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Semantic Activation and Verbal Working Memory Maintenance in Schizophrenic Thought Disorder: Insights from Electrophysiology and Lexical Ambiguity

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Abstract

We have examined language processing using ambiguous words (homographs like panel or toast) and rapid or slow presentation rates while recording event-related brain potentials (ERPs). Homographs allow for tracking the train of thought at points of lexical ambiguity and detecting modulation of associative threads by previous context. Rapid presentation rates stress automatic semantic activation, and slow rates stress controlled verbal working memory contextual modulation. In conjunction with reaction times and performance, ERPs allow for objective measurement of activity related to language processing from word presentation through overt behavioral response. Smaller N400 to related and unrelated items at short stimulus onset asynchronies (SOAs), the presence of a semantic bias, and large N400 to related and unrelated items at long SOAs are present in schizophrenia. We describe a model of initial semantic memory hyper-priming and subsequent decay of information in verbal working memory stores, the *activation-maintenance model* of schizophrenic thought disorder hypothesized to underlie the thought disorder in schizophrenia.

Keywords

Event-related Potentials; Homographs; Hyper-priming; N400; Schizophrenia; Semantic Ambiguity; Semantic Memory; Thought Disorder

THOUGHT DISORDER AND SEMANTIC MEMORY IN SCHIZOPHRENIA

Since Bleuler's¹ description of the fundamental psychological aspects of schizophrenia, disordered associations have been considered a core feature. This thought disorder includes loss of abstraction ability, tangentiality, loose associations, derailment, thought blocking, and overinclusive thinking. Thought disorder may be related to a singular cognitive abnormality, but it is not known *where* in the information processing stream the abnormality occurs or *how* it arises. Like the specific cognitive deficit, the precise physiological abnormality underlying the association abnormality, and thus thought disorder, remains unknown.

Influential attention theories^{2,3} formed a framework for understanding automatic and controlled processes in the information processing stream. Collins and Loftus⁴ proposed words were stored in a conceptual space with automatic spread of activation (ASA) among related

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concepts as a function of “semantic distance.” This ASA is reflected in speeded responses to close associates, termed *semantic priming*.⁵

AMBIGUITY AND SEMANTIC MEMORY

Homographs have been used to probe priming and lexical access.^{6,7} Because context must be used to select the appropriate meaning network, homographs have been used to examine automatic and controlled processes in lexical selection. Typically, a prime, a homograph cue, and a probe word are serially presented (PCP paradigm, WRIST-PALM-HAND vs. WRIST-PALM-TREE). Congruent and incongruent homograph meaning targets are primed when presented under ~250 msec after the priming word, but only the contextually appropriate meanings were primed thereafter.⁶⁻¹⁰

BRAINWAVES AND SEMANTIC MEMORY

Brain activity is sensitive to semantic priming, reflected in the N400 event-related brain potential (ERP), a negative potential between 350 and 800 ms. The N400 is smaller when priming has occurred, and is large to incongruent sentence endings,^{11,12} unrelated words,¹³ and to weakly associated words.^{13,14} Although the precise function underlying N400 is unknown, it can be utilized experimentally as an index of lexical selection within ambiguous networks.

In the first ERP study of homographs in normal subjects, Van Petten and Kutas¹⁵ reported larger N400 to associates of the inappropriate homograph meaning at longer stimulus onset asynchronies (SOAs), suggesting inhibition of early automatic priming. At short SOAs, the ERP to nonappropriate associates was intermediate in morphology between unrelated and primed associate words. Swaab et al¹⁶ reported larger N400 to inappropriate homograph meanings in normal controls and Broca's aphasics. Our work¹⁷ demonstrated that at longer SOAs, N400 showed gradation from unambiguous associates (smallest), through dominant homograph associates, subordinate homograph associates, and unrelated words (largest), suggesting maintenance of meaning networks based on associative strength. Titone and Salisbury¹⁸ used the PCP paradigm, but asked subjects to determine only if the cue and probe were related. N400 was reduced by congruent prime context, but was less affected by incongruous context for dominant targets than for subordinate targets. Despite this initial work, there is at best scarce knowledge of the brain's activity to homographs at either fast or slow presentation rates.

EARLY AND LATE ABNORMALITIES IN SCHIZOPHRENIC SEMANTIC MEMORY

In thought disorder, a central issue is whether semantic memory structure affects the disordered train of thought, or whether such digressions are random. Schizophrenic error patterns are likely not random. In a series of papers Chapman et al.¹⁹⁻²¹ argued that schizophrenic thought was biased towards strong associates, even if contextually inappropriate (a semantic bias). 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, a strong possibility (see esp.²²). An alternative is excessive semantic activation, or hyper-priming. Our hypothesis is that hyper-priming of strongly related associates in schizophrenia leads to the preselection of dominant networks at points of ambiguity in ignorance of contextual cues.

A late attention abnormality with no bias predicts that schizophrenics will make errors unrelated to verbal content. A semantic bias predicts more errors to weakly associated items.

Both chronic and first-hospitalized schizophrenic subjects showed *significantly more comprehension errors* than controls to valid subordinate homograph meanings (Figure 1). Bipolar subjects showed increased errors to all words, indicative of a phasic disengagement of attention. A basic language deficit rather than a late attention abnormality must underlie the differential pattern of errors in schizophrenia. It remains unclear if this semantic bias reflects hyper-priming or the failure to use verbal working memory contextual information to inhibit initial ASA.

Both abnormalities likely exist. There is evidence for semantic hyper-priming in schizophrenia at short SOAs.²³⁻²⁶ Spitzer and colleagues²⁷ further showed that schizophrenics demonstrated increased second order priming (e.g., lemon primes sour, which primes sweet). Schizophrenics show greater initial activation in semantic networks.

At SOAs over 750 ms, schizophrenics appear to perform worse than controls to all words.²⁸ Cohen et al²⁹ argued for a pervasive late stage verbal working memory abnormality in schizophrenia with no semantic bias. However, the SOAs used were 1 and 5 sec. At both of these intervals, hyper-priming may not be apparent. Hagoort³⁰ showed that aphasics showed normal priming effects at SOAs of 100 and 500 ms, but not at 1250 ms. Time intervals approaching 1 sec may not accurately assess automatic processing. Still, it is likely that schizophrenics have abnormalities using context to modulate activation in semantic networks. Kuperberg, McGuire, and David³¹ showed that patients were little affected by preceding syntactic or semantic violations, suggesting less sensitivity to global linguistic context. Titone, Levy, and Holzman³² suggested that patients showed impaired controlled priming with weak biasing context, but normal controlled priming with strong context. Titone, Holzman, and Levy³³ compared priming following idioms 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 associates, but normal priming to abstract associates. Titone and colleagues³³ argued that context was inefficiently used in schizophrenia. Verbal memory context is either deficient or under utilized.

N400 ON A PASSIVE READING TASK

Our program of research uses N400 to examine activation patterns within ambiguous networks to examine semantic activation and verbal working memory processes. The first experiment³⁴ examined N400 to sentence-ending words that disambiguated homographs in a passive reading task. Four word long sentences were presented with long SOAs (*The panel was oak*, *The panel was voting*). Patients showed larger N400 to subordinate meanings (Figure 2, Panel A), consistent with a semantic bias. However, a large N400 was elicited by all sentence endings in the patients relative to controls, suggesting a broad problem in context maintenance.

To assess whether the large N400 above was due to inattention, schizophrenics were required to make sensibility judgments.³⁵ Patients showed a *disproportionate* increase in the number of subordinate sentences judged nonsensical (see Figure 1), and increased N400 on subordinate sentences (Figure 2, Panel B), consistent with a semantic bias. Yet, patients showed large N400 to all endings, suggesting pervasive memory maintenance failure. Still, this experiment showed that the large N400 could not be accounted for by inattention.

Next, subjects were presented sentences containing 2 clauses.³⁶ The first clause biased subjects to one homograph meaning. The second clause contained a probe associate of the dominant meaning. Controls showed increased N400 to the probe with subordinate context, but patients did not. That schizophrenics generated N400 to semantic violations for unambiguous words argues against total memory maintenance failure, although the N400 effect was diminished relative to controls. Thus, although this experiment showed the presence of a semantic bias in schizophrenia, it did not fully elucidate the underlying mechanism.

To separate the semantic incongruity N400 effect from the homograph semantic bias effect, we presented dominant and subordinate homograph sentences and congruent and incongruent sentences.^{17,37} Patients were moderately poorer in detecting semantic incongruities, but showed a marked semantic bias to misunderstand subordinate homographs. By contrast with the graded response observed in controls, the N400 in patients was large to subordinate homographs and nonassociates, and small to dominant homographs and unambiguous associates (Figure 3, Panel A). Once again, however, the N400 was generally more negative in schizophrenia to all sentence types.

To determine if the semantic bias in schizophrenia was due to hyper-priming or memory maintenance failure, we isolated semantic memory from verbal working memory by using short versus long SOAs. Preliminary analysis³⁸ replicated the graded response to the different semantic network types in controls at long SOAs, where patients showed pervasive verbal working memory maintenance failure, with more N400 activity and virtually no modulation of N400 by network type (Figure 3, Panel B). However, at short SOAs, controls seemed to preferentially access the dominant homograph meaning and patients seemed similar to controls, with preferential activation of dominant homograph networks (Figure 3, Panel C). Importantly, they showed N400 evidence of hyper-priming, with *less N400 activity at short SOAs*, replicating Mathalon et al.³⁹

DISCUSSION

Our data showed that the N400 ERP was a sensitive index of semantic network structure, that schizophrenia showed both semantic hyper-priming and verbal working memory impairment, and that disordered thought in schizophrenia was not a random process, but was characterized by a semantic bias.

Hyper-priming in schizophrenia may be due to increased dopaminergic tone.²² Alternately, hyper-priming may reflect too great a spread of activation related to local circuit inhibitory GABAergic defects in neuronal selectivity tuning.⁴⁰ Though highly speculative this may help relate the cognitive abnormality to a general physiological deficit in schizophrenia. Relative overactivation of pyramidal processing units coupled with decreased inhibitory interneuron activity may underlie a vast array of deficits in schizophrenia, with the lexical selection abnormality described here but a single example.

Abnormalities of verbal working memory in schizophrenia were reflected in increased amplitude of the N400 ERP to all stimuli at long SOAs. This N400 increase was observed in schizophrenia even when the semantic relationships between words were correctly detected. This suggests deficits in maintenance rather than utilization, though the matter is still open.

Based on the pattern in schizophrenia of smaller N400 to related and unrelated items at short SOAs, the presence of a semantic bias, and large N400 to related and unrelated items at long SOAs, we proposed a dual model of initial semantic memory hyper-priming and subsequent decay of information in verbal working memory stores, the *activation-maintenance model* of schizophrenic thought disorder.³⁵ Semantic memory disinhibition leads to a wider spread of activation in the network. Related concepts are excited automatically as a function of their associative strength. They decay back below threshold unless maintained in verbal working memory. Schizophrenics are impaired at maintaining activations for longer periods of time and thus in utilizing that information to shut off contextually inappropriate associates. Since verbal working memory is not well maintained, traces decay and by 1 sec only the most strongly associated concepts will remain in the buffer, creating a bias towards strong associates. Over time (> 1 s) 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 close to threshold, resulting in large N400 and delayed response times. At longer intervals, the buffer will be empty and behavior will be random.

We here amend the model by suggesting that verbal working memory is not entirely faulty. Thus the decay rate of items in schizophrenia is not exactly that of semantic activation, but a slightly slower rate of a faulty verbal working memory maintenance module. Thus, schizophrenia patients will show decreased expectancy-based priming at slow rates due to impairment in full utilization of contextual information. N400 will be reduced with hyper-priming at short SOAs, but at slow presentation rates N400 will be increased in schizophrenia. Schizophrenics will show impaired N400s in expectancy priming situations, as they will be governed by semantic priming. This will be exacerbated when expectancy-based and semantic priming are placed in opposition. However, explicit rule explanation and extremely strong biasing context will give patients some benefit, as their controlled processes are impaired, but not completely absent. Future work isolating “bottom-up” automatic activation versus “top-down” controlled processes should help expand understanding of the basic memory deficits underlying schizophrenic thought disorder.

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Figure 1.

Comprehension errors on a homograph disambiguation task in chronic and first hospitalized psychosis. Congruent: Semantically congruent endings for unambiguous nouns. Dominant: Semantically congruent endings for dominant homograph noun meanings. Subordinate: Semantically congruent endings for subordinate homograph noun meanings.

Figure 2.

Panel A. N400 ERPs on a passive reading homograph disambiguation task in chronic schizophrenia. Note the largest N400 to subordinate homograph endings, but large N400 to all sentences in schizophrenia. (After Salisbury et al.³⁵ 2002.) Panel B. N400 ERPs on an active comprehension of homograph disambiguation task in chronic schizophrenia. Note the large N400 to subordinate homograph endings that made sense in schizophrenia (Subordinate) is as large as their N400 to subordinate endings they did not comprehend (Subordinate Errors), whereas controls showed modulation by comprehension. (After Salisbury et al.¹⁷ 2004.)

Figure 3.

Panel A. Graded N400 responses in controls is absent in schizophrenia. (After Salisbury et al.,³⁷ In Press). Panel B. The lack of graded N400 response to different word types in schizophrenia at slow presentation rates confirmed in a new sample. Panel C. Note that with fast presentation rates, the graded response disappears in controls, with as large N400 to subordinate meaning endings as to incongruent endings. The N400 is smaller here in schizophrenia.