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N400 to Lexical Ambiguity and Semantic Incongruity in Schizophrenia

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Abstract

Our previous work showed a semantic bias in interpreting ambiguous words in schizophrenia, with disproportionate misinterpretation of subordinate meanings (*toast* at a wedding). We proposed pre-selection in schizophrenia of dominant meaning networks at points of lexical ambiguity, thereby misleading thought. This selection bias may be due to semantic memory hyper-priming causing strong associates to dominate cognition. Alternately, later access verbal memory maintenance failure may cause weaker associates to fade more quickly than stronger associates from memory due to less initial activation. To further examine this semantic bias, patients and controls were presented short 4 word long sentences (The *toast* was *buttered*). The second word was a homograph or unambiguous noun. The last word disambiguated homographs (dominant or subordinate meaning) or was congruent or incongruent with unambiguous nouns. Previously, we showed increasingly larger N400 from unambiguous associates to dominant associates to subordinate associates to unambiguous non-associates in controls. Pre-selection of dominant meanings predicts schizophrenia patients would show small N400 to dominant associates and as large N400 to subordinate associates as to incongruous endings. Here, controls again showed graded N400 amplitudes. Patients with schizophrenia showed small N400 to congruent and dominant endings and large N400 to subordinate and incongruous endings. These data suggest early pre-selection of dominant associates in schizophrenia. This effect is unlikely solely due to verbal memory maintenance failure, as patients were able to detect incongruity, albeit with a smaller N400 effect, and generally larger N400 to all stimuli. These results suggest alterations in semantic memory associative networks coupled with verbal working memory maintenance decay in schizophrenia.

Keywords

ERPs; Homographs; Incongruity; N400; Schizophrenia; Semantic Memory; Thought Disorder; Verbal Working Memory

Introduction

Thought disorder is a prominent symptom of schizophrenia. It is inferred through bizarre and disordered speech, which at the most extreme instances may result in word salad, an

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incomprehensible, inscrutable jumble of words, and neologisms, the idiosyncratic coinage of words with delusional significance. More commonly, though, thought disorder is subtle, and manifests as a certain looseness in conceptual focus by which the train of thought is normally maintained. Tangential and obliquely related concepts may sidetrack narrative, such that the overarching purpose of the discourse may be ultimately lost. Cohen and Servan-Schreiber (1992) have described this effect as the “local” sentence context having more influence than the “global” discourse context in schizophrenia.

Precisely what mechanisms underlie thought disorder remain unknown. Because it is inferred from language, memory systems related to language are likely involved. Although some have argued that the problem is one of executive, attention mechanisms (e.g., Schwartz, 1982), compelling evidence exists that verbal content influences thought disorder (described below), inconsistent with a purely executive abnormality, wherein phasic lapses in executive functions should be independent from the specific words in memory. Such evidence for processing deficits for specific word-types strongly suggests the cognitive abnormality must, to a great extent, involve language-specific processes. Of course, a general physiological abnormality may impact multiple systems beyond those language-related. However, the crucial point is that basic systems related to semantic memory must be implicated in thought disorder.

Semantic memory represents the lexicon of stored knowledge, and has been referred to as “crystallized” memory, essentially static. Collins and Loftus (1974) proposed that words were stored in a conceptual space and linked with related items (associates) in a semantic network, separated by the “semantic distance”, or strength of association in this conceptual space. This model provided the major framework for understanding the automatic spread of activation among related concepts. For example, upon seeing the word **red**, proximal associates such as **fire** and **orange** receive more initial automatic activation than distal associates such as **sunsets** or **roses**. This is reflected in speeded responses to close associates, termed *semantic priming*. Subjects are able to make judgements about semantically-related words more quickly than unrelated words (Schvaneveldt and Meyer 1973).

The initial semantic memory automatic spread-of-activation may have a relatively short duration. For example, Hagoort (1993) demonstrated that aphasic patients failed to show semantic priming after approximately 1250 msec although they had shown relatively normal priming at shorter intervals. This suggests that as memory demands for semantic priming exceed around one second, a second memory process is necessary to maintain activations and observe priming. This is likely served by verbal working memory, a controlled or executive process, that is veiled, or not accessible to consciousness. Thus, unless overwritten by new information, priming effects may last for several seconds or longer (e.g., Deacon et al., 1999). An intact brain shows a seamless transition between the initial bottom-up activation and the maintenance of this activation in verbal working memory. Aphasic patients impaired at controlled processes, presumably relying on verbal working memory processes rather than initial semantic activation, appear to no longer show priming at slower presentation rates. Thus, the duration of the initial burst can be estimated to last for less than 1 second. In addition, much work in the cognitive literature indicates that, in the case of relatively weak context as provided by one priming word or a short sentence, it takes approximately 250 ms for the context to inhibit the initial activation of contextually inappropriate associates (e.g., Onifer and Swinney, 1981). Thus, a two-stage model of semantic activation and verbal working memory maintenance suggests that in the case of relatively weak context all associates of a word are activated in a bottom-up fashion, with top-down inhibitory mechanisms modulating the initial activation after a quarter of a second. Relatively pure automatic effects are thought to be evident at presentation rates under 300 msec, before controlled processes can exert their effects. The initial burst of bottom-up activation decays by at most a second, unless maintained in verbal working memory. When maintained, semantic priming effects can last for several seconds or

longer due to veiled verbal working memory controlled processes, and without need for conscious awareness of the activated information.

Whether the thought disorder observed in schizophrenia involves deficits in semantic memory organization and bottom-up activation or in later controlled top-down processes such as verbal working memory maintenance or context utilization remains a central question. There is evidence for hyper-priming in schizophrenia at short stimulus onset asynchronies (SOAs). Schizophrenic subjects show an *increase* in the effect of priming on a speeded lexical decision task (Maher, 1983). This facilitation effect on priming has been replicated by several groups (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. Mathalon et al. (2002) and our work (described below) also demonstrated N400 ERP signs of hyper-priming in schizophrenia. It is important to realize that these effects appear only at very short SOAs, and that priming is generally absent or deficient at longer SOAs in schizophrenia, consistent with the two-stage model described above: initial semantic priming with subsequent verbal working memory maintenance of initial activation.

In addition to some evidence for hyper-priming, a large body of literature has argued for a lack of context utilization in schizophrenia. These data show that patients fail to use context to order thought. 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 verbal working memory abnormality in schizophrenia, with no semantic bias. That is, schizophrenics were as likely to incorrectly select a subordinate ambiguous word meaning as a dominant ambiguous word meaning. However, the SOAs used were 1 and 5 s. At both these intervals, hyper-priming may not be apparent. As indicated earlier, Hagoort (1993) showed that aphasics showed normal priming effects at SOAs under 1 sec (100 and 500 ms), but not at over 1 sec (1250 ms). This suggests that time intervals approaching 1 s are not likely to accurately access semantic memory activation in subjects with defective verbal working memory processes, and thus studies that use relatively slow presentation rates cannot rule out semantic memory deficits.

Despite this confound, it is likely that schizophrenics have abnormalities using context to modulate activation in semantic networks. Several studies have demonstrated insensitivity to context in schizophrenia. Kuperberg et al. (1998) showed that thought disordered patients were less impaired in processing words preceded by syntactic or semantic violations, suggesting they were less sensitive to linguistic context. Such insensitivity could be due to a failure to maintain context or to correctly use stored context. Titone and colleagues have argued that schizophrenia is characterized by an inability to utilize context in situations that stress verbal working memory contextual inhibition. Titone et al. (2000) used weak and strong biasing context in schizophrenia and suggested that patients showed impaired controlled priming with weak biasing context, but normal controlled priming with strong context. Titone et al. (2002) compared priming following proverbs that could be literally interpreted (e.g., kick the bucket) or only abstractly interpreted (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. Using the N400 event-related potential (ERP) Condray et al. (2003) showed brainwave reductions in unmedicated patients at slow presentation rates that relied on top-down processing and development of expectancies. Thus, the deficit in schizophrenia must involve some degree of top-down deficits. The question becomes, then, of the relative contributions of bottom-up and top-down deficits to thought disorder.

The N400 ERP, a negative brainwave at roughly 400 msec post-stimulus, appears to be activated by conceptual-level representations. It is larger to incongruent (contextually inappropriate) than congruent sentence endings (e.g., Kutas & Hillyard 1980, 1982) that may be words or pictures (Nigam et al., 1992); to unrelated than to related words (Kutas and Hillyard 1989); and to weakly associated than strongly associated words (Kutas and Hillyard 1989; Polich 1985). The increase in N400 to less related or unrelated words is termed the N400 effect. Although the precise function underlying N400 is unknown, N400 can be utilized experimentally to examine priming effects. The N400 has also been used to examine lexical ambiguity. The first report of N400 to ambiguous words (Van Petten and Kutas, 1987) showed that associates of ambiguous words spelled the same for the different meanings (homographs) showed intermediate N400 amplitudes between unambiguous associates and non-associates.

In our previous research we have further examined the N400 to homograph associates in well subjects, and also used N400 to examine the idea that bottom-up hyper-priming in schizophrenia leads to a semantic bias towards strong associates. Although different homograph meanings necessarily have different patterns of activation in semantic space, they are identical at the feature level and have the same entry point for lexical access. Because homographs share orthography between different meanings, in the absence of context the appropriate meaning of the homograph cannot be determined. We conceive of the different semantic conceptual spaces activated by each homograph meaning to be a separate (though partially overlapping) network. By definition, the networks should not be highly interconnected at the associate level. By using tasks where the homograph precedes the disambiguating information (e.g., the toast was emotional), pre-selection biases can be identified in the responses to the disambiguating information. For example, if toast's browned bread meaning was pre-selected, then the disambiguating word emotional would be incongruent. Through the use of homographs with dominant versus subordinate meanings in the lack of context, semantic biases at points of lexical ambiguity can be examined in schizophrenia. Salisbury et al. (2000) showed larger N400 in schizophrenia to subordinate homograph associates on a passive reading task to sentence ending words than in controls that was associated with greater thought disorder. Salisbury et al. (2002) had subjects make a sensibility judgement for the sentences. Again, schizophrenia patients showed larger N400 to subordinate homograph sentence endings, even when the sentence was interpreted as making sense. Patients showed N400 to subordinate homograph endings judged sensible as large as controls did to subordinate endings they failed to comprehend. Behaviorally, patients failed to comprehend disproportionately more subordinate homograph sentences. At the same time, patients showed overall larger N400s to all sentence types, regardless of noun network type. Sitnikova et al. (2002) examined contextual utilization in schizophrenia by presenting subjects with longer sentences containing 2 clauses. The first clause biased the sentence to dominant or subordinate homograph meanings. The second clause always referred to the dominant homograph meaning. Unlike controls, schizophrenia patients did not generate larger N400 to dominant associates when the first clause biased towards subordinate meanings. However, schizophrenia patients still showed an N400 effect to non-associates, albeit smaller than in controls.

Salisbury et al. (2002) proposed a joint deficit comprising hyper-priming and maintenance failure in schizophrenia to explain the clear behavioral semantic bias and larger N400 to subordinate homographs in schizophrenia coupled with the moderate N400 effect reduction. In that experiment, the responses in schizophrenia patients to truly incongruent endings was not examined. The current study examined the interpretation of ambiguous and unambiguous words in schizophrenia contrasted with controls, by comparison with sentence ending words that were incongruent with unambiguous nouns. If patients were unable to maintain context, then they should show reductions in the N400 effect to incongruent endings and larger N400s to all sentence endings. If they had problems with hyper-priming and pre-selection of dominant networks, then the N400 to dominant homograph endings and unambiguous associates should

be similar and smaller (i.e., more congruent) than the responses to subordinate and incongruent endings (i.e. less congruent), which should be similarly large.

Materials and Methods

Procedures were approved by the local IRB and all subjects gave informed consent. Twenty schizophrenia patients (all medicated except 1, average chlorpromazine equivalents of antipsychotic medication: 200.2 ± 116.3) and 20 matched control subjects (all male, right-handed native English speakers) were tested on a simple sentence reading task. A report of control N400 responses and memory performance on this task was presented in Salisbury (2004). The 20 controls in the current study include 7 from that paper. Patients and controls were culled from larger samples that completed the test. Subjects with scaled WAIS-III Information scaled scores < 8 (3 sds or more below the average mean) were judged cognitively impaired and excluded. Subjects that indicated more than 1/3 of the congruous sentences to be incomprehensible, or the incongruous sentences to be sensible, were also judged cognitively impaired and excluded from analysis. One schizophrenia patient with no apparent N400 peaks between 300 and 600 ms was dropped from analysis. Subjects were further culled to match groups on age (Schizophrenia: $28.6 \text{ years} \pm 10.1$; Controls: 30.0 ± 7.5 , $t(38) = 0.5$, $p = 0.62$), WAIS-III information scaled scores (Schizophrenia: 12.2 ± 3.1 ; Controls: 13.1 ± 2.6 , $t(38) = 1.0$, $p = 0.32$), and parental Socio-Economic Status (Schizophrenia: 2.1 ± 0.8 ; Controls: 1.7 ± 0.8 , $t(36) = 1.7$, $p = 0.09$, Hollingshead, 1965). Although patients showed a trend for lower PSES than controls, patients were generally bright and none scored less than 3 on PSES. Patients had a mean of 14 years of school and controls 16 ($t(38) = 2.4$, $p = .02$), but, again, groups were matched on WAIS-III scaled Information scores, suggesting comparable premorbid intellect.

All patients were medicated, except one. Twelve were taking atypical antipsychotics. Of these patients, four were also taking mood stabilizers, seven were also taking antidepressants, five were also taking anxiolytics, and two were also taking anti-tardive dyskinesia medications. Four patients were on typical antipsychotics. Of these patients, two were also receiving anxiolytics, and one anti-tardive dyskinesia medications. Three patients were on both typical and atypical antipsychotics. Of these patients, one was also taking mood stabilizers, one was also taking antidepressants, two were also taking anxiolytics, and two were also taking anti-tardive dyskinesia medications.

Sentences were 4 words long, presented one word at a time on a CRT 1 meter from the subject (Neuroscan STIM). Sentences read: "The NOUN was ADJECTIVE/VERB PHRASE". The noun was either a homograph (ambiguous) or unambiguous. The last word disambiguated the dominant or the subordinate meanings for homographs, or was congruent or incongruent with unambiguous nouns. All endings were weakly associated with nouns if not incongruent. Fifty sentences had unambiguous nouns, half congruent, half incongruent. Fifty sentences had homographs, half dominant, half subordinate. Dominant homograph meanings had strengths approximately 3 times greater than the subordinate meanings. For normative databases from which the homographs were selected, see Salisbury et al. (2002). Thus, one hundred sentences were presented, 25 of four types: Unambiguous noun-congruent ending (The dog was barking); Unambiguous noun-incongruent ending (The hammer was cloudy); homograph-dominant meaning ending (The suit was gray); and homograph-subordinate meaning ending (The suit was hearts). Unlike the example above, no noun or ending was repeated during the test. Following each sentence, "OK?" appeared on the screen when subjects were required to signify comprehensibility of the sentence via a Yes/No button press. Words were presented for 1 sec with a 250 msec ISI. Thus, words had a 1250 msec SOA, and the adjective/verb phrase followed the noun with an SOA of 2.5 sec. The response prompt (OK?) lasted for 2 seconds, regardless of subject response.

Electroencephalographic activity (EEG) was recorded from the scalp through 28 tin electrodes in pre-configured caps (ElectroCap International). Linked-earlobes were the reference, the forehead was the ground. 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. All electrode impedances were below 3 KOhms, and the ears were matched within 1 KOhm. The EEG (Neuroscience) amplifier bandpass was 0.15 (6 dB/octave rolloff) to 40 Hz (36 dB/octave rolloff). Single trial epochs were digitized at 3.9 ms/sample (256 Hz) and stored for analysis (Neuroscan SCAN). Each epoch was of 1100 ms duration, including a 100 ms pre-stimulus baseline. Averaging and artifact rejection were done off-line. ERP responses were digitally low-pass filtered at 8.5 Hz with a 24 dB/octave rolloff to remove ambient electrical noise, muscle artifact, and alpha contamination. Epochs from each electrode site were baseline corrected by subtraction of the average pre-stimulus voltage, and corrected for eye movement artifact using regression-based weighting coefficients when the standard deviations of the corrections were $<0.01 \mu\text{V}$ (Semlitsch et al., 1986). Trials were again baseline corrected after eye-correction. Subsequently, epochs which contained voltage exceeding $\pm 75 \mu\text{V}$ at F7, F8, Fp1, or Fp2 were rejected. Trials were separated for each sentence type only for sentences that the subject correctly comprehended. N400 was measured as the mean voltage over a 50 millisecond window centered on the N400 peak for each noun type. Peaks were automatically detected with adjustment by the Author after visual inspection if necessary.

Groups were compared on age, WAIS-R/III Information scaled scores, and PSES with *t* tests. Error rates and N400 amplitudes were compared with general linear model repeated measures (SPSS) using multivariate analyses for within subject comparisons. Correlations used Pearson's *r*.

Results

Schizophrenia patients made more comprehension errors than controls ($F_{1,38}=15.8$, $p<.001$). The type of sentence affected comprehension in both groups ($F_{3,36}=52.6$, $p<.001$), but the pattern differed in the groups ($F_{3,36}=5.4$, $p=.003$). Schizophrenia patients made disproportionately more errors to subordinate homograph sentences (Fig 1, Panel A), and this interaction remained significant when overall error rates were adjusted by the base error rate to unambiguous congruent sentences (Fig 1, Panel B). Although patients did not make significantly more errors to unambiguous congruent sentences or dominant homograph sentences (raw or normalized), they made significantly more errors to unambiguous incongruent sentences (raw or normalized) and over twice again more to subordinate sentences (raw or normalized) than controls.

ERP responses along the midline and middle lateral sites are presented in Figure 2. Whereas controls showed graded N400 responses to the different sentence types, particularly at Cz, and right hemisphere sites C4 and CP2, schizophrenia patients showed generally more negative N400 to all words, and generally larger N400 responses to subordinate homograph and incongruent sentence endings, again marked at Cz, C4, and CP2. Analysis of the midline sites (Fz, Cz, Pz) indicated that N400 was marginally more negative in schizophrenia patients ($F_{1,38}=3.9$, $p=.056$). Sentence type affected N400 amplitudes only at trend levels ($F_{3,36}=2.4$, $p=.082$), but this interacted with group ($F_{3,36}=3.5$, $p=.025$). As indicated in Figure 3 for Cz, N400 was graded in controls ($p<.001$), but not in schizophrenia, where the largest N400 was to subordinate sentence, although not reaching significance.

Within the control group, N400 to the different sentences was highly correlated. The lowest correlation was 0.59 between congruent and subordinate sentences ($p=.007$), and the largest was 0.83 between subordinate and congruent sentences ($p<.001$). All other combinations were

significant and intermediate in significance. By contrast the schizophrenia group showed the highest correlations between the N400s to subordinate homograph and incongruent sentences (0.77, $p < .001$) and congruent and dominant sentences (0.69, $p = .001$). The N400 to subordinate sentences did not correlate with that to unambiguous congruent or dominant homograph sentences.

As in Salisbury (2004) total errors to subordinate homographs correlated with WAIS III Information scaled scores in controls ($r = -0.55$, $p = .013$). This same correlation was present in schizophrenia patients ($r = -0.47$, $p = .039$), indicating that in both groups, better premorbid intellect led to better comprehension of subordinate homograph sentences. Unlike Salisbury (2004), Info scores in controls were also correlated with N400 amplitude to dominant homograph sentences ($r = -0.46$, $p = .041$), and simple measures of working memory (WAIS III Digit Span, Symbol Digit, and Trails B) were not correlated with N400 to subordinate sentences. In patients, simple measures of working memory (WAIS III Digit Span, Symbol Digit, and Trails B) were not significantly correlated with N400 to any sentence type, but were correlated with error rates. Scaled Digit Span scores correlated only with errors to dominant homograph sentences ($r = -0.52$, $p = .018$). Trails B time normed t-scores correlated with errors to unambiguous associate sentences ($r = -0.52$, $p = .024$), and with subordinate homograph sentences ($r = -0.52$, $p = .023$).

In patients, the SANS total score correlated moderately with errors to unambiguous associates ($r = 0.44$, $p = .08$), and significantly with errors to dominant homographs ($r = 0.77$, $p < .001$) and subordinate homographs ($r = 0.61$, $p = .009$). The PANSS negative factor was correlated with errors to unambiguous associates ($r = 0.53$, $p = .02$), dominant homographs ($r = 0.52$, $p = .023$), and subordinate homographs ($r = 0.46$, $p = .046$). The SAPS total score correlated with errors to unambiguous associates ($r = 0.50$, $p = .042$) and subordinate homograph sentences ($r = 0.63$, $p = .007$). The PANSS positive factor correlated with errors to unambiguous congruent sentences ($r = 0.51$, $p = .025$) and moderately with unambiguous congruent errors ($r = 0.45$, $p = .054$). This suggests that overall negative symptoms as well as positive symptoms impact performance on the task, most likely in a general way. There was no correlation between the PANSS thinking disturbance factor and error rates or N400s to any sentence type. However a finer-grained analysis of symptoms revealed that conceptual disorganization was moderately correlated with errors to subordinate homograph sentences ($r = 0.43$, $p = .07$), and that deficit in abstract thinking was associated with the N400 response to subordinate homograph sentences ($r = -0.52$, $p = .023$) and unambiguous incongruent sentences ($r = -0.61$, $p = .005$). Both disorganization and concrete thinking clearly play a role in thought disorder.

Discussion

Patients had particular difficulty in comprehending subordinate meanings of ambiguous words, indicative of a semantic bias in schizophrenia. Controls showed a graded N400 response with smallest N400 to unambiguous associates with increasingly larger N400 to dominant homograph associates, subordinate associates, and unambiguous non-associates. The N400 amplitudes were all highly correlated across sentence types. To the extent that the N400 is indicative of the relative activation of semantic nodes, the graded responses are consistent with ordered-access of homograph meaning networks via pre-existing meaning frequency, at least at relatively long SOAs. Yet, in the lack of context to bias meaning activation at the initial homograph presentation, we cannot rule out context-mediated pre-selection, or the likely hybrid model combining contextual pre-lexical access bias and hierarchical meaning selection (Simpson, 1994). Further, these long SOAs likely are more sensitive to veiled controlled verbal working memory processes than to initial semantic activation. Very fast presentation rates should more clearly indicate the initial activation and any contextual biasing effects. We can say that N400 at long SOAs does appear to be sensitive to the nature of the homograph, with

smaller N400s overall and to subordinate meaning associates. It remains to be determined whether precisely matching associates between dominant-meaning networks and unambiguous networks would lead to differential N400 responses, a pattern that would suggest the structure of the semantic memory store can influence N400 even when ease of integration, presumably post-lexical access, is equated.

By contrast, schizophrenia patients showed no effect of word on N400 amplitudes, with N400 responses to unambiguous noun associates and dominant homograph associates being small and correlated, and N400 responses to subordinate homographs and unambiguous non-associates being large and correlated. The N400 to subordinate homograph associates was the largest in this group, although only attaining tend-level significant difference from unambiguous associates ($p = .09$). Along with the increased error rates in schizophrenia to subordinate and incongruent sentences, the pattern of results is consistent with preselection of the dominant homograph network in schizophrenia. Subordinate meaning networks at points of lexical ambiguity seem to be particularly difficult for schizophrenia patients to access. Yet, the overall increase in N400 across all sentences in schizophrenia patients indicate some problems with contextual integration, whether with maintenance or utilization.

Still, although the N400 responses seemed to be coupled between unambiguous words and dominant homographs and between subordinate homographs and incongruent endings in schizophrenia, the pattern did not attain significance. Hence, the present results, although suggestive of the pattern predicted by preselection of dominant networks at points of lexical ambiguity, cannot unequivocally support that hypothesis. Clearly, deficits in maintaining or utilizing activations in conceptual semantic space for all words is involved in schizophrenic thought disorder. The disambiguating words were presented 2.5 seconds after the initial homographs, which is likely to need active maintenance of the initial homograph meaning associations. Still, the suggestion that unambiguous networks were not maintained at all in schizophrenia while dominant homograph networks were is at least consistent with a pre-selection bias. Based on these and previous findings, we have proposed a hybrid model of combined semantic over-activation in the short term coupled with faulty verbal-working memory maintenance in the longer term in schizophrenia, the Activation-Maintenance Model of Schizophrenic Thought Disorder (Salisbury et al., 2004; revised Salisbury, 2008). The two processes work as follow: Semantic memory disinhibition leads to a wider spread of activation in the network in a bottom-up fashion during initial semantic activation. Nodes decay back below threshold unless maintained in verbal working memory with a relatively short time course. Schizophrenics are impaired at maintaining activations for longer periods of time and only the most strongly associated concepts will remain activated, creating a bias towards strong associates. Thus, at longer periods of time the verbal working memory content of the schizophrenic is controlled by the accelerated decay rate of the initially over-activated concepts. Due to the decaying trace, though, these items will have a residual activation closer to threshold, resulting in large N400 and delayed response times to all stimuli. At substantially longer intervals, the verbal working memory buffer will be empty and behavior will be random. Thus, the use of relatively long SOAs in this current project are likely to be towards the temporal limits of the putative initial activations, reflected in a blend between pre- and post-selection deficits.

This issue and several others have been addressed in our ongoing work. The ERPs were noisy and there were only 25 examples of each type of sentence. Patients had significantly fewer trials in averages for subordinate homograph and incongruous sentences, as would be expected from greater errors. Analysis of ERPs rejecting the 5 worst patients did not change the results. Clearly more trials are needed. Our current work has developed a larger corpus of stimuli, 50 + of each type, so that the signal to noise ratio in the ERPs can be improved, and behavior better assessed. Further, by definition dominant associates have stronger associative strengths

to homographs than do subordinate associates. Although all endings were generally only weakly associated with nouns in this study, there were differences in the associative strengths between sentence types. Our current research has precisely matched associative strength between the difference noun types and associates to obviate this potential confound. Our new protocols balance each homograph as a dominant or a subordinate meaning in separate subjects, and disambiguating words are precisely matched for frequency of usage in addition to associate strength. The use of a semantic judgement about the sensibility of the sentences also requires controlled processing, and may interact with identifying a bottom-up, automatic deficit. Our newer work uses lexical decision tasks to avoid deep processing of the semantic aspects of the words. Finally, the Activation-Maintenance model (Salisbury et al., 2004; Salisbury 2008) predicts that patients will be impaired at longer Stimulus Onset Asynchronies (SOAs), so even these short sentences will place demands on verbal working memory beyond the ken of patients. Our newer work uses fast versus slow presentation rates to try to separate bottom-up and top-down processes and deficits.

In summary, patients seem to be particularly impaired at accessing the subordinate meaning of words at points of lexical ambiguity. This deficit seems to be causally related to thought disorder. Not only does local context appear to trump global context, ala Cohen and Servan-Schreiber (1992), but the nature of the word itself as to its lexical ambiguity, appears to affect the train of thought. As speech is produced or interpreted by the patient, these switches at points of ambiguity may have substantial effect of the content and comprehensibility of thought. When coupled with deficit in maintaining or utilizing the larger picture of discourse context, high degrees of thought disorder can develop. Future work with greater control of semantic activation versus verbal working memory processes should help determine the contribution of each of these processes to schizophrenia thought disorder.

The patient sample had a fairly high mean WAIS Information scaled score. Thus, they could be considered a relatively cognitively intact group. The presence of abnormalities in this group suggests that the semantic and verbal working memory deficits reflected in this task may be an important and enduring substrate of thought disorder in schizophrenia, present even in relatively intact individuals. Further, we suggest that the language-related memory systems are a model system for study of schizophrenia, but that the underlying cortical circuit defect that leads to verbal memory failures spans multiple domains of memory, and is likely a fundamental and ubiquitous defect in cortical organization in schizophrenia.

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Figure 1.

Percent errors. Panel A: Raw percent errors to the sentence types. Panel B: Percent error adjusted by the base rate of errors to unambiguous noun, contextually congruent sentences. UNAMB: unambiguous nouns, congruent endings. DOM: Dominant homograph meaning associate ending. SUB: Subordinate homograph meaning associate ending. INCONG: unambiguous nouns, incongruent endings.

Figure 2.

ERP responses to terminal words. Note the large N400 response at approximately 400 ms. Controls show a graded N400, particularly at middle sites. Patients show overall more negativity, and responses to unambiguous nouns, congruent endings and dominant homograph meaning associate endings appear to group, while subordinate homograph meaning associate endings and unambiguous nouns, incongruent endings appear to group. UNAMB: unambiguous nouns, congruent endings. DOM: Dominant homograph meaning associate ending. SUB: Subordinate homograph meaning associate ending. INCONG: unambiguous nouns, incongruent endings.

Figure 3. N400 amplitude to the different sentence types in each group at the central (Cz) site. UNAMB: unambiguous nouns, congruent endings. DOM: Dominant homograph meaning associate ending. SUB: Subordinate homograph meaning associate ending. INCONG: unambiguous nouns, incongruent endings.