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REVIEW

Episodic Memory in Schizophrenia

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Abstract Episodic memory impairments in individuals with schizophrenia have been well documented in the literature. However, despite the abundance of findings, constituent cognitive, neural, behavioral, and genetic components of the deficits continue to elude full characterization. This review provides a characterization of these deficits by organizing findings within three frameworks of interest: 1) neuroanatomical; 2) genetic; and 3) behavioral. Within each approach, evidence from imaging studies as well as behavioral studies is examined. The hope is that by synthesizing the cognitive science paradigms, molecular genetic neurophysiological findings, and computational algorithms applied to medial temporal lobe subregions, we will be able to expand our understanding of the types of compromises in episodic memory systems of individuals with schizophrenia.

Keywords Episodic memory · Schizophrenia

Introduction

Pervasive cognitive deficits have been observed in patients with schizophrenia, albeit with a substantial degree of inter-individual variability. Episodic memory is one function which has been shown to be robustly compromised in this patient population (see, e.g., Aleman et al. 1999; Danion et al. 2007; Lepage et al. 2007). Taken as a whole, the literature suggests that this domain is deficient; however, findings have not been unequivocal.

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Methodological differences may be responsible for discrepant findings even at a gross level of memory processing. For example, studies that have variably employed verbal and nonverbal stimuli to measure episodic memory have found some studies reporting reliable impairment in schizophrenia patients on visual episodic memory tasks (Heinrichs and Zakzanis 1998), and others reporting greater impairment in verbal memory measures (Flor-Henry 1990, Taylor et al. 1979, Taylor and Abrams 1984). Whether these differences in material reflect lateralized dysfunction of neural systems or cohort effect remains to be determined. Discrepancies in recognition generally considered a measure of familiarity with previously observed stimuli as opposed to more detailed recollections that includes knowledge of context have been noted for schizophrenia patients, with findings ranging from intact to severely impaired (as reviewed by Danion et al. 2007). It is unclear if they are psychometric artifacts due to difficulty level, valid differences in effortful retrieval, or encoding adequacy.

A number of excellent reviews have elucidated multiple aspects of episodic memory impairment in schizophrenia, among them Ranganath et al. (2008). In their paper, they identify evidence for disruption of underlying mechanisms of memory systems in patients, and draw the conclusion that disentangling item-specific memory from relational memory may represent an important starting point, particularly in terms of treatment development. What is somewhat confounding about this, and other reviews and initiatives, is why a domain which has proven to be so replicably compromised in schizophrenia continues to elude full characterization of the constituent cognitive, neural, behavioral, and genetic components.

In 1972, Tulving distinguished episodic memory from other types of memory by stipulating that it must be

embedded in a context; that is, the representation results from the integration of item and temporospatial context into an episode (Tulving 1972). A further qualifier to distinguish this memory type from others was proposed by Conway in his model (2001), which specified that episodic memories do not endure unless they are highly significant for the self and become linked to autobiographical memory structures. As such, a reasonable assumption would be that due to the complexity of this particular type of information, the formation, storage, and retrieval of episodic memories necessarily involves multiple brain regions. Candidate regions implicated in episodic memories include medial temporal lobe structures such as the hippocampus and perirhinal cortices, as well as linked parahippocampal gyral regions including entorhinal cortex, which appear to be largely involved in encoding; in concert with regions of the prefrontal cortex (see, e.g., Heckers et al. 1998, 2000), which may be more instrumental in recollection.

Here, we have undertaken to review the literature from a methods-driven perspective. That is, we have examined studies of episodic memory impairment in schizophrenia which variably employ: 1) a neuroanatomical-based model; 2) behavioral manipulations; and 3) genetic methods. Within each of these approaches, we address behavioral findings and imaging findings. By examining the extant literature from this perspective, it is our hope that we will begin to better discern fundamental commonalities in the memory deficits seen in this patient population.

In Vivo Functional Mapping Approaches

Specific neuroanatomic regions have been shown to be abnormal in patients with schizophrenia, most notably and consistently, the hippocampal and parahippocampal regions (Vita et al. 2006). Therefore, a number of studies have taken as their starting point the notion that dysfunction here, and in ancillary brain regions which comprise networks involving MTL (namely, prefrontal cortical regions), may be responsible for episodic memory difficulties. A selective review of the schizophrenia literature that expressly investigated neuroanatomical regions involved in episodic memory or a related process follows.

There is mounting evidence for involvement of non-MTL regions in the neurophysiological literature on episodic memory processes. Most clearly implicated are regions of prefrontal cortex. A recent meta-analysis comprising 18 imaging studies of episodic memory in individuals with schizophrenia found that the regions showing the most consistent differences between patients and controls were located in the prefrontal cortex and in the temporal lobe (Achim and Lepage 2005). Moreover, it was the left inferior prefrontal cortex that proved to most reliably distinguish controls from patients. This region was found to be consistently more active in controls than patients during both encoding and retrieval, relative to baseline conditions. These authors juxtapose their neuroanatomical finding with a brief review of behavioral literature supporting the notion that when explicitly instructed to employ a deep elaborative encoding strategy, patients were able to effectively engage the same regions as controls (for more on this, see Behavioral section below).

A seminal study by Heckers and colleagues investigated activation within dorsolateral prefrontal cortex and hippocampus during verbal episodic memory retrieval in patients with schizophrenia (Heckers et al. 1998). Positron emission tomography (PET) was employed to observe activation during a cued recall task utilizing words that were either studied using a shallow or deep encoding task. Differences were found between groups both behaviorally and in the PET data. Patients showed increased activation in right parietal cortex and right prefrontal areas during recall of shallowly encoded words, which, unexpectedly, was achieved with greater accuracy than controls. This is possibly reflective of greater exertion of effort by the patients throughout the task. In contrast, patients were less accurate when required to use the deep encoding strategy, and showed a reduction of hippocampal activation during recollection of these words. In this condition they did, however, show significantly greater activation than controls in the following regions: left and right inferior parietal regions and right prefrontal regions. These areas are more commonly associated with attentional processing and retrieval. These findings suggest that patients were unable to benefit from higher-level semantic encoding and/or may be engaging a strategy which employs structures distinct from those commonly activated by healthy controls. The researchers posited that a combination of increased hippocampal activation at baseline coupled with impaired recruitment during episodic memory retrieval might reflect abnormal corticohippocampal interactions in schizophrenia. A recent behavioral study that examined the effects of varying levels of encoding nicely complements these findings: Paul et al. (2005) required 21 patients and 26 controls to encode words shallowly, deciding whether the letter "a" was in the word; or deeply, making a semantic (living/non-living) judgment about the word. While patients performed more poorly overall on a recognition task, they were aided by semantic encoding to the same degree as healthy controls (i.e., no group x encoding interaction was found). Another behavioral study used varying levels of interference on a list learning task, hypothesizing that patient performance would be disproportionately hindered by increased interference (Elvevag et al. 2000). Here again, patients failed to show a disproportionate performance decrement in comparison to controls; they were not more susceptible to interference when the overall error rate was

controlled for. What these studies highlight is the problem that classic behavioral manipulations fail to do much in the way of elucidating behavioral aspects of the memory systems of patients that neuroanatomical findings suggest are impaired.

In another study by the Heckers group, PET was employed to investigate the performance of patients with schizophrenia on tasks of visual episodic object recognition wherein three neuroanatomical regions were implicated: MTL, prefrontal cortex (PFC), and thalamus (Heckers et al. 2000). The task used was exposure to novel visual stimuli (line drawings of novel 3D objects, "possible objects"); subjects (9 patients, 8 controls) were to make a judgment as to whether the object would best be used as a tool, or for support (e.g. stepping, sitting, or leaning on). Patients showed attenuated right thalamus (pulvinar) and right prefrontal cortex regional cerebral blood flow during recognition of new objects, and increased left prefrontal cortical activation during (poor) recognition of previously seen visual stimuli. Behaviorally, patients demonstrated rates of false alarm similar to control subjects, but significantly lower recognition rates for previously presented objects (i.e., hits). An interesting implication of the right thalamic reduction of activation is that this region is uniquely involved in attentional processes necessary during the encoding stage of memory for novel visual objects. Consistent with this finding are recent reported functional and/or structural abnormalities of the thalamus in schizophrenia, as reviewed in Heckers et al. (2000) (e.g., Andreasen 1994; Andreasen et al. 1996; Arciniegas et al. 1999; Buchsbaum et al. 1996; Hazlett et al. 1999). The finding of increased left prefrontal activation during impaired recognition of previously seen stimuli is interestingly contrasted by the pattern for normal subjects, who exhibited an increase of right prefrontal activation. As such, the patient response is more consistent with what would be expected in response to verbal (semantic/phonological) stimuli. It is unclear whether this finding is indicative of patients' failure to inhibit this circuitry, failure to activate right prefrontal circuits, or simply the employment of a different strategy. Limitations of the study include an all-male sample of chronic, medicated patients; also, inter-individual differences in brain structure were not taken into consideration.

Using functional magnetic resonance imaging (fMRI), Ongur and colleagues (2006) investigated the neuroanatomical regions associated with relational or associative memory, the ability to learn associations between individual items. Such relational or transitive inference processing may be a feature of episodic memory formation that reliably engages the hippocampus, and some evidence suggests that this type of memory may be selectively impaired in individuals with schizophrenia (as reviewed in Lepage et al. 2006). A task was employed which relies on one form of relational memory, transitive inference, the ability to infer that A>C, knowing that A>B and B>C. A deficit in transitive inference would suggest an inability to benefit from prior learning when making novel inferences. Stimuli used were pattern-filled pentagonal and ellipsoid shapes. Twenty schizophrenia patients and 17 controls had to make discriminations of previously seen and novel pairs of visual stimuli. The behavioral results indicated that after learning a sequence (A>B, B>C, C>D, D>E), patients were able to make correct discriminations of the end pair (AE), but not when making a novel discrimination regarding an embedded pair (e.g., B>D). The imaging data revealed that during sequence learning, patients demonstrated normal activation in presupplementary motor areas typically activated in this type of processing: ventral prefrontal cortex and posterior temporal cortex. However, they showed significantly decreased activation of right parietal cortex and anterior cingulate cortex. The parietal cortex has been proposed as an area involved in the storage of flexible representations of stimuli; the implication is that patients with schizophrenia have a fundamental parietal cortical deficit leading to impairments of relational memory. Between-group differences in hippocampal activation were shown only during the so-called BD trials; that is, trials in which both stimuli had an ambiguous reinforcement history. Only then did patients show reduced activation of left anterior hippocampus. As the authors point out, this study was comprised of patients whose hippocampal volumes were found to be normal, in contrast to many other studies. This could be considered a limitation as they may not be a representative sample, but could also be considered an advantage in that it avoids a volume confound in interpreting hippocampal activation patterns. Another point of concern regards the fact that the findings were predicated on the presentation of only eight embedded pairings, which raises the question of whether transitivity judgments were truly being made, or whether a visual discrimination processing abnormality accounted for the finding of parietal cortical hypoactivation in patients (see Goldberg comment, www.schizophreniaforum.org, posted June 19, 2006).

On the theoretical basis of the notion that memory for items and memory for associations involve partially different processes and MTL regions, another group also investigated this particular memory process in individuals with schizophrenia (Lepage et al. 2006). Given the evidence for modulation of activity in the hippocampal region and prefrontal cortex in healthy controls during tasks of associative memory encoding relative to item encoding, it was hypothesized that a selective associative memory deficit in patients with schizophrenia may be explained by dysfunction in these regions. 15 individuals with schizo-

phrenia and 18 controls were scanned while either encoding stimuli (color clipart single images or pairs of common objects such as animals and insects) or performing a recognition task (for items, old vs. new; for pairs, those that were seen paired before vs. rearranged pairs). Behaviorally, patients performed significantly worse on the associative recognition task, but not on the item recognition task. At the neuronal level, during associative encoding relative to item encoding, healthy controls showed greater activation than the schizophrenia group in the following regions: left dorsolateral prefrontal cortex, right inferior prefrontal cortex, left globus pallidus, left putamen, left premotor cortex, left precuneus, right superior temporal gyrus, and right cerebellum. During recognition, regions that exhibited greater activation in controls relative to patients included a left dorsolateral prefrontal region, a right ventrolateral prefrontal region, two medial frontal regions, a left precuneous region, the superior parietal lobule bilaterally, the left middle temporal gyrus, and the right lingual gyrus. Notably and unexpectedly, MTL was not an area that distinguished controls from patients in this study. The authors suggest that hypoactivation in superior parietal regions may suggest that patients have difficulties at the level of forming representations and relations between memory items. Moreover, the contribution of prefrontal regions to the decisional aspects of recognition memory judgments, as well as conscious recollection and the ability to monitor retrieved information in order to guide recognition memory judgments may be impaired in individuals with schizophrenia.

Another group used fMRI to investigate the differential effects of adopting an incidental versus intentional verbal encoding strategy in patients with schizophrenia (Bonner-Jackson et al. 2008). Prior findings suggested that deficits in episodic memory are more attributable to a fundamental decrement of encoding rather than retrieval (e.g., Talamini et al. 2005, described below). Furthermore, patients have shown recognition memory improvements when oriented to use specific encoding strategies, such as making abstract/concrete judgments or living/non-living judgments for words (as reviewed in Bonner-Jackson et al. 2008; see also Gold et al. 2006). Here, 18 individuals with schizophrenia and 15 healthy controls were asked to make concrete/abstract judgments for each of 50 visually presented words in the Incidental encoding condition; during Intentional encoding, they were instructed to memorize each word for a later memory task. After, participants were given a free recall test and a recognition test. Behaviorally, both patients and controls demonstrated better recognition for items encoded incidentally, with patients showing worse recognition overall. Both groups demonstrated better free recall after intentional encoding; controls again performed better than patients overall. Fewer differences in activation were seen between patients and controls in the Incidental encoding condition than in the Intentional condition. In the Incidental encoding condition, patients showed intact activation in areas typically associated with verbal encoding (left inferior frontal gyrus) while learning items that were subsequently retrieved. During intentional encoding, controls activated a wider network of brain regions than patients, including regions of right inferior frontal gyrus and right parahippocampal gyrus. During encoding of words that were subsequently remembered, controls demonstrated significantly greater activation in left inferior frontal and right middle frontal gyrus. Patients with schizophrenia showed greater activation during encoding of subsequently remembered words in left precuneous. In sum, the Group x Encoding Strategy interaction was driven by significantly greater activation of a large network of regions by controls during the unsupervised but Intentional encoding condition. This suggests that when prompted to do so, individuals with schizophrenia recruited brain regions—including left inferior frontal gyrus, left inferior temporal gyrus, and right inferior parietal lobule—that healthy controls utilized automatically. Further, these results suggest that when memory strategies are provided, schizophrenia patients activate the same neural systems implicated in memory formation as healthy controls.

There is growing evidence for the role of regions outside of MTL in the storage of remote memories in healthy individuals. A recent fMRI study by Smith and Squire (2009) in healthy controls found evidence for increased activity in frontal, lateral temporal, and parietal cortical regions as news items subjects were required to recall became increasingly remote. Importantly, there were no regions in MTL (hippocampus, temporopolar cortex, and amygdala) that exhibited this pattern of activation; here, as items became more remote, a decrease in activity was observed. These findings support the notion of the time-limited role of the hippocampus in the formation and maintenance of memory. As such, applying a similar paradigm to individuals with schizophrenia may allow us to identify the neuroanatomical regions of dysfunction which figure most prominently in the deficits exhibited by patients, who show evidence of impairments in both delayed and immediate recall (see, e.g., Egeland et al. 2003; Moritz et al. 2001), which would argue more strongly for dysfunction of MTL regions during initial encoding, but recruitment of ancillary regions in a temporally graded manner. Determining whether just such a temporal gradient across neuroanatomical regions can be identified in patients will elucidate yet another aspect of the integrity of their memory systems, with specific regard to their storage processes.

A series of recent fMRI studies have investigated abnormal fronto-temporal activation and connectivity dur-

ing episodic memory tasks in schizophrenia (Ragland et al. 2004; Weiss et al. 2006; Wolf et al. 2007). In one study, 14 patients and 15 controls performed a word encoding and recognition task in the scanner (Ragland et al. 2004). Behaviorally, patients demonstrated lower recognition discriminability than controls. Imaging data revealed hypoactivation of bilateral PFC coupled with hyperactivation of parahippocampal regions in patients during encoding. Effective retrieval in patients was associated with a unique pattern of activation including greater activation of orbitofrontal, superior frontal, mesial temporal, and inferior parietal regions. In contrast, the activation pattern seen in controls during retrieval included greater activation of right dorsolateral prefrontal cortex. These same data were used in a subsequent investigation in which within-subject correlations were performed to measure functional connectivity during verbal encoding (Wolf et al. 2007). Relative to controls, patients had reduced connectivity between the dorsolateral prefrontal cortex and temporal lobe areas including parahippocampus and superior temporal gyrus, but increased connectivity between ventrolateral prefrontal cortex and the same temporal lobe regions.

Another group required 16 patients and 16 controls to perform a word list recognition task while making old/new (previously seen vs. not seen) distinctions (Weiss et al. 2006). The findings were unexpected, mirroring the discrepancy between behavioral and imaging results that was touched upon in the Achim and Lepage (2005) review: patients demonstrated nearly identical memory performance to that of controls, but showed significant differences in activation patterns, particularly within the PFC. Unlike their matched controls, patients failed to show increased activation of four discrete areas within right prefrontal cortex when shown previously viewed stimuli. In addition, controls who demonstrated the most efficiency incorporating contextual information to make accurate decisions about previously seen items showed the greatest modulation of hippocampal activation; this modulation of hippocampal activation was not demonstrated by patients, even those in a "high-performing" subgroup. The striking discrepancy between the behavioral and imaging findings of this study points to the need for work which addresses this seeming paradox. The Behavioral section that follows is a selective review of the literature with an eye to those behavioral aspects of episodic memory that may serve as a starting point for distinguishing specific contributions of neuroanatomic regions of interest.

Hippocampal volume reductions and abnormal patterns of activation within neural structures may be only part of the story. Parahippocampal connectivity abnormalities have been hypothesized as the neural origin of episodic memory deficits seen in schizophrenia; in a recent study, this supposition was investigated *in silica*, through the use of a computer simulation model (Talamini et al. 2005). The parahippocampal region includes the entorhinal, perirhinal, and parahippocampal cortices, and it is here that the largest volume deficits within the MTL have been observed for patients. In addition, reductions in density of synaptic and dendritic molecules have been found here. Therefore, the simulated model aimed to produce a pattern of deficits similar to those seen in patients with schizophrenia—a mild impairment in recognition and a more severe impairment in free recall. The model was based on the notion of dual pathway streams conveying both object-based and contextual information (broadly, 1) perirhinal to anterior and lateral entorhinal cortex, and 2) parahippocampal cortex to medial posterior entorhinal cortex), and a two-step binding process for episodic memory storage that serves to maximize the storage capacity of the memory store. A model was generated that was able to perform free recall as well as recognition tasks with accuracy consistent with that generally observed in healthy controls. Reduced connectivity at two levels, inputs to the entorhinal layer and entorhinal outputs to the hippocampal module, resulted in a preferential reduction of free recall and a mild deficit in recognition, thus providing a pattern of deficits that was consistent with those seen in patients with schizophrenia. The selectivity of this model was key to replicating the specific pattern of episodic memory deficits of schizophrenia patients; models with increased noise and decreased hippocampal nodes resulted in a pattern of deficits consistent simply with damage to the hippocampus proper. The authors suggested that the implication of reduced connectivity is an inability to make effective cross-associations of episodic features, and that this represents a fundamental impairment of encoding, which may have heretofore been misidentified as a retrieval deficit.

Taken together, the episodic memory literature reviewed here includes the following findings for schizophrenia patients relative to controls: increased activation in right PFC during recall and recollection of words and decreased hippocampal activation during recollection (Heckers et al. 1998); decreased activation of right PFC and increased activation of left PFC during recognition of visual stimuli (Heckers et al. 2000); decreased activation of left anterior hippocampus when making transitive inference judgments during a relational memory task (Ongur et al. 2006); decreased activation of left dorsolateral PFC, right inferior PFC, left globus pallidus, left putamen, left premotor cortex, left precuneus, right superior temporal gyrus, and right cerebellum during visual encoding (Lepage et al. 2006); decreased activation of bilateral PFC and increased activation of parahippocampal regions during word encoding (Ragland et al. 2004); and decreased activation of right prefrontal cortex during recognition for words (Weiss et al. 2006). Clearly, the findings are not straightforward and

sometimes prove to be contradictory. Indeed they cannot easily be reconciled with a sophisticated meta-analysis of the functional neuroimaging data conducted by Achim and Lepage (2005), which most robustly implicated left inferior prefrontal cortex in the episodic memory dysfunction seen in patients. We note that the Achim and Lepage meta-analysis was published in 2005; most of the literature reviewed here was conducted subsequently and as in any meta-analysis, the results will be driven by all studies selected, not only those with the greatest "merit."

Behavioral Approaches

A wide range of behavioral investigations of episodic memory impairment in schizophrenia have been conducted. The articles reviewed herein focused on delayed recall, source monitoring, false memories, item versus relational memory, recognition versus retrieval, and strategy use. While we do not endeavor to comprehensively review all of the behavioral literature to date, the interested reader can refer to a recent review of behavioral studies of episodic memory by Danion et al. 2007; for a meta-analysis of behavioral studies of episodic memory, see Aleman et al. 1999. In addition, it is important to note that while a number of excellent investigations of memory have employed classical conditioning paradigms (e.g., emotional memory, Holt et al. 2009); we have chosen not to include these here, as we believe that these may be tapping processing networks not explicitly involved in episodic memory.

Delayed recall in schizophrenia may hold important implications for underlying neurobiological mechanisms of long-term potentiation (LTP). Specifically, the mechanisms implicated in the induction of LTP may differ from those involved with the late phase of LTP (as described in Skelley et al. 2008). A recent study administered episodic memory measures at three recall stages: immediate encoding, 30 minute recall, and 24 hour recall (Skelley et al. 2008). Subjects were schizophrenia patients, their non-psychotic siblings, and controls; verbal and visual materials were used. Findings revealed marked impairments in patients at all recall intervals, for both verbal and visual information. Siblings demonstrated recall impairments for verbal materials at all time intervals, but nearly normal performance for visual recall across trials. In terms of savings, or percentage retained in a given trial from the previous trial, patients had impaired short delay savings for visual and verbal information; after 24 hours, the savings differences between patients and controls were still evident (though not significant) for verbal, but not visual material. Siblings demonstrated normal savings over all time intervals for both types of information. As such, these results point to verbal learning deficits (distinct from memory over a delay) as a robust intermediate phenotype for schizophrenia. This may implicate relatively intact mechanisms for late-phase LTP in schizophrenia; in contrast, systems involved in the induction of LTP, which are more reliant on *N*-methyl-D-aspartic acid (NMDA) and AMPA receptors, are more likely impaired. (For a discussion of disruption of late-phase LTP in schizophrenia, see the Discussion section below).

Source monitoring is a feature of cognition in individuals with schizophrenia that may be disrupted, and in turn impinge on the integrity of their memory systems. Keefe and colleagues investigated this deficit, which has been referred to as autonoetic agnosia, or an inability to identify self-generated mental events (as described in Keefe et al. 2002). 29 patients and 19 controls were asked to remember words that were identified either through pictures, word-stem completion (self-generated), or heard (as read by an examiner). They were asked to remember the item and the source of the item (picture, self-generated, heard, or new). Relative to controls, patients demonstrated deficits in monitoring the source of self-generated information, but not visual and auditory information. However, in terms of their recognition for material, patients demonstrated significant deficits that were present regardless of the source of the information. That is, they had poorer recognition for both self-generated and picture items, and showed a nonsigificant trend for recognition deficits for heard words. Furthermore, this pattern was seen in patients both with and without target symptoms (auditory hallucinations, thought insertion) for self-generated items. The patients with the target symptoms did worse recognizing the externally perceived (picture or heard) items. As such, these results fail to support the notion that disrupted source monitoring is responsible for recognition memory deficits. In a large sense, the study illustrates that when overall memory performance is carefully taken into account, many presumptive differences in specific subprocesses cannot be observed.

False memories have been an area of some interest for understanding the nature of memory dysfunction in schizophrenia and some positive symptoms including delusions, which may be related to episodic memory systems. There have been a handful of studies that actually found patients to be less susceptible to false memories than controls (as reviewed in Moritz et al. 2006). One theory to explain this pointed to different underlying cognitive mechanisms in patients than controls; namely, during encoding, controls may be engaging in a sustained spreading of semantic activation (Moritz et al. 2004). In patients, this process may be reduced or absent due to attentional problems or an inability to engage in sustained spreading of semantic activation for longer periods of time (Moritz et al. 2006; Roediger et al. 2001). The deficit exhibited by patients in associative strength of memories at the cognitive level may hold implications for dysfunction of connectivity at the neural level.

Similarly, Elvevag et al. (2004) investigated the notion that patients engage in a 'gist-based' strategy during retrieval and recognition, rendering them more susceptible to foil items. After being exposed to word lists organized around a semantic theme, 22 patients with schizophrenia were compared to 25 control subjects in terms of their susceptibility to semantic lures on a recognition trial, or in a separate free recall trial. The results indicated that patients did not make more false recognition errors overall and in fact made disproportionately fewer false recognition errors to semantic lures than controls. This might lend support to the notion of connectivity deficits, if 'gist-based' inferences are reliant on intact associations.

Another recent study attempted to test this model using visual rather than verbal stimuli (Moritz et al. 2006). The emotional content of the stimuli was manipulated to determine whether patients with current paranoid symptoms would demonstrate better recognition for mood-congruent (i.e. delusion) material as well as greater false recognition of this material. The results revealed a similar rate of false memories for patients and controls, a finding that was not moderated by emotional valence of the stimuli. Where patients and controls differed was in the confidence that they ascribed to their answers. Patients tended to be under-confident for correct responses and over-confident for incorrect responses. These findings may relate more to meta-memory functions that to memory processes per se.

Genetic Approach

Employing a genetic model provides the enticing possibility of uncovering one unitary explanation that can synthesize seemingly paradoxical or difficult to reconcile behavioral and imaging findings of episodic memory impairments in schizophrenia. To that end, a growing literature has attempted to identify the underlying genetic components specifically involved in schizophrenia. Episodic memory deficits have been proposed as one element in an allied neurocognitive phenotype for schizophrenia and bipolar disorder, along with attention, working memory, and emotion processing (Hill et al. 2008). In their review, Hill and colleagues pointed out that establishing such a phenotype may help to identify illness-related gene variants and to complete the gaps between genetic expression and clinical presentation (see also Meyer-Lindenberg and Weinberger 2006, for suggested intermediate phenotypes). Evidence for a genetic basis for deficits in episodic memory has been provided by studies of high-risk adolescents and unaffected family members of patients, as well as neuroanatomical findings of temporal lobe and hippocampal volume reductions in unaffected relatives (reviewed by Hill et al. 2008). A recent finding suggested that a functional polymorphism in brain derived neurotrophic factor (BDNF), which is known to play a part in early and late phase long-term potentiation (LTP), may result in medial temporal lobe (MTL) volumetric differences, which may in turn play a role in genotype based differential engagement of the MTL, and ultimately, behavioral memory differences (Goldberg et al. 2008).

Candidate genes for memory disruption in schizophrenia have been selected on the basis of reported associations. These include an allelic variation of the so-called disrupted-in-schizophrenia 1 (DISC1) gene, and the DAOA (D-amino acid oxidase activator) gene (also known as G72). One group recently looked at DISC1, a candidate gene that is expressed predominantly within the hippocampus (Callicott et al. 2005). Evidence for a causal relationship between DISC1 and memory functions has recently been reviewed (see Hennah et al. 2006). The Callicott group identified an allelic variation, the Ser allele of so-called single nucleotide polymorphism (SNP) 10, within DISC1 that was associated with increased risk for schizophrenia. The putative mechanism underlying this association involves structural and functional alterations in the hippocampal formation. In their analysis of normal subjects, they found that Ser homozygotes had significantly reduced hippocampal gray matter volume bilaterally; these effects were not related to age or gender. Additionally, patients with schizophrenia who were Ser homozygotes had significantly lower left hippocampal formation neuronal integrity (as measured with proton magnetic resonance spectroscopy measures of the intraneuronal marker *N*-acetylaspartate). In terms of cognitive performance, homozygous Ser patients did worse on Logical Memory II of the Wechsler Memory Scale. Furthermore, distinct patterns of hippocampal activation during cognitive tasks as measured by fMRI were observed in subjects possessing the Ser allele; specifically, decreased activation of hippocampal formation during encoding and retrieval of neutral scenes. In addition, overactivation of the hippocampal formation during tasks of working memory (when this area should be disengaged) was observed in Ser subjects; this pattern is consistent with findings for patients and their healthy siblings.

Another group investigated the same SNP, but their findings were not convergent with those of the Callicott group (Di Giorgio et al. 2008). Eighty healthy controls were scanned during encoding and retrieval of novel, complex scenes of neutral emotional valence. Individuals homozygous for the DISC1 Ser allele (Ser-Ser carriers) relative to carriers of the Cys allele showed greater gray matter volume in the hippocampal formation, as well as greater activation in this region bilaterally during memory encoding. The authors explain these discrepant findings relative to the Callicott study as possibly attributable to haplotypic heterogeneity, or related to the so-called 'flip-flop' phenomenon involving the $Ser^{704}Cys$ DISC1 poly-

morphism whereby opposite effects of the same allele are found in populations characterized by different epistatis with other genetic variants affecting hippocampal structure and function.

The Di Giorgio group (2008) found no significant correlation between gray matter volume and activation in the hippocampal formation, precluding the suggestion that modulation of activation here during encoding was driven by local structural differences. A functional connectivity analysis revealed greater effective connectivity between the right hippocampal formation and the right middle frontal gyrus during memory encoding in Ser-Ser carriers than in Cys carriers. These areas may be of key importance in memory encoding.

A mouse model engineered to mimic the deficits seen in carriers of the DISC1 gene was created by generating mutant mice carrying a truncated isoform, the so-called Disc1 mice (Kvajo et al. 2008). Through this model, Disc1 impairments were shown to result in morphological alterations specific to the hippocampus and medial prefrontal cortex, reduction of short-term potentiation in the adult CA1 region of the hippocampus, impaired dendritic growth and reduced number of spines in mature granule cells of dentate gyrus, and robust and reliable deficits in working memory tasks with high executive components. As such, Disc1 was set forth as a useful model which closely mimics the DISC1 mutation, because of its selective effects on brain structure and function.

The gene known as DAOA (G72) has also been identified as a frequently replicated candidate gene for schizophrenia susceptibility (Shi et al. 2007). To our knowledge, there has been only one study to date to identify a link between G72 and episodic memory deficits in schizophrenia (Goldberg et al. 2006). Given the evidence for a potential relationship between G72 and NMDA function taken together with evidence for glutamatergic neurotransmission dysfunction in schizophrenia, this group tested the hypothesis that cognitive processes reliant on these neurotransmitter systems would be impaired in patients with schizophrenia, thus implicating G72 in the underlying etiology. Though a relationship was found for G72 and working memory and attention ($p=0.05$), the association between G72 and episodic memory deficits only reached the trend level of significance. However, healthy controls homozygous for a specific allele (T) at the M24 SNP showed decreased activation of the hippocampus and parahippocampus during an episodic memory task. Another group subsequently explored genetic variation in this, and another SNP in the G72 gene identified as being strongly associated with schizophrenia, M23 and M24 (Hall et al. 2008). Subjects in this study were at-risk individuals identified by a family history of schizophrenia; they participated in a detailed clinical, neuropsychological, and brain imaging assessment at baseline, and at follow-up visits; blood samples for genetic analysis were collected at the end of the study. A total of 61 subjects were included in the study. Using fMRI, activation differences were demonstrated by subjects with the M23 variation in hippocampal and parahippocampal regions during a sentence completion task. As the task became more difficult, activation differences became apparent in the right inferior frontal gyrus/sub-gyral region. A similar pattern was seen for the M24 group. In sum, genetic variation at SNPs M23 and M24 was shown to modulate hippocampal and frontal lobe activation in this group of unmedicated high risk individuals. A limitation of the study was that it did not include a control group.

Rare variants may yet reveal themselves to be associated with cognitive phenotypes. Multiple risk polymorphisms within M23 and M24 of the DAOA gene were recently shown to be significantly associated with poorer episodic memory performance in a subset of schizophrenia patients carrying the mutation (Donohoe et al. 2007).

Additionally, we note that negative findings have also been reported in the literature. A recent investigation revealed that schizophrenia patients with a particular DAOA variant performed better on a semantic fluency task, indicating that while findings for the role of gene variants as markers of schizophrenia are intriguing, the cognitive implications have yet to be well-characterized. This point speaks to the necessity of correctly parsing cognitive phenotypes for use in genome wide association studies (for more on this, the interested reader may refer to Goldberg and Weinberger 2004).

Discussion

Although we limited the present review to three approaches of interest, the possibility of more fruitful routes to understanding deficits in episodic memory in schizophrenia cannot be discounted. For example, there is an ever growing literature addressing the pervasive deficits in basic sensory processing (visual, auditory, olfactory, somatosensory) in individuals with schizophrenia. Indeed, deficits in early visual sensory processing have recently been identified as endophenotypic (see Yeap et al. 2006). Conway (2001) proposed that episodic memory is a system which retains highly specific sensory and perceptual details of recent experiences over time. If episodic memory is therefore assumed to be reliant on retrieving information that was encoded through intact sensory perceptual processes, it follows that episodic memory in patients will be disrupted. However, the link between these “low level” markers and higher order processes such as episodic memory has yet to be made (e.g., Brodeur et al. 2008).

Another avenue of exploration which has yet to be directly addressed in the schizophrenia literature involves the molecular mechanisms underlying memory formation. Epigenetic models, such as one set forth by Mercer et al. (2008) indicating a role played by non-protein-coding RNAs in memory formation and maintenance, may hold important implications for schizophrenia. Developments in our understanding of memory systems such as this have yet to be assimilated into schizophrenia research. Employing genome-wide association studies (GWAS) that use episodic memory as a phenotype represents a strategy that could theoretically result in identification of risk genes specific to this cognitive deficit. To our knowledge this has not yet been done, although one group has employed a working memory phenotype in two recent GWAS studies (Potkin et al. 2009a, b). Additionally, recent reports of various rare copy-number variants associated with schizophrenia may further our understanding of cognitive deficits in patients (see, e.g. DeLisi 2009), though the utility of this approach as an explanation of memory impairment in the vast majority of cases would seem problematic by definition.

Investigating neurochemical abnormalities that impact the neural integrity of learning systems in patients represents another area for further investigation. A recent review describing neurotransmitter and risk gene interactions in schizophrenia (Lisman et al. 2008) focused on the necessity of the hippocampal region in producing a hyperdopaminergic state that is sometimes considered to be a hallmark of the disease (but see Jazbec 2007). Further, the authors speculated, this hyperactivation of the dopamine system likely affects working memory processes of prefrontal cortex. By framing their findings in a circuit-based model, this group began to find converging evidence across neuroanatomical structures and neurocognitive systems which may prove to be heuristic for future studies. Another review proposed that a better understanding of polymorphisms in the BDNF gene in schizophrenia may be an important future direction, given the key role played by BDNF in early- and late-phase LTP and short and long-term hippocampal dependent memory, and the evidence for the impact of BDNF signaling on the etiology and pathogenesis of schizophrenia (Lu and Martinowich 2008). Other groups have chosen to focus on NMDA dysfunction; by inducing psychosis in healthy volunteers through the use of the NMDA antagonist ketamine, a decrement in verbal recall that correlated with plasma ketamine levels was demonstrated (Parwani et al. 2005). Another ketamine challenge study found impairments in spatial and verbal learning, but not retrieval (Rowland et al. 2005). Animal models have also shed light on the implications of LTP dysfunction for memory and learning. In a recent study, a rat model of psychosis was used to demonstrate that treatment with a glycine transporter inhibitor could ameliorate deficits in LTP and learning (Manahan-Vaughan et al. 2008). (For a comprehensive review of the role of NMDA receptor hypofunction in schizophrenia, see Greene 2001). Finally, a recent investigation demonstrated the role of nicotine on hippocampus-dependent learning and LTP in healthy controls (Kenney and Gould 2008). Normative studies such as this may implicate neurochemical systems that merit further exploration in a schizophrenia population.

Studies that focus on sexual dimorphism may also be an important piece of the puzzle, given the marked paucity of female schizophrenia subjects in the majority of studies in the literature and also in light of equivocal findings of sexual dimorphism in hippocampal pathology for this patient population (as reviewed in Exner et al. 2008). Findings of abnormal orbitofrontal cortex to amygdala ratios in men and women with schizophrenia relative to healthy controls have led Gur et al. (2004) to suggest that schizophrenia may involve a reversal of normal sexual dimorphism, i.e., a ‘feminization’ of men and a ‘masculinization’ of women (as reviewed by Guillem et al. 2009). A recent study that investigated hippocampal volumes of male and female individuals with schizophrenia found bilateral hippocampal volume reductions in male, but not female, patients (Exner et al. 2008). The authors proposed that reduced right hippocampal volumes in male patients may be responsible for deficits in visual episodic memory, but point out that the presence of similar deficits in female patients may be attributable to separable pathophysiological mechanisms between the sexes. A limitation of this study was small sample sizes (21 patients, 14 male; 21 matched controls); in addition, all patients were chronic and medicated. Utilizing electrophysiology, another group investigated whether sex differences in cognitive functioning seen in schizophrenia mirror those observed in healthy populations (Guillem et al. 2009). Event-related potentials were recorded from 18 patients and 18 healthy controls during a recognition memory task that employed visual stimuli (unfamiliar faces). Their reported findings were not straightforward; across early, middle, and late latency event-related potentials, they observed different patterns of sex differences between and within groups. In turn, they noted discrepant patterns of reversed versus non-reversed sexual dimorphism (relative to healthy controls) across the sampled processing period. The researchers interpreted these findings as reflective of the non-homogenous influence of sex on cognitive impairment in individuals with schizophrenia, and indicative of temporally separable memory processes that may be differentially impacted by sex.

Despite the elegance of many of the individual paradigms and the importance of the findings described, the results that we reviewed do not easily lend themselves to an overarching, mechanistic model of how memory failures

and lapses in schizophrenia occur; nevertheless, we believe that a multifactorial perspective might offer a principled way to mechanistically understand memory failure in schizophrenia. There are several reasons that may explain why we still lack consensus; first is the possibility of cohort effects and heterogeneity within schizophrenia. Second, there are gaps in the literature, including an examination of the relationship between working memory and executive function with episodic memory at the behavioral level. That is, at the behavioral level, the relative contributions of executive functioning deficits in patients must be extracted from their difficulties in episodic memory. Third, our incomplete understanding of the physiologic abnormalities in prefrontal cortex during memory processing, and what they represent: inefficiency, failures to engage, or something else? Last, the role of individual candidate genes as modulators of episodic memory is not at a final stage, despite intriguing early findings (Koppel and Goldberg in press; Papassotiropoulos et al. 2006; Matynia et al. 2008). Several genes have been shown to be associated with memory in healthy controls (e.g., BDNF val66met), but do not appear to be risk genes for schizophrenia.

Given that evidence of impairments of episodic memory have been robust and replicable, and observed at the level of neuroanatomical, neurophysiological, neurocognitive, and genetic abnormalities/antecedents, it is perhaps frustrating that a unitary characterization of this hallmark feature of schizophrenia has not emerged. This review has undertaken an examination of the literature organized in a methods-driven fashion in the hopes that by doing so, we may gain a clearer sense of promising directions for future research. The genetic approach is beginning to provide emerging evidence of candidate genes associated with memory disruption in schizophrenia; however, employing genetics may help or hinder the search for a clear etiological explanation, given that findings thus far have been equivocal. While behavioral studies have identified a number of aspects of memory systems and cognitive systems in general which may "feed" the impairments in episodic memory, no clear consensus emerges here either. Neuroanatomical studies have provided robust evidence for abnormalities in MTL and prefrontal cortical regions. However, surprisingly little literature has directly addressed the ways in which non-memory related areas of the brain may be modulating memory systems. Of the studies reviewed, Talamini et al. (2005) have developed a mechanistic account at the computational level of how failures in connectivity between subprocesses or subregions of cortex could lead to a surprisingly wide variety of memory impairments. Moreover, this was shown to be neurobiologically plausible (e.g., Harrison and Eastwood 2001; Harrison 2004). However, the model did not examine important manipulations having to do with transitivity, relational memory, or depth of encoding. While it must at best be considered limited or incomplete, it may represent an important direction for future investigations. Indeed, a proliferation of findings in the schizophrenia literature addresses abnormalities in prefrontal cortex, an area of the brain which is gaining in stature as a key player in memory systems. A recent study in healthy controls showed that while medial temporal lobe activity predicted memory strength, activity in prefrontal cortex predicted recollection (Kirwan et al. 2008).

We propose that a combination of computational modeling and functional imaging might provide a way to mechanistically understand memory failure. Such an approach might entail a computational model designed to mimic interactions between prefrontal cortex and medial temporal regions during normal learning and memory responses to cognitive paradigms. This would be followed by various types of in silica lesions to assess the nature of impairments. These results would be used to design functional neuroimaging studies for validation. Obviously, the model and the studies could be manipulated to include genotypic effects.

The theme of functional connectivity may be a useful one to consider, not only connectivity in terms of abnormality in the memory systems of patients, but as a strategy for investigators to employ. That is, by drawing connections from findings in the behavioral literature and allowing them to drive the questions we ask in imaging studies, or using clues from the neuropsychological literature to identify cognitive phenotypes for use in genome wide association studies, we may begin to uncover convergent evidence, and a cohesive understanding of episodic memory deficits in schizophrenia.

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