi et al., 2001). While it is therefore possible that medication use may have contributed to both the behavioural and ERP deficits observed in the current study, other studies have shown antipsychotic medication to have no effect on general cognitive

functioning (Goldberg et al., 2007; Hill et al., 2009), or on visual ERP components such as N1 and P3 (Ford et al., 1994). ERP abnormalities have been found in both first episode (Oribe et al., 2013) and medication naïve patients (Qiu et al., 2014) suggesting that alterations observed in chronic patients are not likely due to medication type or duration of use. Furthermore, ERP amplitude did not significantly correlate with risperidone equivalent doses for any of the components investigated, therefore it may be argued that reductions in N400 and LPP observed here are likely to be characteristic of the illness itself rather than a secondary effect of antipsychotic treatment. Nonetheless, and particularly given the small sample size and reduced power, antipsychotic effects should be taken into account as a potential confounding factor when interpreting the findings of the present study.

Finally, both years of education and premorbid IQ were significantly different between the groups and so may have confounded the findings. We explored this possibility with ANCOVA for behavioural and ERP variables that met the assumptions of this analysis. Premorbid IQ did not meet the requirements of ANCOVA and could not be assessed in this way. The addition of education level did not change the significance of behavioural or LPP results, but it did reduce the significance of between-group differences in P2. While education level and premorbid IQ have been shown to impact behavioural outcomes such as cognitive performance (Weickert et al., 2000), it is not clear whether these variables are related to P2 independent of schizophrenia status. Nevertheless the interpretation of findings should be considered in light of this important limiting factor.

In summary, individuals with schizophrenia had smaller amplitude N400 and LPP components, and possibly reduced P2 amplitudes, but no difference in the N1 component during encoding of words into episodic memory. Schizophrenia-related attenuation of later positive potentials have been previously reported in several studies of memory, however this is the first study to our knowledge to report ERP abnormalities during episodic memory

encoding. These outcomes add to earlier behavioural and fMRI findings of abnormal encoding contributing to episodic memory impairment in schizophrenia, and further suggest that individuals with schizophrenia have difficulties in successfully engaging attention and enhancing semantic and contextual processes during the encoding of words into memory.

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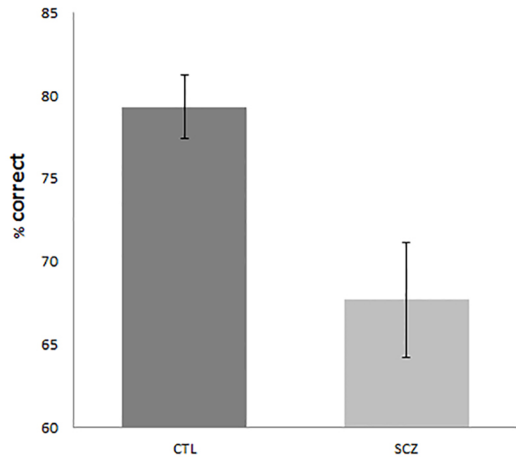
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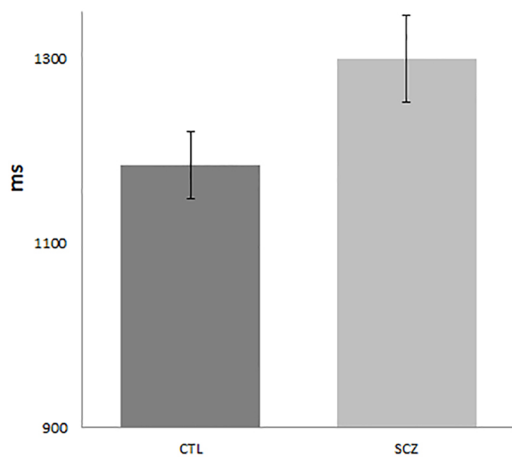
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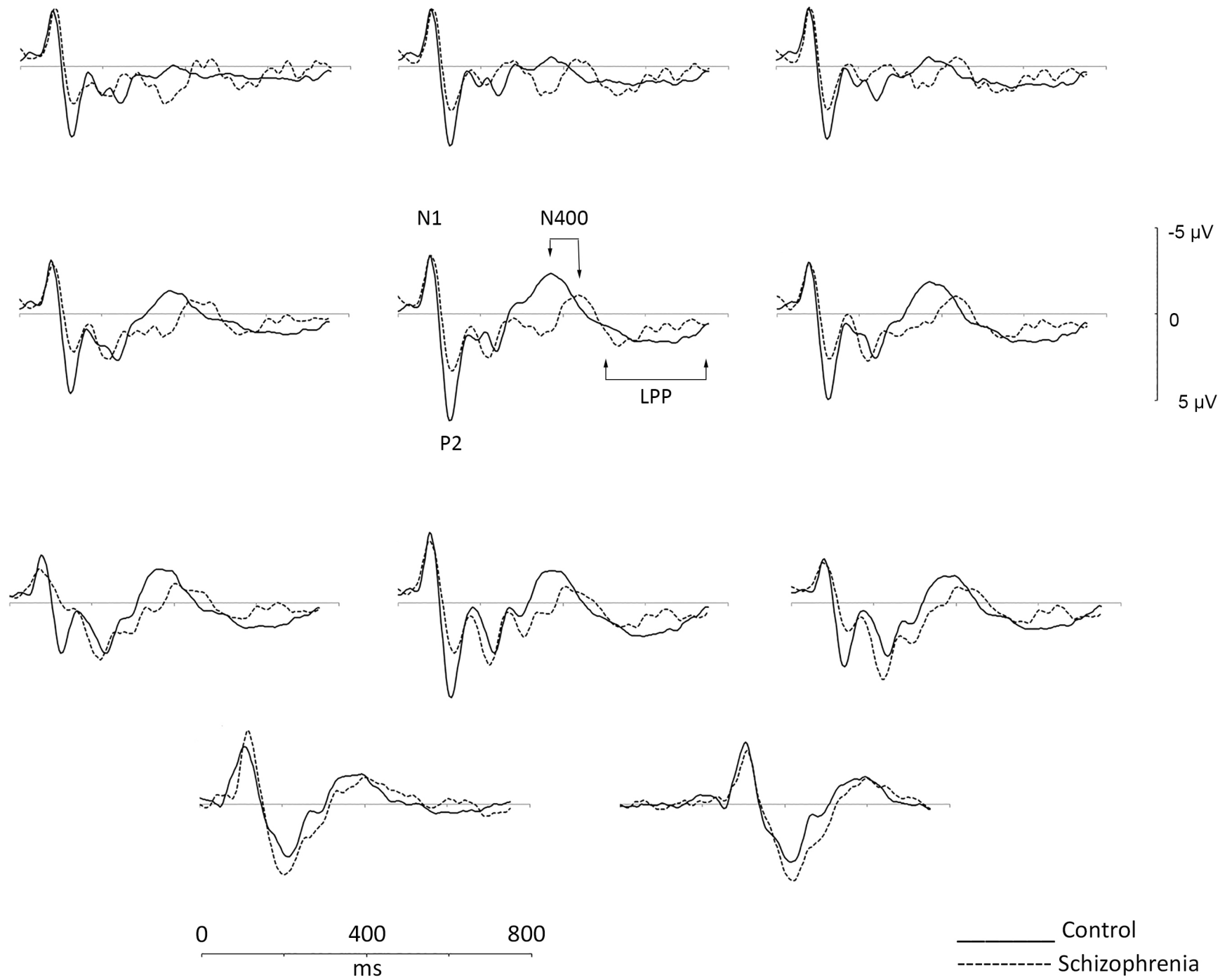
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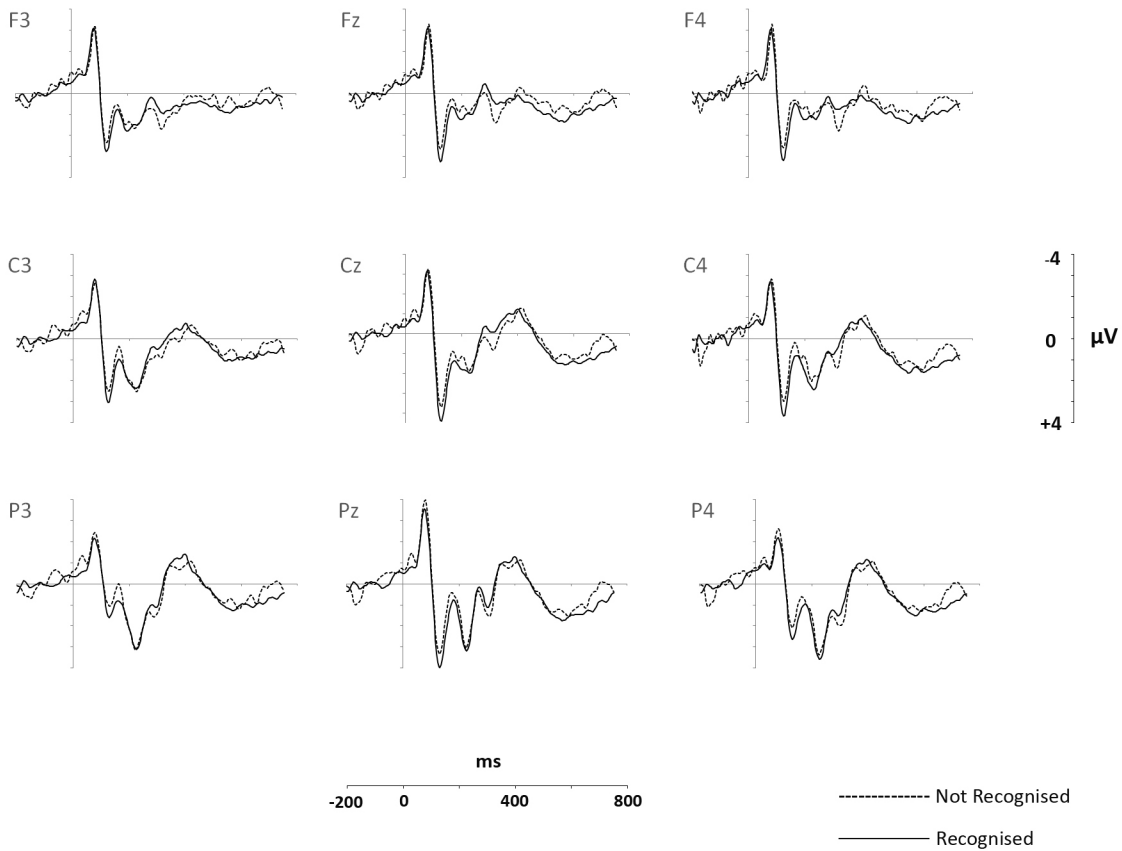
recognition accuracy



response latency







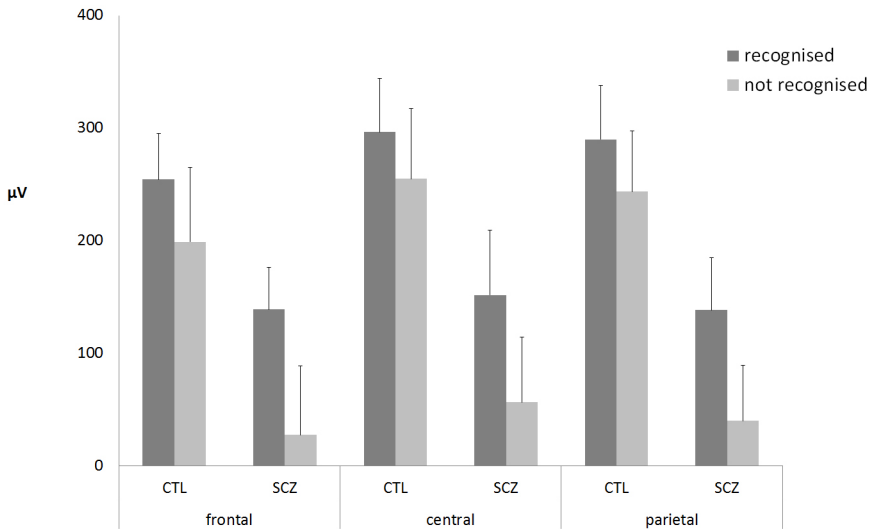


Table 1: Group means, standard deviations (SD) and significance values (p) for between-group differences for demographic and clinical characteristics of patient and control groups.

	<i>Schizophrenia</i> <i>N=24</i>		<i>Healthy Controls</i> <i>N=19</i>		<i>p</i>
Male/Female	12/11		9/10		0.76
Current smoker	43.5%		17.6%		0.08
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>p</i>
Age, y	37.43	7.72	37.05	8.59	0.88
Education, y	13.95	3.26	18.05	3.42	<0.001
WTAR, standardised	107.32	6.30	112.79	6.89	0.02
Age at illness onset, y	21.96	8.88			
Duration of illness, y	15.48	11.05			
Risperidone equivalent dose, mg	4.90	2.90			
Med type: typical/atypical	6/17				
PANSS					
Total score	74.78	12.71			
Positive symptoms	17.48	4.87			
Negative symptoms	19.13	5.93			
General psychopathology	38.17	7.39			
CDSS total	7.30	5.38			

Table 2. Means and standard deviations for N1 occipital (mean of O1, O2), parietal (mean of P3, P4) amplitude (microvolts) and latency (milliseconds); P2 frontal (Fz), central (Cz) and parietal (Pz) amplitude and latency; N400 mean latency at frontal (Fz), central (Cz) and parietal (Pz) sites; LPP mean latency at frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) sites. Significance values (p) for between-group differences for amplitude only as all latency differences were non-significant (all p>0.05)

<i>Component</i>	<i>Electrode/region</i>	<i>Control</i>		<i>Schizophrenia</i>		<i>p</i>
		<i>amplitude</i>	<i>latency</i>	<i>amplitude</i>	<i>latency</i>	
<i>N1</i>	Occipital	-6.05 (3.96)	122.79 (24.99)	-4.73 (4.32)	112.33 (22.86)	0.307
	parietal	-4.04 (1.84)	96.12 (11.92)	-3.53 (2.10)	96.27 (23.18)	0.407
<i>P2</i>	Frontal	6.71 (3.96)	140.68 (11.94)	3.84 (2.51)	151.50 (22.20)	0.006
	Central	6.98 (4.15)	140.05 (10.57)	4.53 (2.69)	151.67 (19.97)	0.024
	Parietal	6.54 (3.57)	149.32 (26.27)	4.65 (2.30)	157.99 (25.39)	0.042
		<i>Mean amplitude</i>		<i>Mean amplitude</i>		
<i>N400</i>	Frontal	-11.61 (256.74)		55.43 (318.26)		0.461
	Central	-216.03 (213.54)		-5.12 (277.99)		0.009
	Parietal	-163.88 (222.92)		-16.11 (176.86)		0.020
<i>LPP</i>	Frontal					
	Recognised	242.39 (124.44)		168.01 (200.32)		0.165
	Not recognised	198.86 (252.52)		27.54 (290.81)		0.066
	Central					
	Recognised	297.59 (172.17)		175.87 (210.52)		0.048
	Not recognised	255.02 (262.60)		56.67 (253.83)		0.026
	Parietal					
	Recognised	308.03 (191.39)		163.56 (211.95)		0.026
	Not recognised	243.65 (212.52)		39.98 (227.82)		0.008