Published in final edited form as:

J Neurolinguistics. 2010 May 1; 23(3): 240. doi:10.1016/j.jneuroling.2009.10.001.

Abnormal N400 Responses But Intact Differential Hemispheric Processing of Ambiguity in Schizophrenia

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Abstract

Disordered thinking in schizophrenia may be a consequence of the selection of conceptual associates of dominant meanings of ambiguous words despite contextual information suggesting subordinate meanings are more appropriate. Previous work using short sentences showed a large N400 event-related potential to subordinate meaning associates and a behavioral semantic bias, but results were variable. The current experiment used word pairs to simplify the procedure and to less tax memory maintenance. Furthermore, hemispheric responses were compared, as evidence suggests the left hemisphere may select dominant meanings, while the right hemisphere may keep all possible meanings active. Subjects indicated whether two words (CUE, TARGET) were related. The CUE, presented for 1 second, could be an ambiguous or an unambiguous noun, and the TARGET, presented 1.25 seconds after the onset of the CUE, was a dominant or subordinate associate, or a related or an unrelated word, respectively. The N400-effect was calculated from difference waveforms over 400-600 msec. Groups (23 schizophrenia, 25 matched controls) showed significantly different N400-effects to the words (group $\times$ word, $p = .04$). Controls showed a graded response, with dominant $<$ subordinate $<$ unrelated. Schizophrenia patients showed the largest N400-effect to subordinate associates, with less activity to dominant meaning associates and unrelated words. Both groups showed a right hemisphere distribution to unrelated words and substantial left hemisphere activation to subordinate associates (word $\times$ hemisphere, $p < .001$). These data support a semantic bias in schizophrenia. They also demonstrate a special role of the right hemisphere in maintaining broad homograph meaning hierarchies. This hemispheric specialization appears to be intact in schizophrenia.

Introduction

Many words in English have multiple meanings, making them ambiguous in isolation. These different meaning may be more or less related (polysemy: foot in a shoe, foot in inches, foot of the mountain), or have different roots altogether (homonymy: bat meaning cudgel from Latin root *batteure* versus bat meaning flying mammal from Scandinavian root *bakka*). In addition to the homonymous written words spelt the same (homographs like bat above), words that are spelt differently but pronounced the same (homophones: bare, bear) also add to conceptual ambiguity. These ambiguous words necessitate the use of context for disambiguation. Getting

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hit by a bat on a playground should bring to mind a different scenario than getting hit by a bat in a dark cave.

Persons with schizophrenia show thought disorder, characterized by loose associations, tangentiality, disorganization, and loss of global focus. A central issue in understanding schizophrenic thought disorder is whether semantic memory structure affects the disordered train of thought in schizophrenia, or whether such digressions are random. There is data to suggest that schizophrenic error patterns are not random (Chapman, Chapman, & Miller 1964). In a series of papers, Chapman and colleagues examined homograph processing in schizophrenia and argued that schizophrenic thought was biased towards strong associates of dominant meanings even if contextually inappropriate. Thus, the associational abnormalities in schizophrenia were dependent on the pull of proximal associates in the semantic network (semantic bias).

For example, Rattan & Chapman (1973) designed two multiple choice homograph tests, one with associated but contextually incorrect choices, the other with no associates. Schizophrenics performed poorly on the task with incorrect associates, but normally without incorrect associates. Roberts & Schuham (1974) reported that schizophrenic subjects' performance dropped directly with increases in associative distractions. Blaney (1974) demonstrated increased bias during lexical access for ambiguous words, and Chapman, Chapman & Daut (1976) showed that schizophrenics were able to detect weak associates when strong associates were not present. These data suggest that schizophrenics may have all meanings of homographs in their lexicon, but cannot use context to choose subordinate meanings, particularly if the contextual cues are temporally remote.

It remains unclear whether this semantic bias reflects an abnormality that is early or late in the processing stream. Chapman and colleagues suggested that a late-stage failure to utilize preceding context was the central abnormality. This lack of controlled context-based inhibition remains a strong possibility (see esp. Cohen & Servan-Schreiber 1992). However, an alternative explanation is faulty early semantic activation, namely hyperpriming. Hyperpriming of contextually inappropriate associates due to their strong semantic relatedness could lead to the preselection of dominant homograph meaning networks despite contextual cues toward subordinate meanings. Thus, another central issue in understanding schizophrenia is the degree to which abnormalities reflect early automatic versus late controlled processes. There is evidence for hyperpriming in schizophrenia at shorter SOAs. Schizophrenic subjects show an *increase* in the effect of priming on a lexical decision task (Maher, 1983). This facilitation effect on priming has been replicated (Kwapil et al 1990, Spitzer et al 1994, Baving et al 2001). Spitzer and colleagues further showed that schizophrenics demonstrated *increased* second order priming (e.g., lemon primes sour, which primes sweet; Spitzer et al 1993). These data suggest that schizophrenics show greater initial activation in semantic networks than controls. By contrast, a large body of literature has argued for a lack of context utilization in schizophrenia. The influential theory of Cohen & Servan-Schreiber (1992; 1993) suggested that thinking in schizophrenia was more highly influenced by the local context or immediate associations of current words rather than the global context of the larger discourse. Kuperberg, McGuire, & David (1998) showed that thought disordered patients were less sensitive to syntactic or semantic violations and thereby linguistic context. This could be understood as a smaller scope or time window of context. At SOAs over 750 ms, schizophrenics appear to perform worse than controls to all words (Barch et al 1996). Cohen et al (1999) argued for a pervasive late stage VWM abnormality in schizophrenia, with no semantic bias whereby patients fail to use context to order thought.

Previously we (Salisbury et al., 2002; Salisbury, 2008) proposed a hybrid model incorporating both early automatic and late controlled deficits, and the idea that lexically ambiguous words

present natural switching points where the train of thought can go awry if context is not used properly to explain thought disorder in schizophrenia. The Activation-Maintenance Model of Schizophrenic Thought Disorder proposes that schizophrenia patients have a semantic bias towards dominant meanings of ambiguous words despite context, and that this bias in turn reflects initial over-activation in semantic memory (hyperpriming, Maher, 1983) with a subsequent rapid decay of weak material in verbal working memory. However, at longer time intervals, patients cannot maintain information in working memory buffers, and what was initially a semantic bias becomes essentially random. If schizophrenia patients with thought disorder incorrectly select the strong or dominant meaning of ambiguous words, then words that disambiguate the ambiguity towards a subordinate meaning should be perceived as incongruent. Patients with schizophrenia tended to show a behavioral semantic bias, having a particularly difficult time comprehending short 4 word sentences (The noun was adjective/verb phrase) when the disambiguating associate indicated the subordinate homograph meaning (Salisbury et al, 2002; Salisbury, In Press). This was in stark contrast to patients with psychotic mania, who showed stably increased comprehension errors to all sentence types regardless of any ambiguity, a pattern consistent with random lapses of attention (Salisbury, 2008).

In addition to reaction times and error rates, neurophysiological measures can shed light on language processing. The N400 brainwave is larger to words that do not fit well with context, and is larger to sentence ending words that do not follow the preceding context than to contextually appropriate endings, and to unrelated words than to related words (Kutas & Hillyard, 1980). Many authors have examined N400 in schizophrenia (e.g., Kiang et al 2007, Kreher et al 2008), but the following focuses on N400 tasks using homographs in schizophrenia. If thought disorder causes an early bias away from subordinate meanings as posited by the Activation-Maintenance Model, N400 should thus be particularly large to subordinate homograph meaning associates in schizophrenia. This pattern was observed in a series of papers that showed larger N400 to associated words in schizophrenia that was particularly big to subordinate homograph associates on short 4 word long sentences, but the N400 to subordinate associates was not always significantly largest (Salisbury et al, 2000; 2002; Salisbury, In Press; see Salisbury, 2008 for review).

Salisbury (2004) showed that the N400 to sentence ending associates in psychiatrically well subjects was graded based on the nature of the word, with the N400 elicited by associates of unambiguous words on short sentences very small, followed by associates of the dominant homograph meaning, then the N400 to subordinate homograph associates, and finally largest to words not related to unambiguous nouns (the classic N400-effect). By comparison, schizophrenia subjects showed nearly identical small N400 responses to unambiguous associates and dominant associates, and nearly identical large N400 responses to subordinate homograph associates and unrelated words (Salisbury, In Press). Thus, the series of papers using short sentences seemed to show strong behavioral support (error rates) but only moderate neurophysiological event-related potential (ERP) support for a semantic bias due to preselection in schizophrenia. A differential bias effect on N400 in schizophrenia was clouded to some extent by a large N400 in patients to all words, likely due to faulty memory maintenance. The study that follows has replaced short sentences with word pairs in an effort to reduce overall memory duration requirements and to avoid strategic processing and sentential constraints engendered by sentence syntax and structure.

Several models have been proposed to explain homograph meaning activation (see Simpson, 1984; 1994 for review). A central question in language processing is whether all semantic associates are activated upon word perception or whether previous material limits the associates activated in semantic memory. This particular field is interested in how context affects the activation of separate entries within the lexicon, particularly pre- versus post-lexical access. Because context must be used to determine the appropriate subset of homograph associates,

homographs have been used extensively to answer this question. Different homograph meanings are understood to have separate networks within semantic memory but to overlap at feature level lexical representations, and the major research tries to shed light on the means of selection of the correct network through context-mediated pre-selection (selective access), ordered-access via pre-existing meaning frequency, or exhaustive post-access search. Data from reaction time (RT) priming (speeded decisions to related words) studies indicate that upon word perception all associates appear to be activated, with some debate whether the activation is a function of semantic distance (ordered-access) or not (exhaustive access), and that context-based inhibition of inappropriate associations happens approximately 250 ms later (Onifer & Swinney, 1981; Simpson, 1984; 1994; Paul et al., 1992; Tanenhaus, Leiman & Seidenberg, 1979). In the first ERP study of homograph meaning activation in normal subjects, Van Petten & Kutas (1987) reported behavioral priming of contextually appropriate homograph meanings at long stimulus onset asynchronies (SOAs), but no differential priming at short SOAs, consistent with RT data. Larger N400 was elicited by associates of the inappropriate homograph meaning at longer SOAs, suggesting inhibition of early automatic priming. At short SOAs, the ERP to non-appropriate associates was intermediate in morphology between unrelated and cued associate words, suggesting perhaps some differential-context based inhibition, but again not enough to alter RT. Swaab et al. (1998) reported smaller N400 to targets congruent with a biased homograph meaning than to unbiased meaning associates at both long and short SOAs in both normal controls and Broca's aphasics, suggesting that context was operating at the level of lexical selection. Still, there is at best scarce knowledge of the brain's activity to homographs at either fast or slow presentation rates. At longer SOAs, Salisbury (2004; In Press) showed that N400 was characterized by a gradation from unambiguous associates (smallest), through dominant homograph associates, subordinate homograph associates, and unrelated words (largest). This pattern suggests maintenance of meanings based on the relative association strength, and would be consistent with an ordered-access model of homograph meaning selection. However, there is evidence for hemispheric differences in the way homograph meanings are activated and maintained over time. Although all meanings may be activated immediately, the left hemisphere is thought to quickly select dominant homograph meanings because the probability of it being correct is highest, while the right hemisphere is thought to maintain all meanings in the case that the dominant meaning is incorrect (e.g., Burgess & Simpson, 1988; Atchley, Burgess, & Keeney, 1999). Kutas & Hillyard (1982) showed that unrelated unambiguous words had a generally right hemisphere N400 maximum, but hemispheric distributions to ambiguous words are not known. Titone & Salisbury (2004) reported moderate modulation of N400 to ambiguity in the different hemispheres consistent with the hemispheric activation model described above. The right hemisphere N400 was larger than the left when context was appropriate for subordinate homograph associates, whereas the left hemisphere N400 was larger for dominant homograph associates in inappropriate subordinate context than the right, although these effects were only detected on uncorrected planned comparisons and not in an omnibus ANOVA. The current study examined different hemispheric patterns of N400 at long SOAs in psychiatrically-ill and -well subjects to determine if any hemispheric differences were apparent, and if so, the degree to which patients showed such effects.

Methods

Subjects

Twenty-three patients with schizophrenia (4 at their first hospitalization) and twenty-five controls matched for age, handedness, Mini Mental status, WAIS Information and Vocabulary scaled scores, and parental socioeconomic status (SES) were compared (Table 1). Patients had lower SES than controls and less overall schooling, as expected for their illness. Still, this was a relatively bright, above average group of patient subjects.

Procedure

Subjects were presented two words, one at a time, on a computer screen approximately 1.1 meter away using Superlab Pro v.2 (Cedrus). The CUE word was on screen for 1 second, and was either an unambiguous noun or a homographic noun. The TARGET word came on screen 250 ms after the termination of the CUE (1.25 sec SOA). Subjects indicated via a dominant hand YES/NO button press if the two words were related or not. A total of 100 pairs were presented, containing 50 unambiguous and 50 homographic nouns. Half of the unambiguous CUE word's TARGET words were related, the other half unrelated. Half of the homographic CUE word's TARGET words were associates of the dominant meaning, and the remaining half were associates of the subordinate meaning. This resulted in 4 TARGET words: Related, Unrelated, Dominant, and Subordinate. TARGET words were matched for associative strength to their respective CUE words based on norms from several hundred undergraduates ($p > .9$), and matched for word length. Unrelated TARGET words were generated by randomly switching associated words with the proviso that the new pair was not superstitiously associated. Each homograph was used with its dominant and its subordinate meaning, and each unambiguous noun was used in an associated and an unrelated pair. No noun was repeated for any subject, resulting in 4 versions of the task, counterbalanced between subjects.

EEG Recording & Measurement

EEG activity was recorded from 60 scalp sites and the nose tip using a pre-configured 64-channel cap (custom designed Electro-Cap International sintered Ag-AgCl caps). Activity was amplified and recorded continuously with embedded digital stimulus triggers using SynAmps and Scan Acquire (Neuroscan/Compumedics USA). During recording the right mastoid served as the reference, with the exception of two bipolar electro-oculogram channels. Two electrodes located medially to the right eye, one above and one below, were used to monitor vertical eye movements and blinks. Electrodes placed at the outer canthi of the eyes were used to monitor horizontal eye movements. The forehead served as ground. All electrode impedances were below 5 kOhms. The EEG amplifier bandpass was 0.10 (6 dB/octave roll-off) to 100 Hz (24 dB/octave rolloff). EEG was digitized at 500 Hz.

Off-line processing was performed with BrainVision Analyzer (Brain Products GMBH). First, recordings were rereferenced to averaged mastoids. Next, EEG was digitally low-pass filtered at 30 Hz (24 dB/octave roll-off) to remove ambient electrical noise. Eye blink and movement correction was performed using the method of Gratton, Coles and Donchin (2000). Bad channels among the 24 lateral sites analyzed (see below) were replaced with the linear average of 6 to 8 surrounding sites. The EEG was segmented into epochs of 1100 ms duration, including a 100 ms pre-stimulus baseline, based on TARGET delivery time. Epochs were baseline corrected by subtraction of the average pre-stimulus voltage at each site. Subsequently, epochs that contained voltage exceeding $\pm 100 \mu\text{V}$ at F7, F8, FP1, or FP2 were rejected. Averages were computed separately for each TARGET type followed by a correct response within 200 to 3000 msec. Groups did not differ in the number of trials used to construct the Related, Dominant, and Subordinate TARGETS, but patients had significantly fewer trials to Unrelated TARGETS than controls (19.0 vs 22.1, respectively, $t_{46} = 2.54$, $p = .014$). Difference waveforms were constructed by subtraction of the ERP to unambiguous noun related TARGETS from the other conditions. The N400-effect was quantified as the average voltage from 400 - 600 msec. ERPs were compared among hemispheres (left and right) and regions (frontocentral, centroparietal). Each region comprised 6 sites. The left and right frontocentral regions comprised FC1/2, FC3/4, FC5/6 and C1/2, C3/4, C5/6. The left and right centroparietal regions comprised CP1/2, CP3/4, CP5/6 and P1/2, P3/4, P5/6. The N400-effect at the Cz midline sites was also measured and analyzed.

Results

Performance

Behavioral data from 1 schizophrenic subject were corrupted. Error rates were constructed for that subject from the EEG using embedded stimulus and response triggers. Reaction time data were not successfully reconstructed. Error rates and RT to correct trials among the 4 TARGET words (Unambiguous-Related, Unambiguous-Unrelated, Homograph-Dominant, Homograph-Subordinate) were compared between groups using Repeated Measures ANOVA, utilizing the Huynh-Feldt epsilon. Error rates were significantly higher in the patients ($F_{1,46} = 4.2, p = .046$). Error rates differed between words ($F_{3,138} = 113.1, p < .001, \epsilon = .74$). The pattern of errors did not differ between groups (Figure 1A). Although patients were consistently slower than controls (Figure 1B), RT on correct trials was not significantly different between groups ($F_{1,45} = 2.6, p = .11$). The between group effect size was approximately $d = 0.47$, suggesting group differences would attain significance with ~50 subjects per group and power of 2/3 as recommended by Cohen (1988). RT was different for the TARGETS ($F_{3,135} = 44.0, p < .001, \epsilon = .70$). Post-hoc comparisons (t-tests collapsed across groups) revealed that the time needed to make decisions about subordinate homograph meaning associates was longest (vs related, $p < .001$; vs dominant, $p < .001$, vs unrelated, $p = .04$), followed by unrelated (vs related, $p < .001$; vs dominant, $p < .001$), then dominant homograph associates (vs related, $p = .03$), and related associates fastest. (Note that differences between related and dominant associates, and between subordinate associates and unrelated words would not survive conservative Bonferroni correction $.05/6 = .008$.) Correct trial RT priming was calculated as the improvement in decision speed relative to unrelated words. Priming among the 3 remaining TARGET words (Unambiguous-Related, Homograph-Dominant, Homograph-Subordinate) were compared between groups using Repeated Measures ANOVA, utilizing the Huynh-Feldt epsilon. Groups showed comparable RT priming ($F_{1,45} = 0.005, p = .994$, Figure 1C). Priming differed among TARGET words ($F_{2,90} = 105.3, p < .001, \epsilon = .84$), and this pattern did not differ between groups ($F_{2,90} = 1.97, p = .12, \epsilon = .84$). It is apparent that RT was shorter to associates of unambiguous nouns and of dominant homograph meanings relative to words unrelated to unambiguous nouns, but RT was lengthened to associates of subordinate homographs relative to deciding 2 words were unrelated.

Raw waveforms and topographic maps are presented in Figure 2. As can be seen in Figure 2A at Cz, controls showed the graded N400 response to the Targets described above. By contrast, Figure 2C at Cz shows schizophrenia patients to show a rather different pattern, with large N400 to associates of subordinate homograph meanings. The raw N400 topography in controls (Figure 2B) shows a generally centrofrontal, leftward relative negativity for Related, Dominant, and Subordinate TARGETS, and a more rightward centrofrontal relative negativity for Unrelated TARGETS. Topography of the raw N400 in patients is similar, although they show an apparent frontward shift in the posterior positivity (Figure 2D). The N400-effect is better visualized in the differential activity between TARGET words of interest and the Related TARGETS. Difference waveforms and topographic maps are presented in Figure 3. Analysis of the N400-effect among Homograph-Dominant, Homograph-Subordinate, and Unambiguous-Unrelated TARGET ERPs was compared between groups using Repeated Measures ANOVA, utilizing the Huynh-Feldt epsilon. For primary hemispheric analyses, the four regions described above were analyzed. (Note that site is essentially meaningless in the regional analysis.)

At Cz, groups did not differ in overall N400-effect amplitudes ($F_{1,46} = 0.3, p = .58$). The N400-effect differed among the words ($F_{2,92} = 4.6, p = .013, \epsilon = 1.0$), but the pattern of the N400-effect differed among groups ($F_{2,92} = 3.6, p = .031, \epsilon = 1.0$). As can be seen in Figure 4, controls showed a graded N400-effect from Dominant to Subordinate to Unrelated TARGETS, whereas patients showed relatively small N400-effects to Dominant and Unrelated TARGETS, and

large N400 to Subordinate TARGETS. Hemispheric and regional analyses revealed that groups did not differ in overall N400-effect amplitudes ($F_{1,46} = 0.6$, $p = .44$; Figure 3). The N400-effect differed among the words ($F_{2,92} = 4.6$, $p = .013$, $\epsilon = 1.0$), but the pattern of the N400-effect differed among groups ($F_{2,92} = 3.4$, $p = .041$, $\epsilon = 1.0$). There was a significant word by hemisphere interaction ($F_{2,92} = 9.9$, $p < .001$, $\epsilon = 0.996$). As can be seen in Figure 3B for controls and Figure 3D for patients, both groups showed relative right hemisphere maximal N400 for unrelated words, but a substantially left hemisphere shift for subordinate homograph meaning associates. Dominant homograph meaning associates were relatively unchanged topographically from related words.

Correlations were conducted between symptoms and the N400-effect from Cz, CP1 and CP2 for patients. For dominant homograph TARGETS, a smaller N400-effect relative to unambiguous related TARGETS was associated with greater PANSS delusions at CP2 ($r = 0.43$, $p = .05$), greater PANSS unusual thought content at CP1 ($r = 0.45$, $p = .04$), greater PANSS positive scores at Cz ($r = 0.5$, $p = .02$) and CP1 ($r = 0.45$, $p = .04$), greater PANSS thought disturbance at Cz ($r = 0.49$, $p = .02$) and CP1 ($r = 0.48$, $p = .03$), and with greater SAPS total scores at Cz ($r = 0.52$, $p = .02$), CP1 ($r = 0.49$, $p = .03$) and CP2 ($r = 0.59$, $p = .004$). Generally, greater positive symptoms and thought disorder were associated with a reduced N400-effect to dominant homograph meaning associates. By contrast, for subordinate TARGETS in patients a larger N400-effect relative to related TARGETS was associated with greater PANSS disorganization at Cz ($r = -0.44$, $p = .05$) and CP2 ($r = -0.61$, $p = .003$), and greater PANSS negative score at CP1 ($r = -0.44$, $p = .05$) and CP2 ($r = -0.5$, $p = .02$), SANS was NS at $-.35$ and $-.38$ respectively). A smaller N400-effect for subordinate TARGETS was observed at CP2 only for SAPS total ($r = 0.53$, $p = .01$, PANSS positive score was $.4$, $p = .07$). A smaller classic N400-effect (unrelated - related) was associated only with greater PANSS conceptual disorganization (Cz: $r = -0.51$, $p = .02$; CP1: $r = -0.52$, $p = .02$; CP2: $r = -0.54$, $p = .01$).

Discussion

The pattern of N400 on this task was consistent with a semantic bias in schizophrenia away from the subordinate meanings of ambiguous words. Those associates elicited the largest N400 in patients, by contrast with controls where a graded, intermediate response was seen. A smaller N400-effect to dominant homograph meaning associates and a larger N400-effect to subordinate homograph meaning associates was associated with greater thought disorder, as predicted by the presence of a semantic bias to preselect dominant homograph meanings. Behaviorally, however, the controls in this study showed a large number of errors to subordinate word pairs, more than previous controls did on short sentences (Salisbury et al., 2004; Salisbury, In Press). Patient error rates were similar between this word pair task and previous short sentence tasks. These data suggest that controls process subordinate homographs similarly on short sentence and word pair tasks in terms of the operations reflected in N400, but may develop additional strategies based on sentential constraints that lead to better overall subordinate meaning comprehension on short sentence tasks. By contrast, patients' N400 pattern and error rates suggest that they process sentence-embedded targets the same as less constrained word pairs. This suggests that the overall structural and global context of sentences are not maintained or utilized in schizophrenia.

The underlying mechanism by which patients with schizophrenia showed larger N400 responses to TARGET words disambiguating CUE homographs to subordinate meanings is not clear. If patients simply did not activate subordinate networks, then one might expect roughly equal N400s to subordinate meaning associates and unrelated words to unambiguous nouns. It is possible that at these relatively long SOAs the response to unrelated TARGET words is approaching randomness with respect to the CUE words, by comparison with a starker contrast for subordinate TARGETS due to the selection bias. This idea might be supported by

the fact that patients showed a reduced N400 effect for unambiguous unrelated TARGET words compared to controls (Fig. 4), were more likely to say unrelated words were related, and their N400 to subordinate TARGETS approximated the unrelated TARGETS of controls. That is, because of the bias towards dominant meaning networks, patients processed the subordinate meanings more like controls processed truly unrelated words, but because of memory deficits patients processed truly unrelated words as possibly related. On the other hand, it is also possible that patients actively inhibited subordinate meanings when faced with homographs such that integration of subordinate meanings was even more difficult than of unrelated meanings. That is, schizophrenic patients may show a bias towards left hemisphere fine semantic coding, which is thought to select the dominant homograph network of strong associates and inhibit subordinate network associates, at the expense of right hemisphere coarse coding that keeps all distinct meaning networks online. Further work should clarify this issue.

A current debate in thought disorder research is the degree to which verbal working memory context maintenance is impaired by contrast with an inability to use context well. Titone and colleagues have argued that schizophrenia is characterized by an inability to utilize context efficiently. Titone, Levy, & Holzman (2000) argued that patients showed impaired use of weak context, but normal use of strong context. Titone, Holzman, & Levy (2002) examined performance in patients to proverbs that could be plausibly interpreted in a literal sense (e.g., kick the bucket) or not (e.g., pay through the nose). Patients showed impaired inhibition to literal proverbs, with increased priming to literal associates, but normal priming to abstract proverbs. Titone and colleagues argued that context was maintained properly in schizophrenia, but inefficiently used when the controlled inhibition of initial semantic activation was necessary. The larger N400 observed in schizophrenia patients to associated words on nearly all studies (e.g., Bobes et al., 1996; Nestor et al., 1997; Niznikiewicz et al., 1997, Salisbury et al., 2004; Salisbury, In Press) suggests however that patients have difficulty integrating even literal associations, which seems more consistent with fading memory maintenance rather than inefficiency. Similarly, the classic N400-effect of larger N400 to unrelated than to related words is moderately smaller in schizophrenia, consistent with a failure to maintain activation of semantic network links, even literal. Perhaps, then, thought disorder in schizophrenia may relate to changing root causes: mild to moderate thought disorder may relate to lesser deficits in memory maintenance and weigh more heavily to utilization defects, whereas more severe thought disorder may relate to extensive verbal working memory failure. This is somewhat supported by the finding that more severe pathological pattern of larger N400s to subordinate homograph meaning associates correlates with thought disorder (Salisbury et al., 2004, this data). Still, the results here cannot unequivocally determine whether maintenance or utilization is more to blame for thinking disturbances in schizophrenia.

Of some interest was the differential hemispheric pattern of the N400-effect to subordinate homograph associates versus words unrelated to unambiguous nouns. Titone (1998) examined hemispheric activation for “central” versus “peripheral” features of homographs, analogous to strong and weak associates here. She showed behavioral priming in both hemispheres for central probes of dominant and subordinate homographs, but a differential pattern for peripheral or weak probes. In that case, the left hemisphere showed priming for dominant meanings, whereas the right hemisphere showed priming for subordinate meanings. The results of this study are consistent with the finding of differential hemisphere activity for weak associates. Recall that TARGETS for all words were matched for associate strength, which necessarily means they were weak associates; subordinate associates are, by definition, weak associates, and set the limit for associate strength. Both groups appeared to show a greater right hemisphere N400-effect to unrelated and dominant TARGETS, and a greater left hemisphere N400-effect to subordinate TARGETS. This topographic difference is consistent with the left hemisphere preselecting the dominant homograph meaning network at longer SOAs, and the right hemisphere maintaining subordinate activations. This differential process seems to be

largely intact in schizophrenia for the left hemisphere, but preselection may in fact span both hemispheres in schizophrenia, as reflected in a large N400 across the scalp to subordinate TARGETS than controls. For unrelated TARGETS, the right hemisphere appears to be operating similarly in patients and well subjects, indicating some maintenance of global context in the patients, but the N400 was smaller in patients than controls, again consistent with reduced maintenance or utilization of such global context.

It is somewhat perplexing that correct decisions about subordinate homograph associates took longer in both group than decisions about unrelated words. This cannot be accounted for by a exhaustive serial self-terminating search, nor by sequential ordered search of activated nodes. Instead, it suggests a somewhat categorical search of networks or activation levels: If dominant networks are inactive, and subordinate networks are inactive, then unrelated decisions can proceed, whereas if subordinate networks are active, a serial search may ensue. Alternately, it may simply take less time to search an unambiguous network and decide on unrelated than to search both dominant and subordinate networks. Currently we are examining strong and weak associates versus dominant and subordinate associates to examine specialized ambiguous network defects versus general storage deficits, and also word triplets to examine related and unrelated words to homographs themselves.

Several caveats to the study need to be indicated. First, TARGET words were matched for length and associative strength, but other pertinent factors such as word frequency were not as well controlled. Current work has precisely matched for length, word frequency, and associative strength. Further, to match for associative strength including subordinate associates that are by definition weakly associated with a CUE, means that only relatively weak associates were used. It is not entirely clear whether weak associates are well maintained in schizophrenia, and whether these results will be the same for very strongly associated words. Current work is examining weak and strong associates to dominant homograph meanings and unambiguous words to determine whether network level deficits or weak associative link deficits are involved in schizophrenic thought disorder. This task used a comprehension task where subjects actively determined whether the words were semantically related. Clearly, information regarding automatic priming-related aspects of semantic processing are clouded in the case where subjects are actively searching for relationships between CUE and TARGET words. In addition, results on lexical decision tasks, where subjects decide if a TARGET is a real word or a non-word and where real word pairs contain related and unrelated words, thereby examining priming effects relatively implicitly, and results on comprehension tasks may be probing different underlying cognitive operations. For example, Faust and Lavidor (2003) used visual hemifield presentation to compare a lexical decision task versus an active comprehension task in each hemisphere using 2 priming words that were either both congruent with a dominant or subordinate homograph meaning or each primed a different meaning, and found that the left hemisphere appeared to preferentially select dominant homograph meaning in lexical decision tasks as reflected in reaction time priming, but appeared to show relatively equal priming for both dominant and subordinate homograph meanings when both priming words agreed on the comprehension task. Thus, task demands may influence the processing of homographs in the hemispheres, and may confound this data, although we used only single priming words. Currently, we are testing patients on lexical decision tasks to remove the controlled aspect active comprehension tasks engender. The fact that all homograph CUE words were followed by an associate means that the design was not fully balanced to have 50% correct and 50% incorrect trials. This may have established a differential bias to respond in patients and controls. Currently our experiments present more incorrect trials to match overall trial outcome types, and manipulate the proportion of related words to compare and contrast automatic versus controlled priming in schizophrenia.

In summary, thought disorder in schizophrenia is associated with a semantic bias towards the selection of dominant meaning networks of ambiguous words. These points of ambiguity in discourse are natural switching points where the strongest local semantic associates may not be in agreement with the global context. Proceeding along lines of strong local associations rather than using context to guide the train of thought appears to be one primary cause of thinking disturbances in schizophrenia. The left and right hemisphere appear to react to ambiguity differently, and this differential activity seems to be relatively intact in schizophrenia. Future work will attempt to better isolate different stages of memory activation, maintenance, and utilization to address the time course of verbal deficits in schizophrenia.

Acknowledgments

Supported by the National Institute of Health R01 MH58704

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Figure 1. Task Performance. Panel A. Percent errors on the task (adjusted for missed trials). Panel B. Reaction time for correct detections. Panel C. Benefit in speed for associated words relative to unrelated, unambiguous words.

Figure 2. ERPs to TARGET words. Panel A. Responses in control subjects. Panel B. Topography of the N400 trough peak in controls. Panel C. Responses in schizophrenic patients. Panel D. Topography of the N400 trough peak in patients.

Figure 3.

Difference waveforms relative to unambiguous related TARGET words. Panel A. Responses in control subjects. Panel B. Topography of the N400-effect in controls. Panel C. Responses in schizophrenic patients. Panel D. Topography of the N400-effect in patients.

Figure 4.
N400-effect among words and groups at Cz.

Table 1

Demographic and Clinical Information.

	Patients	Controls	p
Age	36.7 (11.7)	33.9 (11.3)	0.42
Handedness	0.77 (0.4)	0.74 (0.4)	0.84
Mini Mental State	29.0 (1.2)	29.2 (0.8)	0.59
WAIS Info	12.5 (2.4)	12.8 (3.1)	0.64
WAIS Vocab	11.9 (3.0)	13.3 (3.5)	0.15
Schooling (yrs)	13.3 (2.5)	15.0 (1.8)	0.006
SES	3.7 (1.2)	2.3 (0.7)	<0.001
PSES	1.9 (1.3)	2.0 (1.2)	0.70
Years Illness	14.5 (11.3)		
Medication	234.6 (342.3)		
PANSS Total	70.1 (14.5)		
PANSS Positive	20.3 (5.5)		
PANSS Negative	15 (5.3)		
PANSS Thought Disturbance	11.5 (4.3)		
SANS	9.0 (4.3)		
SAPS	9.7 (4.2)		
GAS	39.4 (10.8)		

Note: Values are mean (sd). Age in years. Handedness from the modified Edinburgh Handedness Inventory (Oldfield, 1971; -1 = fully left handed, 1 = fully right handed). Mini Mental Status: Mini Mental State Examination (Folstein, Folstein & McHugh 1975; 30 max score). WAIS = Wechsler Adult Intelligence Scale, ver 4. Info = Information test scaled scores, Vocab = Vocabulary test scaled scores. SES = Socio-Economic Status, PSES = Parental Socio- Economic Status (Hollingshead, 1965). Medication: chlorpromazine equivalents. PANSS = Positive and Negative Symptom Scale (Kay, Opler, Fiszbein 1986). Scale for the Assessment of Negative Symptoms (Andreasen, 1984a). SAPS = Scale for the Assessment of Positive Symptoms (Andreasen, 1984b). GAS = Global Assessment Scale (Endicott et al 1976), analogous with GAF = Global Assessment of Functioning.