Twice isn't Nice:
Reversed N400 Attenuation to Identity Priming in Schizophrenic Patients

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Introduction

A hallmark feature of schizophrenia is a ‘loosening of associations’. This is most clearly clinically manifest as the disorganized, sometimes incoherent, speech output expressed by some patients. However, it was originally conceived of by Bleuler as reflecting underlying abnormalities in thinking that characterized schizophrenia as a whole (Bleuler & Aschaffenburg, 1911). Today, the term ‘thought disorder’ is used purely descriptively to describe incoherent speech output and is diagnosed through clinical assessments of patients’ speech (American Psychiatric Association, 2000; N. C. Andreasen, 1986). However, there is increasing experimental evidence that abnormalities in the structure and function of associations stored within semantic memory, at both cognitive and neural levels, may, as Bleuler thought, reflect a more a fundamental feature of schizophrenia.

Careful analysis of the stages of language production can provide insight into the precise nature of semantic memory abnormalities in schizophrenic patients. The simple task of naming an apple requires conceptual identification <object, fruit, apple>, leading to the selection of an amodal lexical representation <APPLE> also known as a lemma, which is mapped to a phonological representation <ˈapəl>, from which an articulatory response can be prepared and then articulated, “apple”. These stages represent the minimal layers of representation that must be accessed during speech production (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Levelt, Roelofs, & Meyer, 1999). They also represent critical points at which representations in semantic memory are accessed and processed. Semantic processing is most directly involved with the first two stages of processing, conceptual and lexical.

These representations can be conceived of as a set of nodes in an associative network connected via relational links (J. R. Anderson, 1983a). Two critical properties of this network have been theorized which account for a number of experimental phenomena: spreading activation, and selection by competition. Activation of accessed representations spreads to nearby, related representations; the more closely related the representation, the more activation it receives (J. R. Anderson, 1983b; Collins & Loftus, 1975). Competition for selection between different representations is based on the relative level of activation of the representations (McClelland & Rumelhart, 1981). In short, incoming stimuli activate competing conceptual representations with some activation spreading to related representations; the most strongly activated representation is selected and the process is repeated at the next level of representation.

The priming paradigm provides a method for affecting processing at different stages of representation through residual and spreading activation. Priming is characterized by a decrease in reaction time to a target stimulus (called the "target") due to of some type of preexposure (called the "prime"). For example, reaction time to the target "apple" would decrease if it was preceded by the related word "pear" than if it was preceded by the unrelated word "bear". This is thought to be because residual or spreading activation from representations associated with the prime affects the activation and processing of the target (Neely, 1991). By manipulating the relationship between the prime and the target, the activity at various levels of representation can be affected. Differences between reaction times to targets primed by related and neutral stimuli can be attributed to relationships between the prime and the target. However, it is important to consider other experimental variables; stimulus onset asynchrony (the temporal relationship between stimulus presentation – SOA), stimulus modality and representation (seen or heard, written vs. graphic) and task (naming, lexical decision, semantic judgments, etc) have all been shown to have an impact on how subjects process target stimuli.

In healthy individuals, there is substantial evidence to suggest that semantically related concepts are remembered more accurately, learned more easily and processed more efficiently than semantically unrelated concepts (J. R. Anderson, 1983b; Barsalou, 1983; Collins & Loftus, 1975; McKoon & Ratcliff, 1979). The semantic priming paradigm builds upon this logic. The response to target words that are preceded by semantically related (versus unrelated) prime words is facilitated (Meyer & Schvaneveldt, 1971; Neely, 1977; Neely, 1991). This facilitation of reaction times is known as the semantic priming effect.

Semantic relationships don't always facilitate, however. In picture naming tasks, the presence of semantically related words has been shown to lead to an increase in naming times of target pictures relative to unrelated words under certain experimental circumstances (Lupker, 1979; Rosinski, 1977). This is known as the semantic interference effect. Some posit that this interference is due to competition between the context word and the picture target at the lexico-semantic level of representation (Levelt et al., 1999; Roelofs, 2004). Others argue that the competition between the context word and the picture target is at the later stage of response selection (Finkbeiner & Caramazza, 2006; Lupker, 1979).

Behavioral results are limited by showing only the culmination of multiple stages of processing. Event related potentials (ERPs), measurements of electrical activity on the scalp, which are time locked to specific events, provide a method of observing the neurocognitive mechanisms engaged in language processing as it occurs. Many years of ERP experimentation has identified multiple ERP 'components', which are patterns of electrical activity that are reliably elicited by specific types of experimental manipulations, and are thought to reflect particular neurocognitive processes. One component that is consistently affected by manipulations of semantic content is the N400, so named for its negative polarity and tendency to peak around 400 ms after stimulus presentation (M. Kutas & Hillyard, 1980). The amplitude of the N400 is affected by the context in which the target stimulus is presented: an incongruous context leads to a larger (more negative) N400, while a congruous context leads to N400 attenuation (M. Kutas & Hillyard, 1980), for both words (M. Kutas & Federmeier, 2000) and pictures (Sitnikova, Kuperberg, & Holcomb, 2003). For example, word repetition and semantic priming lead to N400 attenuation (Bentin, McCarthy, & Wood, 1985; Rugg, 1985). N400 attenuation is seen as reflecting reduced semantic processing due to pre-activation of conceptual and amodal lexical representations of the stimulus (M. Kutas & Federmeier, 2011). The N400 component provides a way of determining the ease of semantic processing, and to compare semantic processing between patients and control subjects.

The pattern of results of semantic priming in schizophrenic patients is rather complicated. Schizophrenic patients have been reported to show every possible type of result relative to healthy controls: hypo-priming, normal priming, hyper-priming, and even reversed priming (See Kuperberg, Kreher, & Ditman, 2010; M. Kutas & Federmeier, 2011; Minzenberg, Ober, & Vinogradov, 2002 for reviews). Patients can also show hyperpriming when the target is only related to the prime through an unseen mediator (lion – *[tiger]* – stripes) (Kreher, Holcomb, & Kuperberg, 2006; M. Spitzer, Braun, Hermle, & Maier, 1993). N400 attenuation to word targets preceded by categorically related picture primes has also been observed (Mathalon, Faustman, & Ford, 2002). Hyperpriming has been taken as evidence for a faster and further implicit and automatic spread across the semantic network.

While the semantic priming paradigm has yielded valuable insights into the structure and function of semantic memory in schizophrenia, it has limitations. The underlying assumption in interpreting such studies is that any detected abnormalities in semantic memory lead to thought disorder, as measured through speech production. This assumption, however, has yet to be validated. Speech production does not start and end in semantic memory, and abnormalities in semantic memory can, in theory, affect multiple stages of the production. Patients both with and without thought disorder show abnormalities in semantic priming (e.g. Mathalon et al., 2002; Ober, Vinogradov, & Shenaut, 1995). Thus, it remains unclear how, precisely, such abnormalities lead to disorganized speech. The assessment of abnormalities in semantic memory that contribute to thought disorder should include as a task the behavior that is used to assess thought disorder, namely language production. Overt picture naming coupled with semantic priming provides a method of investigating semantic memory, with the ecological validity of a language production task.

There are relatively few studies in patients using overt picture naming. One behavioral study, showed an effect of accuracy as a result of the relationship between a context word and the target picture in patients with formal thought disorder (Soriano, Jiménez, Román, & Bajo, 2008). Non-thought-disordered patients and controls showed a similar pattern of naming accuracy for pictures preceded by semantically related words, relative to unrelated words, but patients with formal thought disorder showed no difference in naming accuracy for pictures preceded by related or unrelated words, i.e. no semantic interference (Soriano et al., 2008); suggesting a difference in spreading activation in semantic memory between patients with thought disorder and those without. However, there was no main effect nor interaction for naming times across all groups in the picture word interference task. Since naming times are the traditional primary dependent measure of the task, the between-group differences of naming accuracy must be carefully evaluated. The authors conclude that no difference in accuracy between related and unrelated targets displayed by thought disordered patients indicates a failure of lexical level inhibitory processes that are responsible for the traditional interference effect (Soriano et al., 2008). But there is little evidence to suggest that the locus of interference is necessarily at the lexical level. Behavioral measures are inherently limited in terms of what conclusions may be drawn about the stages at which semantic associations might interfere with production, since a whole host of processes must take place before a response may be generated.

The Present Study

The present study utilized the temporal acuity of ERPs to assess the nature of semantic processing in schizophrenic patients during production. We have recently developed an overt picture naming paradigm, allowing us to measure both ERPs and naming times during production. Here we applied this paradigm to study language production in schizophrenia patients. Participants were presented with a briefly exposed prime word, followed quickly by a picture target. They were asked to verbally name each picture as quickly and accurately as possible. ERPs were time-locked to the onset of the picture targets. The context words were related to the target pictures in one of three different ways, i.e. the context word and the name of the target picture overlapped at one of three different levels of representation. Phonemic onset related context words overlapped with target pictures' phonological representation, and articulatory responses (e.g. pawn <picture of a pig>). Categorically related context words overlapped at the conceptual and lexical level of representation with target picture (e.g. cashew <picture of a peanut>). Identity related context words had complete overlap with target pictures at conceptual, lexical, and phonological levels of representation (e.g. ladder <picture of a ladder>). Each of these related pairs was compared to an unrelated pair, in which the name of the target picture was completely unrelated (on any of these dimensions) to the context word.

Below, we describe the findings of our previous study in young, healthy individuals using this paradigm. We then present our predictions in schizophrenia. The underlying assumption being that the strength and type of representational overlap between the context word and the picture can determine whether the electrophysiological and behavioral response to the target picture is facilitative or inhibitory (relative to the unrelated words). Representational overlap effects, in particular semantic overlaps effects, have been shown to be experimentally robust, although whether the effect is facilitative or inhibitory can be dependent on a wide range of factors. Chen and Mirman recently argued that facilitation or inhibition can be explained by the *degree* of activation of related items at the same representational level (Chen & Mirman, 2012). In their domain-general Interactive Activation and Competition model, they showed that weakly co-activated related items exerted a facilitative effect on targets, while strongly co-activated items exerted an net inhibitory effect on targets by competing for selection (Chen & Mirman, 2012). Based on these findings we predicted that we would see a facilitation effect on the N400 and/or naming times if the context word weakly activated a representation of the target picture at a given stage of processing, but interference if activation exceeded a certain threshold.

Categorical Relationship

In our previous study of young, healthy individuals, naming times to pictures preceded by categorically related context words were longer than those preceded by unrelated context words. This is known as the semantic interference effect and has been attributed to competition between the context word and the picture target. Given our electrophysiological findings (see below), we suggested that this interference occurred at a post-lemma stage of processing. We predicted that we would see this interference pattern in older healthy controls as well. In schizophrenic patients, any facilitation of naming times (behavioral priming), would indicate that categorically related representations are only weakly active at a post-lemma stage of processing, speeding the selection of the correct candidate through shared activation at the lexical-conceptual level. If neither facilitation nor interference were observed, this would also indicate that residual activity from the categorically related context word was too weak to affect processing at post-lemma stages. An observation of behavioral interference to naming pictures primed by categorically related words would indicate that categorical relationships between primes and targets have the same effect on the selection and articulation in patients as controls, residual activation leading to competition at a post-lemma stage of processing.

Despite observing behavioral interference to categorically related stimuli, our previous results showed electrophysiological priming through N400 attenuation of pictures preceded by categorically related context words. This indicated that, at earlier stages of processing, the residual activation of related representations at the conceptual or lexical level facilitated selection, but did not exceed the threshold at which the residual activation of those representations competes with the target representation. We expected to observe similar semantic priming in older controls. In patients, any hyperpriming (increased N400 attenuation relative to controls) could indicate that activation from the context word spreads to more related conceptual and lexical representations, but that activation does not exceed the threshold to result in competition. In contrast, hypopriming (decreased N400 attenuation) could indicate that that activation at from the context word at related conceptual and lexical representations decays more rapidly, and is less facilitative. Reverse N400 priming (an increase in the amplitude of the N400 to targets as a result of the presentation of categorically related context words relative to unrelated context words) would indicate that activation from the context word spreads to more related conceptual and lexical representations which were so strongly activated that they competed with the target representation for selection at conceptual and lexical levels of processing.

Identity Relationship

In our previous study, we observed both behavioral and electrophysiological priming to pictures preceded by identity related context words. We suggested that this behavioral facilitation resulted from residual activity from the identity related context word at the phonemic level of representation. Based on these results we expected to find the same pattern in older controls. If schizophrenic patients failed to show behavioral facilitation, this would indicate that activation from identity related context words did not facilitate at post-lemma stages of processing. In contrast, behavioral interference in patients would indicate that spreading activation from the identity related context word (e.g. “apple”) activated nearby competitors (e.g. “pear”, “plum”, “orange”, “cherry” etc.) at post-lemma stages of processing above the threshold required for competition.

In our previous study, picture targets elicited a smaller N400 when preceded by target pictures preceded by identity related context words, relative to unrelated words. This indicated facilitation at the conceptual-lemma stage of processing due to residual activation of the identity related context word’s conceptual and lemma representations. In schizophrenic patients, hyperpriming would indicate increased residual activation from the context word or more spreading activation to related representations without exceeding the threshold for competition. Hypopriming would indicate decreased residual activation at target representations from the context word. Reverse N400 priming could be attributed to increased spreading activation from the conceptual and lexical representations of the context word and the target picture to related representations. The resulting activation at related representations would exceed the threshold for competition to manifest as an increase in the amplitude of the N400 relative to unrelated context words.

Phonemic Onset Relationship

In our previous study, young healthy controls showed behavioral facilitation in the naming times of pictures that were primed by phonemic onset (vs. unrelated prime), but no modulation of any ERP components. We argued that the behavioral facilitation was due to overlap between the phonological encoding of the prime word and the name of the target pictures, which facilitates the preparation of the articulatory response (Ferrand, Segui, & Grainger, 1996; Schiller, 2008). We predicted the same pattern of findings in older controls. In patients, any modulation of the N400 component in patients would indicate abnormal feedback from the phonemic level of representation to the lexical level of representation. If schizophrenic patients failed to show facilitation of naming times to phonemic onset primed pictures, this would indicate that residual activation of the phonological representation of the context word was too weak for facilitation or was so strongly active that competition occurred.

Methods

Design and Stimuli

The stimuli were almost identical to those described in our previous study in young healthy adults (Blackford, Holcomb, Grainger, & Kuperberg, 2012). They consisted of 270 pixel images (256 x 256) of household items, animals, food items, and other easily recognizable objects, against a white background, taken from the Hemera Photo Objects database (Hemera Technologies Inc., 2002). They were pruned down from an original set of 330 images through an independent norming study, which selected the images that were most consistently named (by at least 70% of 24 participants). Each image in this set of 270 pictures was paired with a context word (always a noun) to construct a word-picture pair that had one of three types of relationship: Identity related, Phonemic Onset related, and Categorically related. Ninety related pairs were constructed for each type of relationship. An example of each type of relationship is given in Figure 1.

Identity related pairs consisted of a context word that corresponded to the name of the picture, e.g. socks - <picture of socks>. The Phonemic Onset related pairs consisted of a context word that shared the same initial phonological segment as the target picture name, but not the same initial syllable (e.g. mushroon - <picture of a mousetrap>). If the name of the picture began with a consonant-consonant compound before its initial vowel, a context word with the same compound was selected (e.g. sparrow - <picture of a spider>). If the name of the target began with a vowel, then a context word beginning with a vowel of the same phonology was used (e.g. orchid - <picture of an orange>). Sixteen out of the 90 Phonemic Onset related word-picture pairs had overlap on the first vowel, but this overlap was orthographic only – not phonological (e.g. canoe - <picture of a cat>), as verified using norms from the English Lexicon Project http://elexicon.wustl.edu/. All primes were concrete words.

Categorically related pairs consisted of context words and target pictures that were both associated and co-category exemplars (Van Overschelde, Rawson, & Dunlosky, 2004), e.g. cake - <picture of a pie>. Association was determined by selecting context words that elicited the name of the target picture during free association, as indexed using the Florida Free Association

Norms database (Nelson, McEvoy, & Schreiber, 2004). Prime words were at least the third most common associate of the target word, with a mean association value of 0.17. In addition, Latent Semantic Analysis (LSA) (Landauer & Dumais, 1997) was used to confirm semantic relatedness between context words and target picture names. We obtained pairwise comparison values for primes and targets using the LSA database available at www.lsa.colorado.edu. All categorically related word-picture pairs had a minimum correlation value of 0.10 ($M = 0.422$, $SD = 0.193$).

For each Relationship Type (Identity related, Phonemic Onset related, and Categorically related), Unrelated pairs were created by pseudo-randomly pairing the picture targets with a word from another target picture. This resulted in a 3x2 design that crossed Relationship Type between the context word and the target picture (Identity, Phonemic Onset, and Categorical) by Relatedness (Related and Unrelated). There was no significant difference in log frequency ($F(2, 263) = 0.066$, $p = 0.936$), number of letters ($(2, 263) = 0.886$, $p = 0.414$), number of phonemes ($F(2, 263) = 0.737$, $p = 0.479$), or number of syllables ($F(2, 263) = 1.205$, $p = 0.301$) of the names of target pictures across the three Relationship Types (see Figure 1; values taken from English Lexicon Project http://elexicon.wustl.edu/). The pictures were also matched across the three Relationship Types on familiarity (values taken from the MRC Database and available for 73% of the targets used, $F(2, 194) = 1.129$, $p > 0.325$).

These word-picture sets were then pseudo-randomly counterbalanced, within Relationship Type, across two experimental lists (to be seen by different participants). For example, referring to Figure 1, a <picture of socks> might be preceded by the word ‘socks’ in list 1 (Identity related) but by the word ‘waffle’ in list 2 (Unrelated). A <picture of a starfish> might appear with the word ‘stomach’ in list 1 (Phonemic Onset related) but with the word ‘ball’ (Unrelated) in list 2. And the <picture of a pie> might appear with the word ‘cake’ in list 2

(Categorically related), but with the word ‘chalk’ in list 1 (Unrelated). Thus, each list constituted 270 word-picture pairs: 45 Identity related, 45 Phonemic Onset related, 45 Categorically related, and 135 Unrelated pairs. This meant that no individual saw the same target more than once, but across all participants, the same target picture for a given Relationship Type was seen in both the related condition and the unrelated condition.

Participants

Twenty-four patients with DSM-IV diagnosed schizophrenia were initially recruited from the Erich Lindemann Mental Health Center, Boston, and sixteen healthy volunteers were initially recruited by advertisement. One patient chose to withdraw from the study and, as noted below, four patients were subsequently excluded because of ERP artifact. This left a total of 19 patients and 16 controls whose ERP data were analyzed. Healthy volunteers were screened using the SCID to exclude the presence of psychiatric disorders (R. L. Spitzer, Williams, Gibbon, & First, 1992). Patients’ symptomatology was assessed on the day of ERP testing using the Positive and Negative Syndrome Scale (PANSS (Kay, Flszbein, & Opfer, 1987) and the SANS (N. C. Andreasen, 1982)). Seventeen of the included patients were receiving stable doses of antipsychotic medication: Chlorpromazine (N=1) Clozapine (N=5), Risperidone (N=2), Olanzapine (N=2), Haloperidol (N=1), Fluphenazine (N=1), Aripiprazole (N=4), Perphenazine (N=1), and Lozapine (N=1). Two patients were not receiving any antipsychotic medication. Three patients were taking anticholinergic medication. Healthy volunteers were not on medication affecting the central nervous system.

All participants were right-handed and had normal or corrected-to-normal vision. Participants were excluded if they had a history of neurological injury, head trauma with documented cognitive sequelae, and medical disorders that can impair neurocognitive function, or if they met DSM-IV criteria for substance abuse within the previous three months or any had lifetime history of substance dependence. Patients and controls matched closely in gender and race/ethnicity distributions and there was no significant difference between the groups in age ($t(33)= 1.074$, $p = 0.291$). The patient and control groups also showed no significant difference in parental socioeconomic status ($t(33)=0.294$, $p = 0.770$), as determined by Hollingshead Index scores (Hollingshead, 1957). Demographic characteristics of all participants and clinical details for the patient group are given in Table 1. Written informed consent was obtained from all participants according to the guidelines of the Massachusetts General Hospital and Tufts Human Subjects Research Committees.

Stimulus Presentation and EEG recording

Participants were randomly assigned to one of the two lists used for counterbalancing. Nine patients viewed list 1 and ten viewed list 2; seven controls viewed list 1 and nine viewed list 2. In order to ensure fairly high naming accuracy during the ERP experiment itself, and following the usual practice for studies of picture naming, all participants were familiarized with the pictures and their expected names prior to the ERP experiment itself. They viewed the pictures they would see in the ERP experiment, and each picture was followed by the target name (which, as described above, had been obtained in an independent norming study). When the picture appeared on the screen, participants were asked to name the picture out loud. Then the expected target word appeared on the screen. The participants were asked to repeat the expected target word and to use the supplied target word during the experiment if it differed from the one spontaneously uttered. All participants saw the practice list once.

During the ERP experiment, participants sat in a comfortable chair in a dimly lit room separate, approximately 60 inches away from a 19-inch CRT monitor, and away from the experimenter. On each trial a fixation prompt appeared for 250ms followed by a forward mask ("#########") for 200ms, followed by the context word for 60ms (in white Arial font against a black background), followed by the target picture which remained on the screen until it was named. The timing of a typical trial is depicted in Figure 2. Participants were instructed to name the pictures as quickly and accurately as possible. Their responses were recorded with in-house software that began recording as soon as the target picture appeared. A blank screen was presented between trials for a variable inter-trial interval between 1500 and 2500ms during which participants could blink to avoid artifact during trials. Participants were given breaks every 15 trials during which they were told they could move freely.

Twenty-nine tin electrodes recorded the electroencephalogram (EEG), held in place on the scalp by an elastic cap (Electro-Cap International, Eaton, OH). Electrodes were placed in standard International 10–20 System locations as well as 10 additional sites situated primarily between frontal and central sites and between central and parietal sites (see Figure 3). Electrodes were also placed below the left eye and at the outer canthus of the right eye to monitor vertical and horizontal eye movements. The EEG signal was amplified by an Isolated Bioelectric Amplifier System Model H&W-32/BA (SA Instrumentation, San Diego, CA) with a bandpass of 0.01– 40 Hz and was continuously sampled at 200 Hz by an analogue-to-digital converter.

Behavioral Data Analysis

We excluded one participant from the behavioral analysis because his naming time data were missing due to technical problems. Error rates (producing the wrong name to a picture) were examined with mixed model ANOVAs in which Group (patients, controls) was the between-participant factor, and Relationship Type (Identity, Semantic and Phonemic Onset) and word-picture Relatedness (Related vs. Unrelated) were within-participant factors.

Following outlier removal (responses exceeding two standard deviations above the mean of that participant's mean reaction time across all conditions), we logarithmically-transformed the mean naming times on correctly-answered trials in each condition to reduce skew and between-group variance. The data were then analyzed with mixed model ANOVAs. In a subjects analysis, we used the log-transformed mean naming times across all correctly-answered items within each condition; the between-participant factor was Group, and the within-participant factors were Relationship Type (Identity, Semantic and Phonemic Onset) and word-picture Relatedness (Related vs. Unrelated). In an items analysis, we took the log-transformed naming times to each target picture, across the participants who correctly named that picture; Relationship Type was the between-items factor and Relatedness and Group were within-items factors.

ERP Data Analysis

ERPs were averaged off-line at each electrode site for each experimental condition using a -50 to 50ms baseline and lasting until 1170ms post-picture onset. Across all participants, the lowest value in the range of mean naming times was 761ms, and so, to avoid speech-related artifact, we only analyzed and show ERP activity up until 650ms post-picture onset (in some participants, there were some individual trials with naming times less than 650ms but these constituted less than 3% of all trials across all participants). Trials contaminated with eye artifact (detected using a polarity inversion test on the left eye channel) or amplifier blockage were excluded from analyses. As noted above, four patients were excluded altogether from the ERP analysis because of a high artifact rejection rates (more than 50% of trials excluded). Across the remainder of the participants, artifact contamination from eye movement or amplifier blocking led to the rejection of 17.0% of trials in patients and 13.4% in controls. This did not differ between patients and controls (all $ps>0.171$, $Fs<1.849$) but did differ between Relationship Type ($p<0.005$, $F(2,66)=7.572$) due to more rejections in the Identity condition than either the Phonemic Onset ($t(34)=2.606$, $p < .05$) or the Categorical ($t(34)=4.065$, $p < .001$) conditions. There was no Relatedness x Relationship Type interaction ($F(2,66)=0.973$, $p = 0.372$).

ERP data from a representative sub-array of nine channels were used for analysis. This sub-array constituted three columns over left, center, and right hemisphere locations, each with three electrode sites extending from the front to the back of the head (see Figure 3). This allowed us to use the same analysis strategy that we used in our previous study using the same paradigm in young healthy controls (Blackford et al., 2012) and it strikes a good compromise between simplicity of design (a single ANOVA can be used in each analysis epoch) and characterizing the overall distribution of effects. We carried out a series of ANOVAs in four consecutive time windows: 100-200ms, 200-350ms, 350-450ms and 450-550ms post-stimulus onset. Previous work in our lab, including our study in young healthy controls using this same paradigm (Chauncey, Holcomb, & Grainger, 2009) has used these windows to assess activity of the N/P150 (100-200ms), the N250/N300 (M. Eddy, Schmid, & Holcomb, 2006; M. D. Eddy & Holcomb, 2009), the early N400 (350-450ms) and the late N400 (450-550ms).

Mixed model omnibus ANOVAs were carried out with Group (patients, controls) as the between-participant factor, and Relationship Type (identity related, categorically related, phonemic onset related), word-picture Relatedness (related, unrelated), Laterality (left, midline, right), and Anterior Posterior (AP) Distribution electrode placement (frontal, central, parietal) as within-participant factors. We followed up any interactions involving Relatedness and Relationship Type by carrying out ANOVAs examining effects of Relatedness and/or Group for each of the three different Relationship Types. In these analyses, interactions involving Group were followed up by examining effects of Relatedness in the control and patient groups separately. In the reporting results of these repeated measures ANOVAs, we use the Greenhouse-Geiser correction (Greenhouse & Geisser, 1959).

Results

Behavioral Results

One control subject's behavioral data was missing (due to equipment failure) and was therefore excluded from the behavioral analyses.

Accuracy

Error rates are shown for each condition in each group in Figure 4. The percentage of errors overall and the pattern of errors across conditions did not differ between patients and controls (no main effects of Group and no interactions between Group and either Relatedness and/or Relationship Type, all $Fs < 1.725$, $ps > 0.19$). Across all participants, there was a main effect of Relatedness ($F(1,32) = 17.48$, $p < 0.01$) due to more errors in the related than the unrelated conditions, and a main effect of Relationship Type ($F(2,64) = 18.3$, $p < 0.01$) due to significantly more errors in the semantic than either the identity ($t(33) = 3.730$, $p < 0.01$) or the phonemic onset ($t(33) = 3.366$, $p < 0.01$) conditions.

Naming times

The averages, standard errors and ranges of participants' mean naming times for each correctly-named target picture in each condition are shown in Figure 4. Patients took longer overall to name the pictures than controls, significant on the items analysis ($F2(1,267)=54.858$, $p < 0.01$), although not on the subjects analysis $F1(1,32) = 0.361$, $p = 0.552$). The pattern of naming times did not differ between patients and controls (no interactions between Group and either Relatedness and/or Relationship Type (all $Fs < 2.217$, $ps > .117$). However, across all participants, there was a significant interaction between Relatedness and Relationship Type ($F1(2,64) = 9.923$, $p <0.01$; $F2(2,267) = 9.757$; $p < 0.01$), which we followed up by examining the effect of Relatedness for each Relationship Type. Identity related pictures were named significantly faster than unrelated pictures ($t(33) = 3.800$, $p < 0.01$; $t(89) = 3.443$, $p < 0.01$). Phonemic Onset related pictures were named very slightly faster than unrelated pictures, but this effect approached significance only in the subjects analysis ($t(33) = 1.983$; $p = 0.056$) and did not reach significance in the items analysis, ($t(89) = 1.463$; $p < 0.147$). In contrast, Semantically related pictures were named more slowly than unrelated pictures, an effect that reached significance in the items analysis ($t2(89) = 2.311$; $p < 0.05$) and approached significance in the subjects analysis ($t1(33) = 1.891$; $p < 0.067$).

ERP results

Voltage maps in the N250/300, early and late N400 time windows are plotted in Figure 5. Grand averages of central midline ERPs, time-locked to the presentation of target pictures are plotted in Figure 6. These figures and the analyses reported below use ERPs averaged across all trials (this had the advantage of maximizing power and maintaining counterbalancing across lists).

100-200ms: N/P150

There were no main effects or interactions involving Relatedness in this time window (all Fs < 1.362, all ps > 0.244).

200-350ms: N250/N300

The omnibus ANOVA revealed an interaction between Relatedness, Relationship Type and Group ($F(2,66) = 3.497$, $p < 0.05$) as well as between Relatedness, AP Distribution and Group ($F(2,66) = 3.818$, $p < 0.05$). In comparing the identity related and unrelated targets, there were interactions between Relatedness and Group ($F(1,33) = 7.451$, $p < 0.05$) as well as between Relatedness, Group and AP Distribution ($F(2,66) = 3.996$, $p < 0.05$). These interactions arose because the patients showed a larger N250/N300 to identity related than unrelated pictures ($F(1,18) = 6.777$, $p < 0.05$), but there was no effect of Relatedness in controls ($F(1,15) = 1.493$, $p < 0.241$). Comparisons between the Phonemic Onset related and Unrelated targets, and between the Categorically related and unrelated targets revealed no significant effects involving Relatedness and/or Group (all Fs < 2.175, all ps > 0.136).

The N400: 350-450ms and 450-550ms

The omnibus ANOVA revealed an interaction between Relatedness, Relationship Type and Laterality ($F(4,132) = 3.084$, $p < 0.05$) in the early N400 time window, and between Group and Relatedness ($F(1,33) = 5.065$, $p < 0.05$), Group, Relatedness and AP Distribution ($F(2,66) = 3.644$, $p < 0.05$), and Group, Relatedness and Relationship Type ($F(2,66) = 5.087$, $p < 0.01$) in the late N400 time window.

The contrast between identity and unrelated targets again showed an interaction between Relatedness and Group (early N400 time window: $F(1,33) = 5.156$, $p < 0.05$; late N400 time window, $F(1,33) = 14.073$, $p < 0.01$). Follow-ups revealed an N400 priming effect in controls (a smaller negativity to related than unrelated targets) but a reverse effect in patients (a larger negativity to related than unrelated targets). In the early N400 time window, these within-subject comparisons approached significance (controls: $F(1,18) = 2.186$, $p < 0.15$; patients: $F(1,15) = 3.065$, $p < 0.10$), and in the late N400 time window, both the priming effect in controls and the reverse effect in patients were significant (controls: $F(1,15) = 9.822$, $p < 0.01$; patients: $F(1,18) = 4.829$, $p < 0.05$).

There were no differences between the patients and controls in how the N400 was modulated to the categorically related and unrelated targets (no interactions involving Relatedness and Group, all all Fs < 2.748, ps > 0.05. However, across all participants, there were interactions between Relatedness and AP Distribution (approaching significance in the early N400 time window: ($F(2,32) = 2.977$, $p < 0.10$); significant in the late N400 time window: $F(2,66) = 3.705$, $p < 0.05$), reflecting an N400 semantic priming effect that was maximal at central and parietal sites (C3, P3, Pz, P4, all ps < 0.05).

In comparing phonemic onset related and unrelated targets, there were no significant interactions with Group, and no effects involving Relatedness in either the early or late N400 time window (all Fs < 1.026, ps > .118).

Discussion

The purpose of this study was to investigate semantic processing in schizophrenic patients by examining language processing at different levels of representation. We presented word-picture pairs with various relationships to manipulate activation at different levels of representation, while measuring ERPs and naming times. We expected that the relationship between the context word and the target would affect processing at the corresponding level of representation. Any differences between control subjects and schizophrenic patients would provide insight into abnormalities in thought in schizophrenia.

Different relationships between the context word and the target picture appeared to affect processing in different ways. Pictures preceded by Identity related context words resulted in N400 and behavioral priming; Categorically related context words also had an attenuating effect on pictures, but resulted in behavioral interference; Phonemic Onset related context words had no effect on the N400 but did show behavioral priming on naming times. Patients responded in largely the same ways as healthy controls to target pictures preceded by related context words, with the notable exception of their reaction to target pictures preceded by Identity related context words (vs. unrelated.).

Identity Relationship

Control subjects showed attenuation of the N400 component to target pictures preceded by Identity related context words and behavioral facilitation, replicating our previous findings in college aged adults (Blackford et al., 2012). Analysis of the early N400 time window (350-450 ms) showed an N400 priming effect in controls (related items evoked less amplitude) However, a reversed N400 priming effect was observed in patients (related items evoked greater amplitude) relative to unrelated items, a dramatic contrast with the priming effect observed in control subjects. N400 attenuation is associated with ease of processing; contrariwise, an N400 of greater amplitude is associated with difficulty of processing. This pattern therefore implies that patients had a harder time processing target pictures when a word that matched the picture's name had just been presented to them than when an unrelated word preceded the picture. Although patients' ERP results indicated processing difficulty due to identity related context words, they were able to name target pictures more quickly (behavioral priming), similar to healthy controls.

This processing difficulty could be due to competition between the representations of the target picture and related representations activated via increased spreading activation. Based on the findings of Chen & Mirman (Chen & Mirman, 2012), this could occur if the activation of related words reached sufficient strength to become a competitor to the target. This would indicate that in the present study related representations at the conceptual/lemma interface were relatively more active at the time of target processing in patients than in controls. If increased activation of related representations is responsible for the reversed N400 attenuation effect in patients, then residual activation of related representations as a result of context word processing would have to be greater in patients. In order for related representations to be more active in patient processing, activation would have to spread more to related concepts or lemmas than in healthy controls. In the case of identity related stimuli, the residual activity of context word processing overlaps with the spreading activation of target picture processing at the conceptual and lemma level of representation. The sum of this spreading activity to related representations appears to exceed the threshold for competition, observed as a reversed N400 effect.

Increased spreading activation or a reduced facility of inhibition of competition has long been posited in schizophrenia (Cohen & Servan-Schreiber, 1992; M. Spitzer et al., 1993). Faster and further spread of activation from context words to related conceptual and lemma representations, combined with identical activation from the target pictures, could have resulted in enough activation to exceed the threshold at which facilitation becomes interference through competition.

This increase in competition at the conceptual and lemma level of representation did not translate to an increase in naming times of target pictures. Instead, patients showed the same pattern of naming facilitation (faster naming times to related targets) as healthy controls. This indicates that competition at the early stage of conceptual-lexical processing does not persist into post-lexical processing.

Categorical Relationship

In contrast to the identity relationship, patients and controls exhibited similar results to word picture pairs that shared a categorical relationship. We observed N400 attenuation to target pictures preceded by categorically related context words (electrophysiological priming) in both patients and controls. Behaviorally, pictures preceded by categorically related context words were named more slowly by patients and controls (vs. unrelated words), a semantic interference effect. This replicates the results of our previous study. The dissociation between the electrophysiological and behavioral results indicates that ease of processing at the conceptual or lemma level does not result in facilitation at later stages of speech production.

These results indicate that spreading activation from categorical, semantic relationships in patients appears to follow the same pattern in patients as in controls. A posited increase in spreading activation could still be occurring as patients are processing stimuli, but according to our observations, it was insufficient to result in competition. Instead it served to facilitate early conceptual and lexical processing in patients and controls.

Phonemic Onset Relationship

Patients and controls showed a similar pattern of results to word picture pairs that shared a phonemic onset relationship, namely a behavioral facilitation relative to unrelated word picture pairs and no modulation of any ERP components in the time frame analyzed. This replicates our previous findings. Behavioral studies of the phonemic onset priming effect argue that facilitation occurs during the preparation of the articulatory response (Ferrand et al., 1996; Schiller, 2008). No differences between patients and controls were seen in the behavioral or electrophysiological results. The presence of a phonemic onset priming effect suggests that phonological processing during articulatory response preparation is intact in patients

Implications of findings

Finding an increased N400 to targets in the identity related (versus unrelated) condition for patients, but N400 attenuation in the categorically related (versus unrelated) condition presents an interesting dilemma; partial semantic overlap resulted in facilitation of lexical conceptual processing, but complete overlap resulted in interference. Although related items at the conceptual and lemma level would have been pre-activated by a categorically related context word, the incomplete overlap between the prime and the target appears to result in enough activity at potential competitors to facilitate, but not inhibit, target processing, The fact that a difference between the physiological response of control subjects and patients is only seen when the conceptual and lexical overlap between the context word and the target picture is complete gives some indication as to what level of representation is disturbed in patients. Categorically related context words share some conceptual overlap with target pictures, but no actual overlap at the lexical level. That is, the difference between the Identity and Categorical relationship is quantitative at the conceptual level, but qualitative at the lexical level. This suggests that patients processing is likely disturbed at the lexical level of representation rather than at the conceptual level.

This study builds on previous findings of disturbed semantic processing in schizophrenia patients. Other ERP studies of schizophrenic lexical processing have involved passive reading or implicit semantic categorization tasks (Kreher et al., 2006; Kreher, Holcomb, Goff, & Kuperberg, 2008; Mathalon et al., 2002). The task of articulation used in this study allows generalization more to typical speech production, which is how thought disorder is diagnosed (American Psychiatric Association, 2000; N. C. Andreasen, 1986). Importantly, by measuring ERPs during picture naming, we were able to examine the neurocognitive processes engaged at multiple stages of production and detect a difference between control subjects and schizophrenic patients that was not apparent from the behavioral results.

The results of this study indicate a disturbance in conceptual-lexical processing of schizophrenia patients that is not specific to positive thought disorder. A follow up with more fine grained distinctions of stimuli relationships could determine how much overlap is required to elicit a reverse N400 priming effect in patients, and whether solely conceptual or lexical relationships would be sufficient. Context words that had lexical overlap but not conceptual overlap could be approximated by using words with multiple senses, in which an abstract sense was the most common, and therefore would not necessarily lead to preactivation of the conceptual representation of the picture; for example the verb train (to practice a skill for a period of time) and a picture of a locomotive. Part-whole relationships between context words and target pictures could simulate conceptual overlap without lexical overlap (e.g. (Chaffin, Herrmann, & Winston, 1988)).

Conclusion

We compared the ERP and behavioral results of schizophrenic patients and healthy controls in a cross representational priming picture naming study and found that, relative to unrelated targets, identity related context words led to more difficulty in lexical-conceptual processing of target pictures in patients than controls. Despite this, similar to controls, these context words did lead to facilitated naming, relative to unrelated words. We suggest that this abnormality in patients resulted from interference, due to increased competition at a lexical-conceptual stage of processing. In other words, increased spreading activation in patients led to inappropriate competition for selection of the lexico-semantic representation of the target picture. This increase of activation was observed only when the context word and the target had complete conceptual and lexical overlap, suggesting that this increased activity in patients was primarily at a lexical level of representation.

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Word-Picture Relationship		Context Word	Picture Target	Length (Target)	# Phonemes	# Syllables	Log Freq.
Identity				5.8 (2.2)	4.6 (1.7)	1.7 (0.8)	7.9 (1.9)
	Related	socks					
	Unrelated	waffle					
Phonemic Onset				6.0 (2.0)	4.9 (1.8)	1.8 (0.7)	7.9 (2.0)
	Related	stomach					
	Unrelated	ball					
Categorical				5.7 (1.8)	4.7 (1.5)	1.7 (0.7)	8.1 (1.3)
	Related	cake					
	Unrelated	chalk					

Figure 1. Example of word-picture stimuli pairs

Stimuli consisted of a context word matched to a target picture on one of three types of relationships: Identity, Phonemic Onset, or Semantic. For each Relationship Type, an Unrelated context word was paired with the same picture. Counterbalancing within Relationship Type across two experimental lists (to be seen by different participants). For example, a <picture of socks> might be preceded by the word ‘socks’ in list 1 (Identity related) but by the word ‘waffle’ in list 2 (Unrelated). The <picture of a starfish> might appear with the word ‘stomach’ in list 1 (Phonemic Onset related) but with the word ‘ball’ (Unrelated) in list 2. The <picture of a pie> might appear with the word ‘cake’ in list 2 (Semantically related), but with the word ‘chalk’ in list 1 (Unrelated). Thus, no individual participant saw a given target more than once, but across all participants, the same target picture for a given Relationship Type was seen in either the related condition and the unrelated condition.

The average length, number of syllables, number of phonemes and frequencies of the names of the target pictures are given, with standard deviations in parentheses. Values were taken from the English Lexicon Project, http://elexicon.wustl.edu/. The pictures were presented in color and were taken from the Hemera Photo Objects database (Hemera Technologies Inc., 2002).

Parameter	***Controls***	***Schizophrenia patients***
Gender (M/F)	12/4	15/4
Race(C/AA/Other)	9/4/3	13/2/4
Age (years)	46.75 (6.9)	44.24 (10.4)
Education (years)	13.31 (1.4)	12.71 (1.7)
Hollingshead Index	3.06 (1.2)	2.94 (1.1)
Premorbid IQ	111.18 (6.2)	94.78 (10.4)
CPZ equivalent (mg)	N/A	326.15 (200.7)
Duration of illness (years)	N/A	22.07 (9.7)
PANSS total	N/A	53.67 (13.9)
PANSS hallucination	N/A	2.6 (1.8)
PANSS delusion	N/A	2.73 (1.6)
PANSS disorganization	N/A	2.47 (1.4)
SANS total	N/A	41.4 (19.0)

Table 1. Demographic and clinical data of healthy controls and patients with schizophrenia. Means are shown with standard deviations in parenthesis. M, Male; F, Female; C, Caucasian; AA, African American; Hollingshead Index was used as a measure of parental socioeconomic status (Hollingshead, 1957). American version of the Nation Adult Reading Test was used as a measure of premorbid IQ (Blair & Spreen, 1989). CPZ, chlorpromazine equivalent; PANSS, Positive and Negative Syndrome Scale; SANS, Scales for the Assessment of Negative Symptoms.

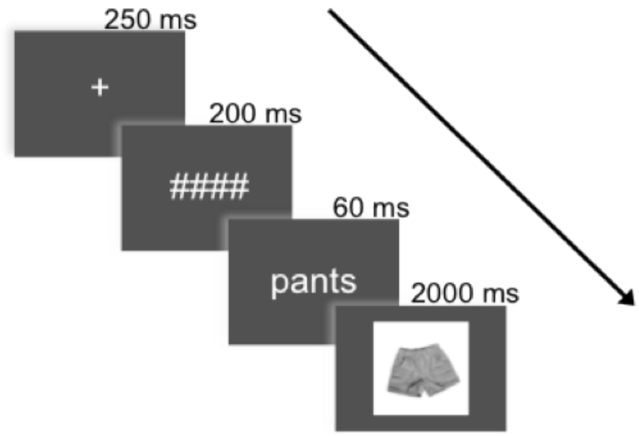


Figure 2. The presentation of a sample trial

Each trial consisted of a fixation prompt, a forward mask, the context word, and the target picture, in that order.

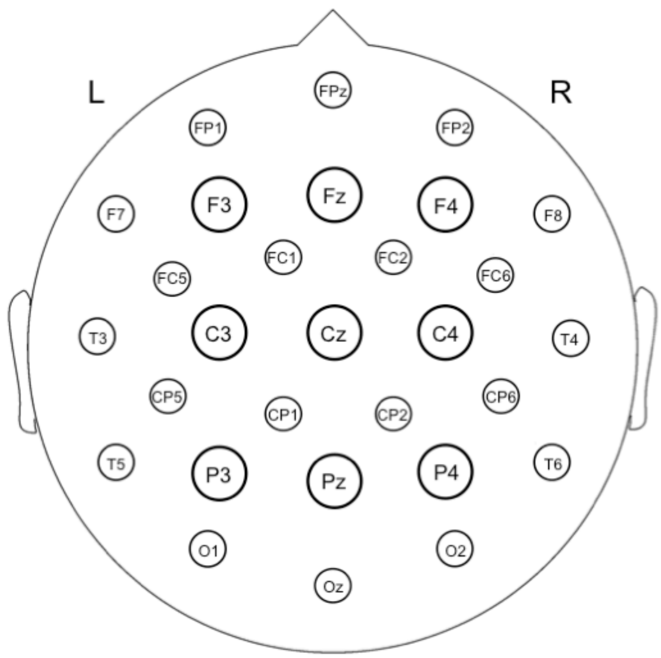
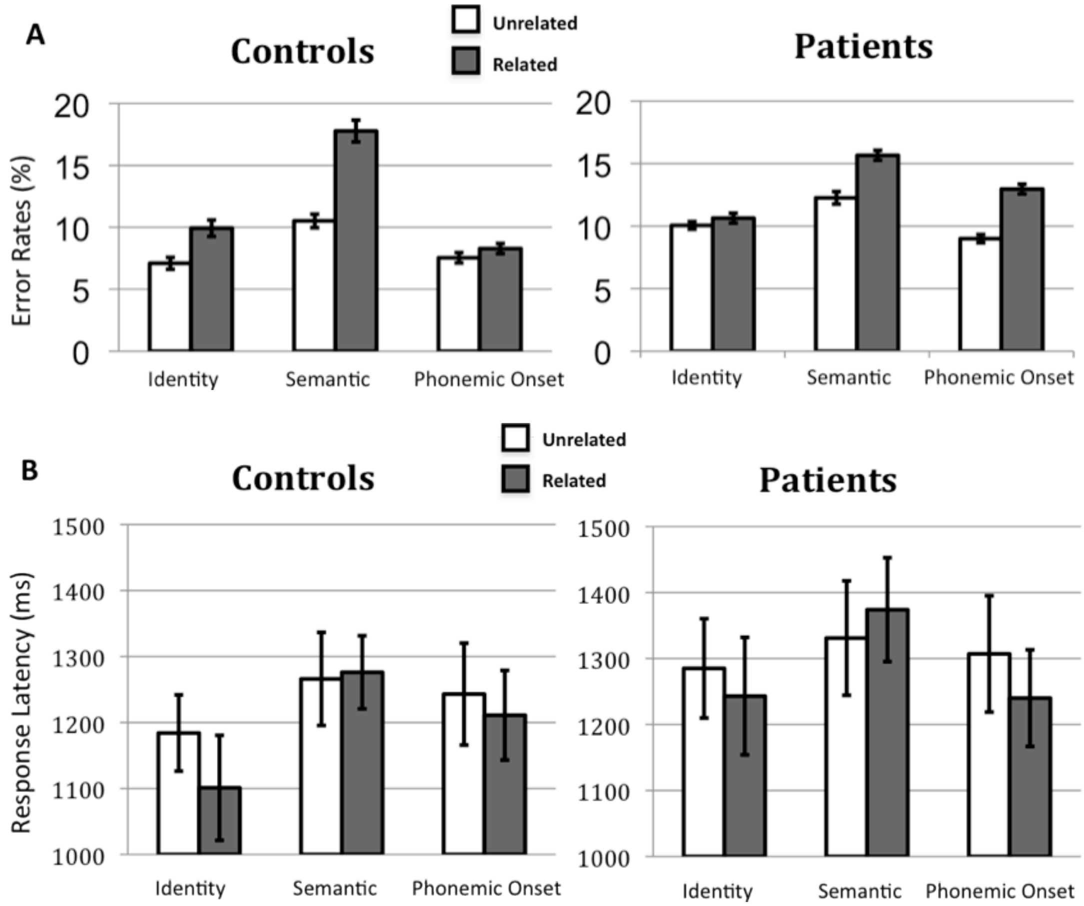


Figure 3. EEG Recording Array

The sites used for recording EEG were the standard International 10–20 System locations as well as 8 additional sites. Larger circles indicate the 9 sites used for analysis.



Figures 4a and 4b. Picture Naming Behavioral Data

Bar graphs showing the mean percentage of errors (4a) and the mean (across subjects) of the mean naming times across correctly named items in a given condition, not including outliers two standard deviations above each participant's mean response time (4b) to pictures preceded by unrelated and related context words. The related pairs were either Identity related, Semantically related or Phonemic Onset related. Solid line error bars depict standard errors of these scores.

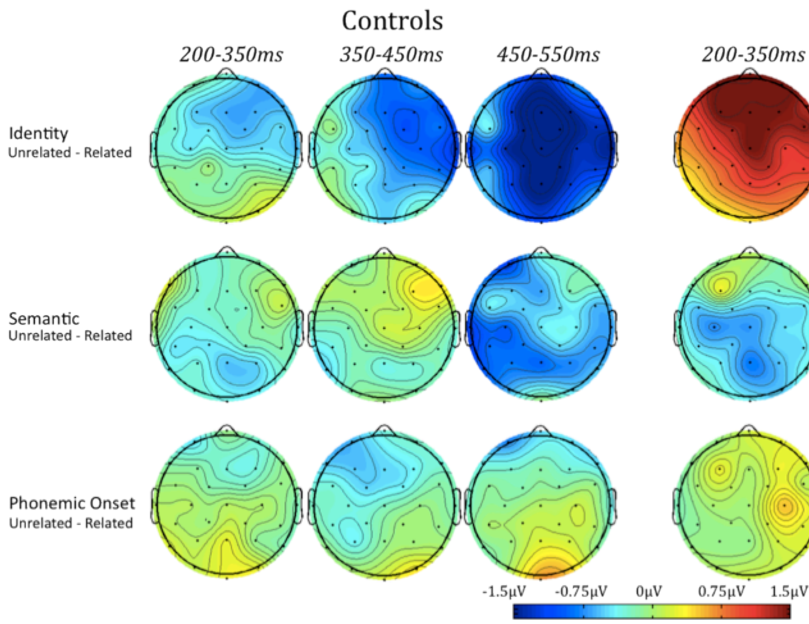


Figure 5. Linearly interpolated voltage maps showing the scalp distribution of differences in ERPs elicited by target pictures preceded by related vs. unrelated context words for the three different relationships used in this study.

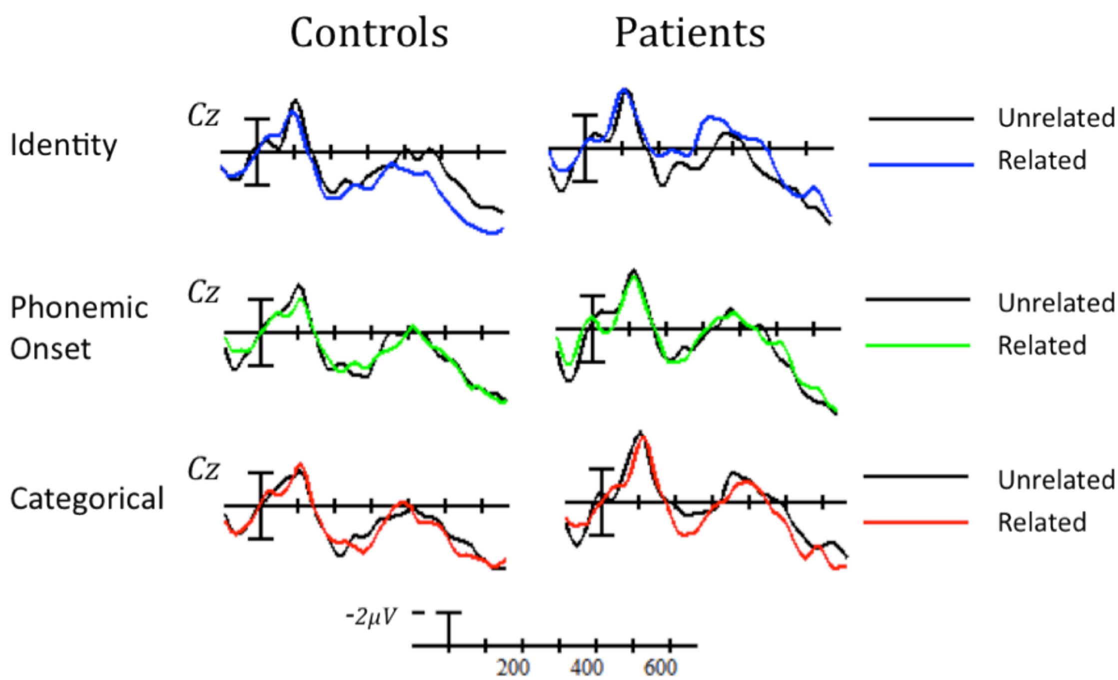


Figure 6. Event-Related Potentials (ERPs) to target pictures at a central midline site (Cz) for healthy controls and schizophrenic patients in each of the three relationship types.