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Brain/behavior Asymmetry in Schizophrenia: A MEG Study of Cross-modal Semantic Priming

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Abstract

Semantic priming has long been used to investigate how concepts and ideas are related at the level of language, and has become a convenient tool for assessing conceptual and semantic dysfunction in cognitive disorders, including schizophrenia. The study of semantic priming in schizophrenia has led to diverse results: enhanced priming, reduced priming, and priming equivalent to that found in nonpsychiatric comparison groups. A number of hypotheses have been proposed to explain some of the observed deficits in schizophrenia patients. For example, difficulties in word recognition may be due to hyperactivation of too many lexical representations or to a failure to inhibit lexical competitors. One way to distinguish between these possible explanations is to move beyond reliance on behavior alone and to examine the neural processes involved in lexical recognition. Here we present a magnetoencephalographic study of semantic priming in schizophrenia. Importantly, schizophrenia patients and healthy controls did not differ in performance on a priming task. We show that normal behavioral performance can occur in a context of aberrant neural responses. These findings suggest that normal behavioral responses in schizophrenia can be achieved through neural mechanisms that differ from those seen in the psychiatrically well brain.

INTRODUCTION

Word recognition is a complex process involving several distinct cognitive operations, including (at least): activation of lexical representations, competition between related representations, inhibition of incorrect competitors, and selection of the correct lexical representation (e.g. Marslen-Wilson 1990). The number of competing representations activated, and therefore the speed and accuracy of word recognition, are influenced by semantic context (among other factors), such that words preceded by semantically associated words are *primed* – that is, recognized faster and more accurately than words preceded by unassociated words (Neely, 1991). Priming paradigms therefore provide a method for examining the organization of meaning representations, in both normal and

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pathological situations. Here we present a study of brain responses to priming in schizophrenia.

Behavioral Studies

Abnormalities in semantic memory and lexical access are consistently documented as part of the cognitive dysfunction in schizophrenia, but investigations of semantic priming in schizophrenia have yielded inconsistent findings (see Minzenberg, Ober & Vinogradov (2002) for a review). Some studies report enhanced priming with faster response times (RTs) in schizophrenia compared with control participants (e.g., Spitzer, Braun, Hermle & Maier, 1993; Manschreck, Maher, Milavetz et al., 1988; Moritz, Woodward, Küppers et al., 2003; Chenery, Copland, McGrath & Savage, 2004; Kwapil, Hegley, Chapman & Chapman, 1990). Others report reduced priming in schizophrenia, relative to controls (Vinogradov, Ober & Stenaut, 1992; Henik, Priel & Umansky, 1992; Ober, Vinogradov & Shenaut, 1997; Kubicki, McCarley, Nestor et al., 2003; Mathalon, Faustman & Ford, 2002). Still other investigators found normal priming in schizophrenia patients (e.g., Chapin, McGown, Vann et al., 1992; Blum & Friedes 1995; Quelen, Grainger & Raymond, 2005).

An association has been observed between increased semantic priming and the presence of thought disorder – for example, Pomarol-Clotet, Oh, Laws & McKenna (2008) found that schizophrenic patients with thought disorder showed increased semantic priming, whereas patients without thought disorder did not differ from controls (see also Manschreck, Maher, Milavetz et al., 1988). This result is intriguing because semantic anomalies (deviant use of language) are the cardinal feature of the thought disorder observed in schizophrenia patients in all phases of the illness (Solovay, Shenton & Holzman, 1987; Holzman, Shenton & Solovay, 1986; Makowski, Waternaux, Lajonchere et al., 1997; Spohn, Coyne, Larson et al., 1986). However, studies have shown that semantic priming in schizophrenia is affected by many variables, with experimental variables interacting with population characteristics. Key experimental variables include stimulus onset asynchrony (e.g., Barch, Cohen, Servan-Schreiber et al. 1996; Morgan, Bedford & Rossell, 2006), the typicality of semantic category exemplars (e.g., Ober, Vinogradov & Shenaut, 1995), and percentage of related words presented in experimental tasks (Passeriuex, Segui, Beche et al., 1997). Relevant population characteristics include illness duration (Rossell, Shapleske & David, 2000; Rossell & Stefanovic, 2007), and presence vs. absence of thought disorder (Pomarol-Clotet et al., 2008; Manschreck et al., 1988).

The nature of the underlying impairments affecting lexical access and semantic processing in schizophrenia remains unclear. Reduced semantic priming has been posited to arise from difficulties maintaining representations of context (Barch et al., 1996). This formulation is consistent with other problems observed in schizophrenia, for example, in structuring narratives and discourse (Kramer, Bryan & Frith, 1998; Mitchell & Crow, 2005). Other investigators have suggested that the “semantic store” – a mentally-represented, meaning-based network of lexical items – is disrupted by either greater than normal spread of activation or by failure to inhibit competing representations. For example, Pizzagali, Lehmann & Brugger (2001) proposed that word recognition impairments in schizophrenia are most likely due to deficits affecting early processes, especially activation: hyperactivation of representations results in a breakdown of later competition and inhibition processes. Conversely, Titone, Levy & Holzman (2000, 2002) proposed that activation of lexical representations in schizophrenia may be normal, but competitor inhibition is disrupted (see also Sitnikova, Salisbury, Kuperburg, & Holcomb, 2002; Titone & Levy, 2004; Titone, Libben, Niman et al., 2007). On the basis of behavioral data alone, it is difficult to determine which of these competing hypotheses about the nature of lexical processing disturbances in schizophrenia is correct. Psychophysiological and neuroimaging

methods, however, hold promise for elucidating the underlying processes affecting language and cognition by providing a window into associated neural activity.

Psychophysiological Studies

Neurophysiological examinations of semantic priming in schizophrenia have primarily focused on the N400, a negative-going evoked response potential (ERP) that shows greater amplitude in response to semantic anomaly (Kutas & Hillyard, 1980). In schizophrenia patients N400 amplitudes are typically reduced. This attenuation has been variously understood as reflecting failure to utilize information from preceding words or context (Matsuoka, Matsumoto, Yamazaki et al., 1999), slower and more diffuse semantic activation (Nestor, Kimble, O'Donnell et al., 1997), impaired neurophysiological activation of related concepts (Kiang, Kutas, Light & Braff, 2008), or difficulties integrating semantic and syntactic information (Kuperberg, Sitnikova, Goff & Holcomb, 2006). Greater N400 attenuation in schizophrenia has been associated with increased severity of thought disorder (Ditman & Kuperberg, 2007; Kostova, Passerieux, Laurent & Hardy-Bayle, 2005) and with higher incidence of delusions (Kiang et al., 2008); N400 attenuation may also be associated with other factors, such as later age of psychosis onset (Olichney, Iragui, Kutas et al., 1997) or higher medication dosage (Salisbury, O'Donnell, McCarley et al., 2000).

The association between reduced N400 amplitudes and anomalous lexical activation is intriguing but not conclusive, because the N400 is a sustained potential lasting up to 300 milliseconds, and is therefore likely to index an amalgam of distinct stages in lexical processing (Pylkkänen & Marantz, 2003; Federmeier & Kutas, 2000). In contrast with ERP investigations, magnetoencephalography (MEG) has a unique combination of very fine temporal resolution (typically sampling every millisecond) and relatively good spatial resolution. MEG non-invasively measures magnetic fields associated with electrical currents in the brain, so it is related to EEG but also distinct from it. One important difference is that MEG data on each participant can be analyzed separately, without necessarily resorting to grand averaging (which is typically necessary in ERP analyses). MEG therefore lends itself well to the study of populations in which within group heterogeneity is likely – as in schizophrenia. Furthermore, subcomponents of the neural response are more likely to be identifiable in MEG than EEG. MEG field patterns indexing pre-lexical processing (the M250), activation of the mental lexicon (M350 initial peak), and word recognition (possibly M350 second peak) have been identified (Pylkkänen & Marantz, 2003; Pylkkänen, Stringfellow & Marantz, 2002; Embick, Hackl, Schaeffer et al., 2001). Investigations of the M350 have shown that the component peak latency is affected by lexical and sublexical frequency (Embick et al., 2001; Pylkkänen et al., 2002), and that its amplitude is sensitive to morphological family frequency (i.e., cumulative frequency of words derivationally related to the target) (Pylkkänen, Feintuch, Hopkins & Marantz, 2004). These findings together have been interpreted as suggesting that the M350 is an index of non-decisional activation stages in lexical access, but not of later stages involving competition and inhibition.

Some research suggests that the interpretation of the cognitive significance of the M350 may not be as straightforward as it seems, however. Stockall, Stringfellow & Marantz (2004) demonstrated an interaction between phoneme probability and phonological neighborhood density on M350 amplitude. This finding led them to question Pylkkänen et al.'s (2002) conclusion that density does not affect the M350 and that, therefore, this component may not index initial, pre-competition stages of lexical access. In fact, Stockall et al. found that high probability stimuli actually inhibited the earlier M250 response, suggesting that the effects of competition may, under certain circumstances, be observed earlier than previously thought. Thus, the different stages of lexical access seem to interact with each other in complex ways. We elected to focus on the M350 for the purposes of the present investigation, since establishing differences in the earliest stages of lexical activation

requires the manipulation of sublexical variables, whereas our examination of semantic organization required manipulation of semantic relatedness – a supralexical property.

The present study was developed as a preliminary investigation of the neural correlates of lexical activation in a group of clinically stable chronically ill adult outpatients with a diagnosis of schizophrenia or schizo-affective disorder. All of the patients were psychotic, as evidenced by the severity of symptoms on the Brief Psychiatric Rating Scale (BPRS: Overall & Gorham, 1962). All of the patients were reasonably high functioning considering their chronic illnesses (see Table 1 for scores on the Global Assessment of Functioning Scale (GAS: Endicott, Spitzer, Fliess & Cohen, 1976) and other demographic and clinical data). We purposefully chose a relatively high functioning group of patients with the expectation that they would perform equivalently to healthy comparison subjects on a cross-modal semantic priming task. In that case, it would be possible to assess the neural organization of lexical activation subserving equivalent behaviors in the two groups.

Since the M350 is one component believed to be associated with early stages of lexical access, abnormalities in the M350 could support the interpretation that lexical access in schizophrenia is impaired at earlier, activation stages (Pizzagali et al. 2001). A finding of increased amplitude and/or shorter latencies at the M350 would support a “hyperactivation” view of the lexical access difficulties in schizophrenia. In contrast, if the M350 does not show abnormalities, it could be argued that a “disinhibition” mechanism is underlying abnormalities in word processing in schizophrenia (Titone et al. 2000) – although such a finding would not rule out the possibility that abnormalities involving competition or inhibition may be present downstream. Effects of competition and inhibition earlier than M350 can be elicited, as discussed, but thus far only through systematic manipulation of sublexical properties, which are not a focus of this investigation. A cross-modal paradigm was selected over an ipsi-modal priming paradigm because of recent results suggesting that results using cross-modal priming are more robust in schizophrenia (e.g. Surguladze, Rossell, Rabe-Hesketh & David, 2002).

METHODS

Research participants

The participants were 7 individuals who met DSM-IV criteria for schizophrenia or schizo-affective disorder (SZ) (American Psychiatric Association, 1994) and 7 nonpsychiatric comparison subjects. One schizophrenic participant was excluded because he did not show typical RT priming (i.e., faster responses to related prime-target pairs than to unrelated pairs) on the experimental task, resulting in a sample size of 6 in the SZ group. All patients received a structured clinical interview (Spitzer, Williams, Gibbon & First, 1994), administered by experienced clinical interviewers. Diagnoses were assigned by an independent group of senior clinicians, who reviewed interview material and all available hospital records. All diagnoses were assigned by consensus using “best estimate” methods (Leckman, Sholomskas, Thompson et al., 1982). Nonpsychiatric controls were recruited from the local community and were screened for personal history of psychiatric disorder. None of the study participants had a history of substance abuse or dependence. All gave written informed consent and were paid a small honorarium for participation. All procedures were approved by the Internal Review Boards of the authors’ respective institutions.

Demographic and clinical characteristics of the samples are shown in Table 1.

Procedure

A cross-modal semantic priming paradigm was utilized in a lexical decision task. MEG data were simultaneously acquired with a 156-channel whole-head axial gradiometer system

(KIT/MIT MEG Lab) in a magnetically-shielded room. MEG data were recorded and analyzed using MEG160 software developed by the Kanazawa Institute of Technology. Headshapes, five marker coil locations, and positions of the nasion and left/right preauricular points were digitized for all subjects, using a Polhemus Fastrak system. All stimuli were controlled by a Macintosh computer running Psyscope under OS9. Sound files were recorded and digitized at 44100Hz in SoundEdit, and were presented to participants via silicon air tubes and E-A-Rtone 3A insert earphones (AEARO Company, Indianapolis, IN). Visual targets were presented in white on a black background in lowercase (Arial, 36-point font). The image generated on the computer monitor was mirrored by an InFocus LP425 projector at 800 × 600 dpi resolution onto a ground glass screen, producing a focused image size of approximately 18 cm × 18 cm at a distance of 24 cm from the participants.

Auditory primes were followed immediately by visually presented target words; the stimulus onset asynchrony (time from onset of prime to onset of visual target) ranged from 350-950 milliseconds (mean SOA 674.48 msec, SD 147.28). Participants made binary choice lexical decisions about visual targets (word vs. non-word) via button press; reaction times (RTs) and response accuracy were recorded. There were 105 lexical decision trials (35 each of related and unrelated prime-target pairs, and 35 unrelated non-word targets). All word stimuli had frequencies between 1 and 800 per million (determined using CELEX: Baayen, Piepenbrock & Gulikers, 1995), and word targets and primes were matched for frequency across conditions (mean frequency: 49.3 per million; SD: 101.59). Related words were either in object-property (e.g., *laundry-dirty*) or exemplar-exemplar (e.g., *walnut-almond*) relations. Examples of unrelated word pairs are *rubber-soy*, *boulder-sham*. Non-words were legally spelled and pronounceable, and were derived from real words by changing one letter (e.g. *fanch*, *heaf*). To ensure continued auditory attention, 20 trials were interspersed in which participants were asked to repeat aloud the word they had just heard. Items were presented in a pseudo-random order, different for each participant, with the stipulation that no more than three exemplars from the same condition followed each other sequentially. The experimental trials were preceded by 15 practice trials (using different items) to familiarize participants with the task.

DATA ANALYSIS & RESULTS

Behavioral data

Error rate (accuracy) and RTs (for all trials, regardless of accuracy) were examined within and between groups, using paired samples and independent samples t-tests, respectively, to evaluate statistical significance. Pearson product-moment correlations were used to examine relations between RT, error rate and demographic variables (age, years of education, medication dose in chlorpromazine (CPZ) equivalents, duration of illness); no significant correlations were found (all Pearson r s > 0.7, all p -values > 0.06). Comparisons were evaluated for effect size using Cohen's d statistic; d > 0.4 indicates a medium effect size, and d > 0.75 indicates a large effect size (Cohen, 1988,1992).

Accuracy was better in the Related Prime-Target condition than in the Unrelated Prime-Target condition in both groups (SZ: mean errors in Related condition - 1.83, SD: 2.99; Unrelated condition - 4.33, SD: 4.97; Controls: mean errors in Related condition - 0.14, SD: 0.38; Unrelated condition - 3.14, SD: 2.61). This difference was statistically significant in the control group ($t(12) = 3.01$, $p = 0.012$, $d = 1.74$), but not in the SZ group ($t(10) = 1.06$, $p = 0.32$, $d = 0.66$). Although group comparisons within condition were non-significant (Related items: $t(12) = 1.36$, $p = 0.17$, $d = 0.79$; Unrelated items: $t(12) = 1.60$, $p = 0.11$, $d = 0.92$), effect sizes were large, suggesting that the lack of significant effects is related to the small sample sizes.

Reaction times were aggregated by item (35 per condition). RTs to related targets were significantly faster than RTs to unrelated targets in both groups, consistent with priming to related targets (controls: $t(34) = -4.6$, $p < 0.001$, $d = 2.66$; SZ: $t(34) = -2.4$, $p = 0.024$, $d = 1.39$). SZ patients had significantly slower RTs than the control group in the Related condition, but the RT difference between the groups did not reach significance for Unrelated items. Effect sizes, however, were large in both conditions (SZ group - mean $RT_{RELATED}$ 1024.62 msec, SD: 218.15; $RT_{UNRELATED}$ 1270.47 msec, SD: 526.99; Control group - mean $RT_{RELATED}$ 917.93 msec, SD: 161.29; $RT_{UNRELATED}$ 1134.80 msec, SD: 207.70; $t_{RELATED}(68) = -2.33$, $p = 0.023$, $d = 1.41$; $t_{UNRELATED}(68) = -1.42$, $p = 0.16$, $d = 0.86$).

The key measure of behavioral performance is the magnitude of the priming effect (mean $RT_{UNRELATED} - \text{mean } RT_{RELATED}$). Crucially for this study, the magnitude of the priming effect did not differ between groups ($t(68) = -0.253$, $p = 0.80$, $d = 0.15$; controls - mean priming effect 216.87 msec, SD: 280.75; SZ - mean priming effect 245.85 msec, SD: 616.12). This result indicates that the patient group experienced priming effects equivalent to that of controls, at least at the level of behavioral responses.

Reaction times and accuracy for both groups in both experimental conditions are summarized in Figure 1.

MEG data analysis

MEG data were noise-reduced by extracting recordings from three reference sensors situated on top of the magnetically-shielded chamber. Data were averaged off-line, low pass filtered at 40Hz and baseline corrected with reference to a 150-millisecond pre-epoch interval. The M350 field pattern was operationally defined as a posterior source / anterior sink across left hemisphere sensors, with latencies between 270 and 500 milliseconds post-onset.

First, all word recognition epochs were averaged together for each individual. A group of sensors showing the expected field distribution over the left hemisphere in the M350 time window was identified. Using averaged data for each condition, the root mean square (RMS) was calculated from all sensors in the identified region. The RMS peak over the relevant sensors was identified, and its latency and amplitude recorded. For the control group, data from all relevant sensors were grand averaged to yield a plot of mean M350 responses. However, for the SZ group, examination of the data revealed extreme variability. Data from the SZ participants are therefore presented individually.

Control Group

Two control participants did not show an identifiable M350 field pattern. Such difficulties in M350 identification have been previously reported (e.g. Almeida, Nevins & Poeppel, 2006) and thus were not unexpected. MEG data from these two participants were included in the group grand average, however (but see Appendix). The other five control participants showed the expected M350 latency shift, and peak latencies and amplitudes for these five subjects are provided in table 2. For these five subjects, peak latency for Related prime-target pairs was significantly shorter than that for Unrelated pairs, consistent with priming at the M350 (latency for Related pairs: mean: 344.4 msec, SD: 60.78; latency for Unrelated pairs: 384.2 msec, SD: 55.09; $t(4) = 10.13$, $p = 0.001$, $d = 0.77$). M350 amplitude did not differ significantly between the two conditions (mean amplitude of RMS sensors to Related stimuli 183.36fT, SD: 174.64; to Unrelated stimuli 136.14fT, SD: 102.38; $t(4) = 1.18$, $p = 0.305$, $d = 0.37$). Figures 2 and 3 show the M350 field distributions and RMS waveforms for grand averaged data for all 7 control subjects (including data from the two who did not show identifiable M350 peaks) in the Related and Unrelated conditions; M350 peak latencies in

the grand average were somewhat later than those reported in table 2, possibly due to the two participants without identifiable M350 peaks.

To summarize the control data, the highly significant behavioral priming found in the Related condition was associated with a significant reduction in M350 peak latency and a slightly stronger M350 field. Compared with responses to related prime-target pairs, the Unrelated condition was associated with a later M350 peak and somewhat smaller M350 field responses.

SZ group

These analyses were purposefully restricted to the subgroup of schizophrenia patients who showed typical behavioral priming. However, examination of the MEG data revealed extreme variability in brain responses, and the data for the SZ group are best interpreted individually. Therefore, the MEG results for these six participants are presented case-by-case. Results are represented graphically in Figure 4.

Patient 1

P1's MEG data revealed an RMS peak in the M350 time window distributed over left hemisphere temporo-parietal sensors, similar to control participants. However, P1's field pattern was consistently reversed from normal (i.e., anterior source, posterior sink – the opposite field orientation from that found in controls) in response to both related and unrelated targets. Paradoxically, the latency of this reversed M350 was shorter in the unrelated condition than in the related condition despite faster behavioral reaction times to related targets. Peak amplitude was not affected.

Patient 2

P2's MEG data showed evidence of multiple activations throughout the experimental epoch, making it difficult to distinguish clear field patterns at any latency. The most likely candidates for the M350 in both conditions were observed rather early, with peak latencies of 280 msec in the Related condition, and 294 msec in the Unrelated condition. Later fields observable in the epoch were all reversed in comparison with typical M350 distributions, and none showed clear RMS peaks. P2 showed a large amplitude reduction in the Unrelated condition.

Patient 3

Like P2, P3 showed a large amplitude reduction at the candidate M350 peak in response to the Unrelated targets. P3's brain data were unusual in showing a very early, stable M350-like pattern from around 100 milliseconds post target onset through to the end of the epoch. The field pattern was reversed in the Related condition, but showed a more typical distribution in the Unrelated condition. However, the RMS waveform revealed a large peak in the M350 time window in both conditions, suggesting that despite the stable distribution of the field, there was some shift in field strength and/or underlying generator organization around the time indicated. P3 showed no M350 latency difference between Related and Unrelated target responses; however, a somewhat weaker field was observed in the Unrelated condition (around 60 fT less than in the Related condition). The field reversal, apparent only in the Related condition, is difficult to explain and might suggest atypical semantic field activation in the presence of closely-related competitors.

Patient 4

P4, like P3, showed a long-lasting and stable field pattern emerging early in the epoch (around 200 msec) and persisting throughout. However, it is not possible to determine

conclusively whether an M350 is present for this individual. Multiple source activations are apparent throughout the epoch; unlike P3, however, P4's data did not show good evidence of periodic shifts in activation, making it difficult to identify a peak in the RMS sensors around the M350 time window. This could indicate a disorder in inhibition of neuronal activations. The field distribution observed for P4 is reversed from the typical M350. Snapshots of the field distributions at likely time points (the first RMS peak in the M350 time window) are shown in figure 4.

Patient 5

Also like P3, P5 showed a field reversal in the Related condition, but a more typical field distribution in response to Unrelated targets. The M350 peak was somewhat earlier in the Related than in the Unrelated condition, but amplitude differences were very small between conditions.

Patient 6

P6 showed a field distribution that approximated that of the comparison group; however, the average field strength was much lower, which made the RMS peaks in the appropriate time window somewhat difficult to identify.

To summarize, the MEG data collected from the schizophrenic participants are highly variable and bear little resemblance to the MEG data collected from the comparison group. Abnormal field distributions, especially polarity reversals, were featured in several individual recordings and additional dipolar sources were apparent in at least one recording; field strength was extremely variable both within and between individuals. There was some evidence to suggest abnormalities in the inhibition of neuronal responses during early stages of sensory processing, which may have interfered with downstream processes involved in word recognition.

Correlations were examined in the SZ group between amplitude and latency of the M350-candidate peaks (summarized in table 3), and SES, medication dosage (in CPZ equivalents), GAS scores, and illness duration. No significant correlations were found (all p s > 0.09). Planned comparisons were used to investigate effects of Condition on candidate M350 peak latency and amplitude. Unlike the findings for the control group, there was no significant effect on latency (latency for Related pairs – mean: 335.3 msec, SD: 31.66; latency for Unrelated pairs – mean: 340.3 msec, SD: 41.89; $t(5) = -0.274$, $p = 0.795$, $d = 0.17$). The effect on amplitude was significant, with the Unrelated condition being associated with lower amplitudes at the M350-candidate peaks than the Related condition (mean amplitude of RMS sensors to Related stimuli 87.39fT, SD: 44.08; to Unrelated stimuli 60.54fT, SD: 20.59; $t(5) = 2.824$, $p = 0.037$, $d = 1.79$).

Between-Group Comparisons

A $2(\text{group}) \times 2(\text{condition})$ repeated measures ANOVA, to investigate effects of Condition (Related vs. Unrelated) and Group (Control vs. SZ) on features of the component peaks, revealed no significant effects on either amplitude or latency as a function of either Group or Condition. This is likely due to large variance around the means for the SZ group, since significant differences were found within groups, with the Controls showing effects of condition on peak latency and the SZ group showing effects of condition on peak amplitude.

DISCUSSION

These results indicate that no consistent neural pattern of abnormality or adaptation characterizes M350 activations in the SZ group, despite the presence of behavioral priming

effects comparable to those of controls. These results illustrate an important principle: normal behavioral responses can occur in the context of abnormalities at the neural/functional level of brain organization. In typical brain imaging studies of schizophrenia, behaviors are targeted for study precisely because the poor performance of schizophrenic patients is thought to make their brain functional counterparts especially probative. However, the result is that differences in regional brain activations between patients and controls are correlated with differences in performance. Such findings are difficult to interpret, because causal inferences are impossible – does the patients' poorer performance cause anomalous activation, or does the latter cause the poorer performance? A more powerful approach, the one used here, involves examination of brain activations in comparably performing patients and controls. Our results underscore the potential value of studying brain functional correlates of normal behaviors and illustrate that all normally performed behaviors are not necessarily subserved by the same neural mechanisms.

Anatomical and physiological abnormalities impacting the temporal lobes have been frequently reported in schizophrenia (e.g. Honea, Crow, Passingham & Mackay, 2005). Since the M350 localizes to temporal regions (Pylkkänen & Marantz, 2003), M350 abnormalities in schizophrenia could be attributed to temporal lobe abnormalities. Structural MRIs were not available for participants in the present study, but a careful localization analysis (mapping magnetic field sources onto individual MRIs) would have been useful in elucidating the abnormalities observed here. Prior to our experiment, participants underwent a localizer task that involves playing a series of pure tones, as a means of identifying sensors that reflect the auditory M100 response. Identification of the auditory M100 was clear-cut in every single participant. Since the pure tone localizer permitted identification of temporal lobe activation in a passive sensory paradigm, it would not be parsimonious to attribute the observed M350 abnormalities to temporal lobe abnormalities *per se*. Rather, the M350 changes we found are probably more parsimoniously explained as a reflection of disorganization of lexical processing. It has frequently been observed that individuals with schizophrenia show abnormalities of activation in studies involving brain imaging – changes in expected lateralization, regional cerebral blood flow and signal intensity have all been reported (e.g. see Fusar-Poli, Perez, Broome et al. (2007) for a review). The between-group comparisons on M350 latency and amplitude do show significant differences in these measures between the SZ group and the Control group overall, and it is therefore unclear whether we can describe the responses recorded for the SZ group as “abnormal” rather than “adaptive” – that is, as pathologically-based modifications to more typical neurological functioning¹. The striking differences in field distribution and organization of the candidate M350s observed in the SZ group compared with the controls, suggest that some underlying abnormality or abnormalities may be involved. A clear distinction between adaptive and abnormal M350 responses in schizophrenia must await further work, since this would require a deeper understanding of the interactions between underlying pathologies, abnormal presentations of expected neural responses, and adaptive reorganization of neurocognitive processes in this population.

At the cognitive level as well as the neural level, dysfunctions of working memory and attentional resource allocation are commonly associated with schizophrenia and are likely to interact with semantic priming abnormalities. These deficits have been well-documented in the neuroimaging literature. For example, Schneider, Habel & Reske, et al. (2007) conducted fMRI investigations of activations in individuals with schizophrenia during tasks associated with working memory and attention. Their participants, like ours, showed behavioral performance that was comparable with controls; however, dysfunctions were

¹Thanks to an anonymous reviewer for raising this point.

observed in a ventrolateral-prefrontal-parietal network for working memory and in parietal regions for attentional processing. Schneider et al. interpreted these findings as being related to basic impairments of retrieval, storage and maintenance. Erkwow, Sabri, Schreckenburger et al. (2002) reported that SZ patients with higher levels of thought disorder showed activations in the fusiform gyrus and precuneus (regions associated with object recognition and processing of visual imagery) during a selective attention task, suggesting that clinical subgroups assign different task-solving strategies (visual rather than the expected attentional and memory-based strategies) to achieve similar levels of performance on the same task. Given such findings, it is plausible that deficits of memory and attention, and concomitant (possibly adaptive) changes in neural and cognitive organization, have impacted the brain responses of the participants in our study; this view is supported by a consideration of the differing response profiles recorded for the individuals in our SZ group.

Four schizophrenic patients showed M350 field reversals. In two cases these were present in both the primed (related) and non-primed (unrelated) conditions, and in two other cases the field reversal was present only in the primed condition. Polarity changes are perhaps not unexpected in pathological conditions; MEG, like other electrophysiological brain imaging techniques, records summed dipolar sources at the scalp, so small changes in cortical organization can result in apparent differences in source orientation. However, selective source orientation changes under conditions of priming only are difficult to explain.

Two patients showed multiple activations throughout the experimental epoch, and two others showed early establishment of a stable and long-lasting field distribution. These responses might suggest either hyperactivation, such that responses are established too early and/or involve multiple sources, or disinhibition, such that sensory responses persist long after they are typically superceded by later, more cognitive kinds of processing. The key observation here is that disinhibition or hyperactivation is unlikely to be limited to one cognitive operation. The activation abnormalities observed here were more widespread, and possibly obscured specific anomalies associated with single processing operations.

It is possible that the magnetic field peaks we were able to identify in the schizophrenic participants could be associated with different stages of word recognition rather than with lexical activation. Stockall et al. (2002) and Almeida et al. (2006) have suggested that the M350 may index later processes in lexical access, not solely the early activation stages, and that effects of competition and inhibition may be seen earlier than M350 responses. This possibility suggests a possible explanation for P1's unexpected latency shift, where the candidate M350 peaked *earlier* (287 msec) in response to Unrelated prime-target pairs and *later* (366 msec) in response to Related pairs. If the identified peak were not really associated with the activation stage, but rather with the *inhibition* stages of word recognition, the activation of semantically-related competitors would be expected to slow down final selection of a target representation in a primed situation. However, given that the peak identified for P1 in the Unrelated condition was early for an M350 (287 msec), it is not clear how P1 could have proceeded through the earlier stages of lexical activation and competition by this time point. Such an interpretation could, however, be consistent with a view of lexical access as profoundly disordered at multiple stages, including disruptions to the processes of activation, competition and inhibition.

It seems clear that the M350 does not necessarily provide a window into activation as a distinct stage in lexical processing. If it did, then an examination of the M350 would permit identification of abnormalities affecting solely activation processes, which would provide an opportunity to disambiguate between the two primary hypotheses about the lexical processes responsible for aberrant word recognition in schizophrenia: the "hyperactivation" view of Pizzagali et al. (2001) and the "disinhibition" view of Titone et al. (2000). However, given

the complexities of interpreting the interactions between distinct stages in lexical processing, together with the variability in our findings concerning M350 presentation in the schizophrenia group, a clear-cut distinction between the competing hypotheses concerning lexical activation in schizophrenia was not possible.

To conclude, this paper contributes to the ongoing search for the neural basis of lexical access and lexical processing impairments in schizophrenia by using MEG to probe beyond the level of behavioral performance. A strength of MEG in investigations of psychopathology is the opportunity to evaluate both individual and group performance (see also Zipse, 2008, for a similar case-by-case approach using MEG with aphasic patients post-stroke). Thus, M350 studies can provide an index of the presence or absence of a deficit in lexical activation as well as help to parse the neural correlates of these behaviors. Failures to inhibit neuronal activations would be likely to impact downstream processing mechanisms, whereas temporal lobe pathologies would likely result in idiosyncratically organized (but otherwise functional) cognitive/neuronal processes. The findings reported here underscore the potential value of larger scale MEG studies to help understand how individual differences in symptomatology and neurocognition relate to the neural basis of language dysfunction in schizophrenia.

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Appendix

APPENDIX:

Isofield contour map, grand averaged Normal Comparison Group, including only those participants who showed expected M350 response ($n = 5$). Circled area shows sensors contributing to M350 field pattern at 354 msec (Related) and 401 msec (Unrelated). White circles on head map show positions of sensors that are not contributing to the field pattern; contributing sensors are indicated by filled circles. Individual sensor traces (thin lines), with the Root Mean Square of the sensors indicated (thick line), are plotted below.

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FIGURE 1. Accuracy (left) and reaction times (right) to Related and Unrelated targets, for the SZ and Control groups. Error bars show standard error of the mean.

FIGURE 2.

Isofield contour map, grand averaged Normal Comparison Group ($n = 7$), Related condition. Circled area shows sensors contributing to M350 field pattern at 354 msec. White circles on head map show positions of sensors that are not contributing to the field pattern; contributing sensors are indicated by filled circles. Individual sensor traces (thin lines), with the Root Mean Square of the sensors indicated (thick line), are plotted below. (See appendix for grand averaged isofield contour maps and waveforms for the 5 control participants who showed the expected M350 response.)

FIGURE 3.

Isofield contour map, grand averaged Normal Comparison Group ($n = 7$), Unrelated condition. Circled area shows sensors contributing to M350 field pattern at 396 msec. White circles on head map show positions of sensors that are not contributing to the field pattern; contributing sensors are indicated by filled circles. Individual sensor traces (thin lines), with the Root Mean Square of the sensors indicated (thick line), are plotted below. (See appendix for grand averaged isofield contour maps and waveforms for the 5 control participants who showed the expected M350 response.)

FIGURE 4.

Isofield contour maps for individual participants in the SZ group: “M350-like” reversed field distributions in response to related (left) and unrelated (right) targets for each participant.

Table 1

Demographic and clinical information.

	Controls (<i>n</i> =7)		Schizophrenia patients (<i>n</i>= 6)	
	Mean	(SD)	Mean	(SD)
Age (yrs)	43.2	(5.2)	44.9	(3.9)
Gender (F/M)	4/3		3/3	
Handedness (R/L) ^a	6/1		6/0	
Education (yrs)	15.4	(0.5)	14.8	(1.6)
Socioeconomic Status ^b [range]	1.86 [1–2]	(0.4)	2.0 [1–3]	(0.6)
Medication, mg/day ^c [range]			507.8 [199.5–899]	(263.5)
Duration of illness (yrs) [range]			23.9 [17.75–30.75]	(5.3)
BPRS score ^d [range]			29.83 [23–41]	(6.3)
GAS score ^e [range]			39.71 [30–51]	(8.64)

^a Handedness was determined using an informal 18-point handedness questionnaire based on Coren (1992).

^b Calculated on the basis of years in education and occupation/occupation of head of household (Hollingshead & Redlich, 1958).

^c In chlorpromazine (CPZ) equivalents (Taylor, McConnell, McConnell, & Kerwin, 2001). One participant was taking both atypical and typical antipsychotic medications, one was taking two atypical antipsychotics, and the other 4 patients were taking one atypical antipsychotic.

^d Brief Psychiatric Rating Scale (Overall & Gorham, 1962).

^e Global Assessment Scale (Endicott et al., 1976).

Table 2

Latencies and amplitudes of M350 peaks identified for each individual in the nonpsychiatric control group (5 out of 7 showed the M350 component).

Participant #	Related condition		Unrelated condition	
	RMS peak amplitude (fT)	RMS peak latency (ms)	RMS peak amplitude (fT)	RMS peak latency (ms)
1	494.22	436	297.73	464
2	113.21	272	101.16	321
3	76.59	364	30.35	412
4	110.55	327	85.84	365
5	122.25	323	165.61	359
Mean	183.36	344.40	136.14	384.2
(SD)	(174.65)	(60.78)	(102.38)	(55.09)

Table 3

Latencies and amplitudes of M350 candidates identified for each individual in the schizophrenic group ($n=6$).

Participant #	Related condition		Unrelated condition	
	RMS peak amplitude (fT)	RMS peak latency (ms)	RMS peak amplitude (fT)	RMS peak latency (ms)
1	76.11	366	82.60	287
2	113.27	280	69.32	294
3	162.24	365	101.77	375
4	67.85	325	40.12	366
5	68.14	340	48.17	384
6	36.73	336	21.24	336
Mean	87.39	335.33	60.54	340.33
(SD)	(44.08)	(31.66)	(29.59)	(41.89)