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Mol Psychiatry. Author manuscript; available in PMC 2019 April 26.

Published in final edited form as:

Mol Psychiatry. 2019 May ; 24(5): 633–642. doi:10.1038/s41380-018-0231-1.

Memory and Cognition in Schizophrenia

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Abstract

Episodic memory deficits are consistently documented as a core aspect of cognitive dysfunction in schizophrenia patients, present from the onset of the illness and strongly associated with functional disability. Over the past decade research using approaches from experimental cognitive neuroscience revealed disproportionate episodic memory impairments in schizophrenia (Sz) under high cognitive demand relational encoding conditions and relatively unimpaired performance under item-specific encoding conditions. These specific deficits in component processes of episodic memory reflect impaired activation and connectivity within specific elements of frontal-medial temporal lobe circuits, with a central role for the dorsolateral prefrontal cortex (DLPFC), relatively intact function of ventrolateral prefrontal cortex and variable results in the hippocampus. We propose that memory deficits can be understood within the broader context of cognitive deficits in Sz, where impaired DLPFC related cognitive control has a broad impact across multiple cognitive domains. The therapeutic implications of these findings are discussed.

Keywords

episodic memory; cognitive control; schizophrenia; frontal-medial temporal lobe networks; DLPFC

Cognitive impairments have long been accepted as core features of schizophrenia (Sz) that contribute significantly to disability and are generally treatment refractory [1]. Indeed, Keefe [2] recently recommended including cognitive impairment in the formal diagnostic criteria for this illness and highlighted the need for research on developing treatments to improve cognitive abilities in Sz. Numerous neuropsychological studies demonstrate a broad range of measurable cognitive deficits in Sz including impairments in attention, working memory (WM), episodic memory, processing speed and executive functions [3]. Among these traditional cognitive domains, episodic memory has frequently been highlighted as showing the largest effect sizes among cognitive deficits in Sz [4], regardless of factors such as

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Conflict of interest statement

We warrant that the article is the authors' original work. All authors have seen and approved the manuscript being submitted. The article has not received prior publication and is not under consideration for publication elsewhere.

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antipsychotic medication treatment [5], duration of illness [6], stage of illness [7] or level of psychotic symptoms [8], and of being particularly relevant for the functional deficits that characterize the illness [9].

In recent years, episodic memory has been extensively studied in Sz using fine grained cognitive neuroscience methods to identify the specific components of memory systems that are impaired in the illness. These studies have led the field to two important conclusions, both of which have implications for our understanding of the illness and for the development of novel therapeutics. Firstly, these studies, reviewed in detail below, suggest that specific aspects of episodic memory are either spared or impaired, in contrast to the more global learning and memory impairment seen in amnestic disorders [10]. Secondly, deficits in episodic memory may be best understood in the context of a broader pattern of deficits in higher cognitive functions in Sz that are often accompanied by dorsolateral prefrontal (DLPFC) dysfunction, and most likely to be observed when organizational and cognitive control demands are high.

Cognitive models of episodic memory deficits in Schizophrenia

Experimental cognitive studies of episodic memory in schizophrenia have generally focused on the function of recall and recognition mechanisms in the brain. In healthy subjects the use of recall paradigms has revealed many discrete component memory processes including the serial position effect (e.g. primacy and recency) [11, 12], the impact of levels of processing (deep and shallow encoding) [13] and the effects of self-initiated organizational encoding strategies [14, 15]. Schizophrenia patients have been shown to exhibit comparable serial position effects as healthy controls (HC), suggesting intact shallow encoding, and are able to benefit from instructions to use semantic strategies to support encoding [16–19]. However, they fail to self-initiate these semantic encoding strategies, suggesting impaired deep encoding mechanisms [20]. These results, in aggregate, highlight the view that there are specific strategic memory deficits that limit encoding into episodic memory under high levels of processing demand in the illness, overlaid on a set of basically intact more automatic learning and memory mechanisms.

To obtain a deeper understanding of encoding and retrieval mechanisms, cognitive neuroscience researchers employed a variety of recognition paradigms, where individuals learn material during a study phase and are then probed as to whether it is “old” or “new” during a test phase. One common approach has been to examine recognition performance using incidental encoding paradigms in which individuals alternate between two types of encoding: item-specific (e.g. words denoting living things) or relational (e.g. beer and milk from beverage category). Several analytic methods can then be used to pull apart two forms of retrieval: familiarity (e.g., novelty detection) or recollection (e.g., associative recognition) [21]. Performance on old/new recognition tests has been modelled using either signal-detection theory or threshold model approaches. Signal-detection assumes that recognition judgements fall on a continuously distributed memory strength variable (e.g. old items with high familiarity fall on the high end and new items with low familiarity fall on the low end) [22, 23]. The threshold model assumes discrete mental states where only items with sufficient episodic details to describe the state of memory (over threshold) can be recalled [24, 25]. A

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third “dual-process” modelling approach obtains confidence ratings that are examined using a receiver operator characteristics (ROC) analysis to generate quantitative and orthogonal recollection and familiarity parameter estimates [26, 27]. Recollection involves a sense of “remembering” and is accompanied by retrieval of qualitative aspects of the encoding event, such as context-item associations or source details. Conversely, familiarity involves a sense of “knowing” based on a global (or gist-like) sense of memory strength or novelty, and is not accompanied by retrieval of qualitative details of the encoding context.

In a series of studies using a dual-process modelling approach in Sz, Ragland and colleagues demonstrated that familiarity is unimpaired when item encoding is utilized, familiarity is severely impaired when a relational encoding strategy is required, and recollection is severely impaired regardless of encoding processes used (Figure 1) [28–30]. In relation to these findings, a meta-analysis which reviewed nineteen studies of recollection and familiarity in Sz using a variety of quantitative methods including remember/know/new, process dissociation, and ROC modeling found that effect sizes of impairments in Sz are medium to large on recollection and small to medium on familiarity estimates [31]. Thus it appears that Sz patients can successfully utilize encoding strategies that focus on item features to support a sense of familiarity, however, relational encoding strategies do not promote successful familiarity processes and recollection shows the most pervasive impairment regardless of what encoding strategy is applied.

Neural circuitry dysfunction underlying episodic memory deficits in Schizophrenia

While early neuropychological studies of episodic memory focused on the critical role of the medial temporal lobe (MTL), and specifically the hippocampus, in episodic memory [32, 33], with the advent of whole brain functional imaging in the 1990’s it became clear that encoding and retrieving information in episodic memory depends on dynamic interactions between mutliple prefrontal and medial temporal lobe systems [34, 35]. It is not suprising that functional imaging studies in schizophrenia pointed to alterations in the function of these networks during memory performance. The overall pattern of results in these studies suggest that, as in behavioral studies of component memory mechanisms, there is a specificity of these effects to distinct elements of neural circuitry that has implications for our understanding of the illness and future therapeutics.

The majority of previous functional imaging studies of episodic memory encoding processes in Sz reported reduced DLPFC activation during deep encoding [e.g. 36, Meta-analysis: 37], while one study by Bonner-Jackson [18] found increased DLPFC and inferior frontal gyrus activation during deep encoding in Sz patients compared to HC that was interpreted as a compensative hyperactivation. Guimond and colleagues [19] further illustrated that hypoactivation of the left DLPFC plays a critical role in the impairment of self-initiating semantic encoding strategies in Sz. Interestingly, these studies also showed unimpaired activation in the ventrolateral prefrontal cortex (VLPFC) when patients were provided item-specific encoding strategies [37, 38]. With regard to the MTL component of episodic memory circuitry, to date, fMRI studies in Sz have yielded heterogeneous results with hyper- or

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hypoactivation of MTL structures during novel stimuli encoding, such as hypoactivation in the right posterior hippcampus and hyperactivation in the right anterior hippocampus [39], hyperactivation in the left inferior temporal gyrus, right MTL and bilateral parahippocampus [40], and hypoactivation in the bilateral parahippocampal and hippocampal-parietal network [41]. Such contradictory results may reflect whether a given study controls for encoding success [42], on the types of materials being encoded [18] and whether deep or shallow levels of processing are examined. When Ragland and colleagues [38] utilized a deep versus shallow encoding paradigm to control for strategic memory deficits, they found unimpaired VLPFC activation during shallow encoding, and reduced DLPFC and increased hippocampal and thalamic activation during deep-encoding. In summary, these combined results point to consistently reduced DLPFC activation during deep encoding, and when no encoding strategies are provided, relatively intact VLPFC activation during shallow or item-specific encoding, and mixed findings of both under- and over-activation or no group differences in the MTL and hippocampus.

To understand neural circuits underlying episodic memory recognition processes, Ragland et al. [43] demonstrated DLPFC hypoactivation in Sz patients compared to controls during old/new recognition of items following relational vs item-specific encoding, whereas no group differences were found in VLPFC activation regardless of encoding condition. However, Lepage et al. [44] revealed hypoactivation in left DLPFC, right VLPFC, and two medial frontal cortices in Sz patients compared to controls during recognition following relational versus item encoding. Across both studies, reduced DLPFC activity was associated with recognition deficits in Sz, whereas VLPFC results were more variable – possibly due to whether or not encoding strategies were provided [45] or had to be self-initiated [44]. However, at a meta-analytic level [37], there is an absence of VLPFC group differences, while the DLPFC appears consistently impaired. Functional connectivity evidence of reduced hippocampal to DLPFC connectivity and enhanced hippocampal to VLPFC connectivity [46] suggests that the VLPFC may be engaged in patients to support item encoding and familiarity-based retrieval in an effort to compensate for more intractable DLPFC and hippocampal dependent relational encoding and recollective memory deficits.

Given the strong association between the hippocampus and episodic memory in classical neuropsychology it is not surprising that this has been a primary focus in fMRI studies of episodic memory impairment in Sz [See review: 47]. However, accumulating inconsistent evidence of hippocampal hyperactivation, hypoactivation and no differences in Sz patients compared to controls have complicated our understanding of the role of the hippocampus in these deficits. An early PET study demonstrated that Sz patients exhibited increased regionalcerebral blood flow (rCBF) in the hippocampus during recall after perceptual encoding and decreased hippocampal rCBF during recall after semantic encoding compared to controls [48], suggesting a dysfunction of cortico-hippocampal network integration in Sz [49]. However, two subsequent meta-analyses have revealed that Sz patients exhibit abnormal brain activation in the prefrontal cortex during encoding but not in the medial temporal lobe during either encoding or retrieval [37, 50]. More recent studies have revisited the role of hippocampal dysfunction in Sz by utilizing paradigms that require recollection and associative processing or by examining differences along the longitudinal axis of this structure. Regarding this longitudinal axis, the anterior hippocampus has fairly consistently

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shown increased resting state activity in Sz (e.g. cerebral blood volume (CBV) and cerebral metabolic rate of oxygen (CMRO2)) [See book chapter: 51, See review: 52] in SZ. For example, Schobel et al. [53] reported increased CBV in anterior subfield of hippocampus (CA1) and the orbitofrontal cortex in Sz patients without a history of antipsychotic medication exposure. The same group extended this result in the early prodromal stages of the illness with a follow-up study, in which individuals at ultra-high risk (UHR) of psychosis exhibited increased CBV in the left anterior hippocampus (CA1) and spreads to anterior subiculum after psychosis onset [54]. Thus, CA1 hypermetabolism has been considered as a regional vulnerability characterizing psychotic symptoms in Sz [See review: 55]. Furthermore, a substantial body of work in basic and behavioral neuroscience suggests that anterior and posterior divisions subserve different functions in episodic memory (figure 2)[56, See review: 57, e.g. 58, 59]. Specifically, posterior hippocampal subregions are more likely to be involved in visual spatial memory encoding [60], whereas anterior hippocampal subregions are more involved in other complex behaviors (e.g., anxiety related behaviors [61]and stress [62]). When Ragland and colleagues [63] recently examined this using an eye-tracking fMRI paradigm that manipulated either item information or spatial information in previously studied scenes, they found that the task-specific impairment (worse relational versus item memory) was explained by a reduction in posterior hippocampal activation for relational versus item changes. However, the anterior hippocampus, unexpectedly, showed hyperactivation in Sz patients for the item change condition. If the above findings of differential impacts of Sz on anterior versus posterior hippocampal function are confirmed in future studies, it suggests that looking separately at the head and tail of the hippocampus may help to reconcile some of the current variability in the literature.

Cognitive impairments in schizophrenia as a context for understanding deficits in episodic memory

As noted above, episodic memory is just one of a range of cognitive domains that are impaired in Sz [e.g. 64, 65]. For example, Keefe et al. [66] demonstrated that Sz patients performed at 2.5 standard deviation below controls in 7 domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning/problem solving and social cognition, indicating a profound cognitive impairment in schizophrenia. Across the cognitive domains that have been interrogated from an experimental cognitive neuroscience perspective, attention and working memory were also shown to be robustly impaired in the illness. In the following section we will briefly review findings in these two higher cognitive domains and then introduce the concept of cognitive control, which may provide an integrative framework for understanding impaired congition in Sz and a link between the specific impairments in episodic memory that are seen in the illness and the broader range of congitive deficits that are also observed.

Attention

In examining component processes of attention, selective attention can be examined by Stroop Color and Word task [67], wherein participants are required to name the ink color of color words (e.g., the word “green” written in red ink). Altered Stroop task performance in Sz, reflected by increased errors or reaction times has been reported by many investigators

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[68–70]. Subsequent neuroimaging studies suggested that these deficits are associated with reduced activity in frontal-parietal attentional control systems and anterior cingulate related conflict monitoring [71]. Sustained attention/vigilance can be examined by various types of continuous performance tests (CPT) [72, See review: 73]. In general, patients have shown no performance difference on vigilance versions of the CPT compared to controls [e.g. 74, 75, 76]. When task difficulty is increased through the use of degraded stimuli [77], patients are reliably impaired. However, whether this reflects a pure vigilance deficit or the contribution of increased perceptual discrimination on decision making is unclear. In neuroimaging studies, Sz patients have exhibited reduced activation in ACC and inferior frontal gyrus, increased activation in inferior parietal lobule and mixed results in subcortical regions during various types of CPT tasks e.g. [78, 79–83]. These contrasting results may reflect interaction of sustained attention and other cognitive demands. Indeed, Roth and colleagues [84] revealed that both X-CPT and identical pairs (IP)-CPT reliably detected more impaired sustained attention in Sz smokers compared to nonsmokers when IP-CPT exhibited larger effect size to detect group differences than X-CPT, suggesting IP-CPT taxes working memory.

Working memory

Working memory impairments in Sz are characterized by reduced accuracy and increased response time, which have been documented in various stages of Sz, such as UHR [See meta-analysis: 85], early onset of schizophrenia patients [86], first-episode schizophrenia patients [See meta-analysis: 87] and especially in chronic Sz [88]. The majority of neuroimaging findings suggest that regions comprising the dorsal frontal-parietal network are affected in Sz, and that this neuropathology may underlie WM impairments in Sz [89]. It has also been proposed that the inverted U–shaped relation of DLPFC activation to WM loads is shifted to the left side in Sz patients compared to controls [e.g. 89, 90, 91, 92]. Similar abnormal brain activation is also revealed in the dorsal parietal cortex in Sz suggesting a frontal-parietal dysfunction underlying high cognitive demands during WM [93].

Cognitive control

Cognitive control is defined as the ability to actively maintain contextual information (including information related to stimuli, task rules and goals) in order to guide task-relevant responding [94, 95]. Cognitive control is domain general, supporting a wide variety of cognitive domains, including attention, working memory and episodic memory [e.g. 96, 97–99]. Cognitive control is supported by a distinct neural network in which the DLPFC serves as a central hub [See meta-analysis: 100, 101]. Theoretical models of cognitive control have dissociated proactive (or endogeneously guided) and reactive (in response to conflict, errors and other indicators of negative utility) elements subserved by both distinct and overlapping neural systems [102, 103]. In schizophrenia research, there is considerable evidence that DLPFC hypoactivation is related to impaired proactive control in first episode Sz [104, 105], medication naive Sz [106] and chronic Sz [71]. Moreover, Sz patients show a significant reduction of DLPFC-related functional connectivity (e.g. fronto-parietal functional connectivity) under conditions requiring high cognitive control [107, See review: 108].

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Cognitive control and episodic memory deficits in Schizophrenia

Drawing on the cognitive model of episodic memory outlined at the beginning of this review, the pattern of impaired and preserved component processes of episodic memory seen in Sz suggests that memory impairments may be most severe when DLPFC mediated cognitive control demands are greatest. Thus, a general cognitive control deficit model provides a parsimonious link between the prominent deficits in episodic memory and the broader range of higher cognitive deficits including impaired attention and working memory. As reviewed above, the design of relational versus item memory task was intended to distinguish high and low cognitive control conditions by introducing paired versus item specific cues, while the majority of studies revealed a strong link of deficits in the DLPFC with the more cognitive control demanding associated relational encoding condition [28, 37, 109]. This view is also supported by the results of the meta-analysis by Ragland et al. [37], which showed the most prominent prefrontal deficits in Sz during both encoding and retrieval of episodic memory tasks. Specifically, persistent DLPFC deficits are not secondary to providing semantic encoding strategies, suggesting a general impairment of cognitive control. The hypothesis that there is impaired cognitive control of episodic memory in Sz has also been directly tested using a directed forgetting paradigm (DF), where HC are required to successfully encode and retrieval target stimuli into long-term memory while intentionally preventing non-target stimuli from being encoded. During a subsequent recognition phase, participants are required to respond to a probe of to-be-remembered (TBR) or to-be-forgotten (TBF) stimuli [See review: 110]. Behavioral data index the engagement of cognitive control, as reflected by a longer reaction time to TBF than TBR stimuli and greater recognition of TBR than TBF stimuli (DF effect) [e.g. 111]. fMRI neuroimaging studies consistently demonstrate that intentional forgetting engages DLPFC and parietal regions, suggesting that inhibition of encoding a recent stimuli is effortful [112, 113]. Moreover, brain lesion studies also support a causal relationship of frontal lobe lesions with reduced DF effects and abnormally high recognition of TBF stimuli [114]. In Sz, behavioral studies reported reduced DF effect in patients compared to controls [115, 116]. During fMRI, Ragland and colleagues [117] found that increased DLPFC activation was associated with increased cognitive control during intentional forgetting trails in controls, but not in Sz patients. Sz patients show prominent deficits in some aspects of episodic memory (e.g. relational encoding, intentional forgetting) while other aspects appear to be spared, which is a pattern of selective deficits that is seen across a range of cognitive domains including attention, working memory and cognitive control. Common elements across the neural systems that support these “domain specific” deficits include the DLPFC, which must integrate with parietal, cingulate and medial temporal networks under demands for high levels of contextual processing and cognitive control. As a central, and domain general, hub in these domain specific networks the DLPFC can be understood as a critical target for efforts to restore cognitive functioning, including episodic memory, in Sz.

Conclusion

In the current review, we have argued that memory deficits in Sz are specific to encoding and retrieval conditions with high cognitive demands and which depend on cognitive control and relational memory functions of the DLPFC as it participates in frontal-MTL network

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function. Such deficits provide a link for understanding the relationship between episodic memory deficits and other cognitive deficits, such as attention and WM in the illness. Therapeutically, these conclusions support the development of treatments that target the function of the DLPFC, pharmacologically or through neurostimulation. Such an approach should have generalizable benefits for memory as well as other kinds of cognitive deficits in Sz.

Acknowledgements

We sincerely thank our colleague Vanessa Zarubin for her diligent proofreading.

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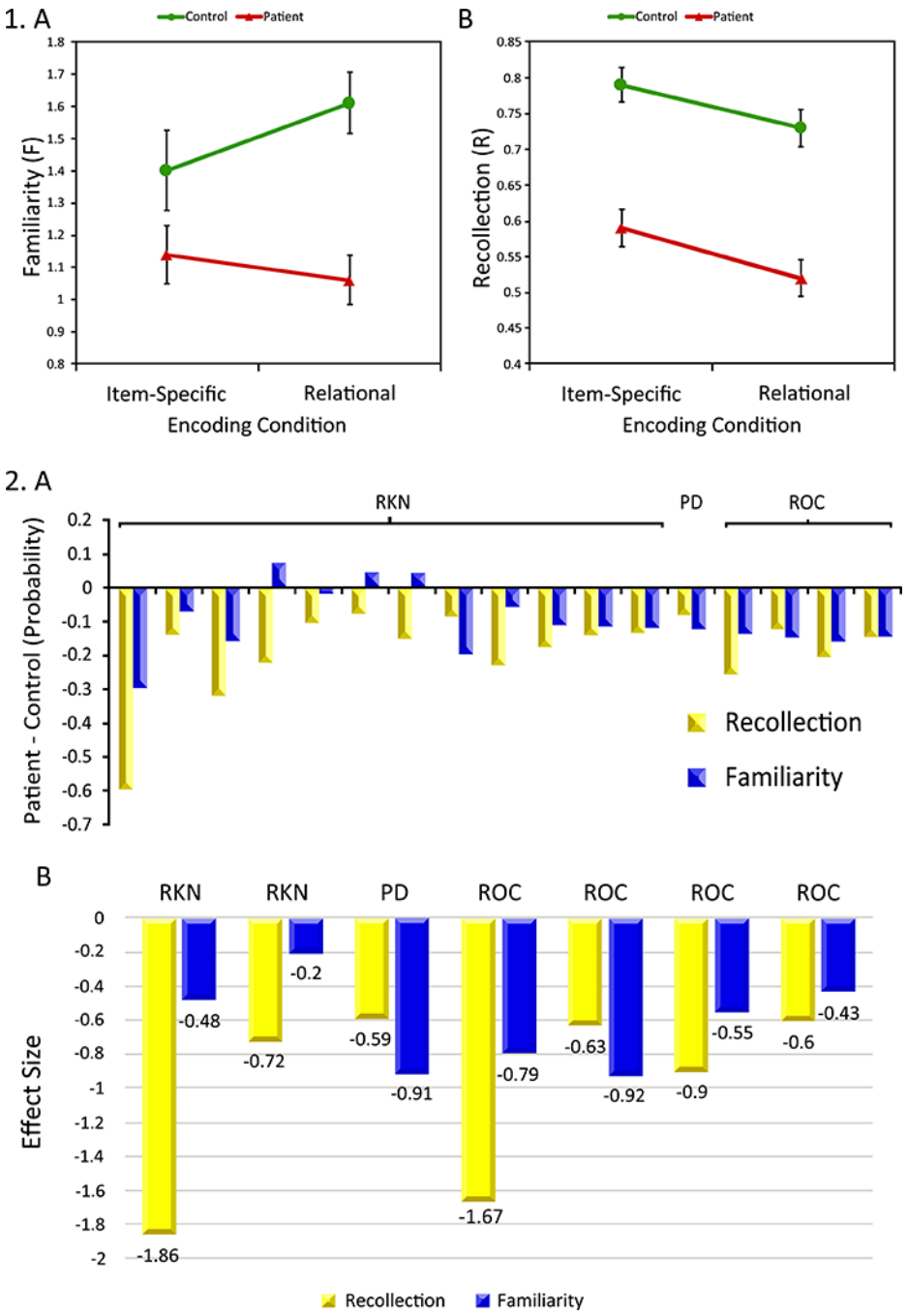

Figure 1:

Panel 1, Mean (±SEM) familiarity and recollection in healthy controls (blue circles) and Sz patients (red triangles). (A) Familiarity reveals a group by encoding interaction, with more severe patient deficits following relational versus item-specific encoding, (B) Recollection reveals a main effect of group across both encoding conditions, with lower patient versus control performance. See Ragland, Ranganath [28] for additional results. Panel 2, Meta-analysis of recollection and familiarity deficits across 19 previous studies utilizing remember/know/new (RKN), receiver-operator characteristic (ROC), or process dissociation

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(PD) methods. (A) Recollection and familiarity estimates were recalculated with three probabilities models from three types of studies respectively, showing more impaired recollection in Sz patients than controls across studies. (B) Effect sizes of Sz on recollection were slightly larger than on familiarity. See [31] for study references.

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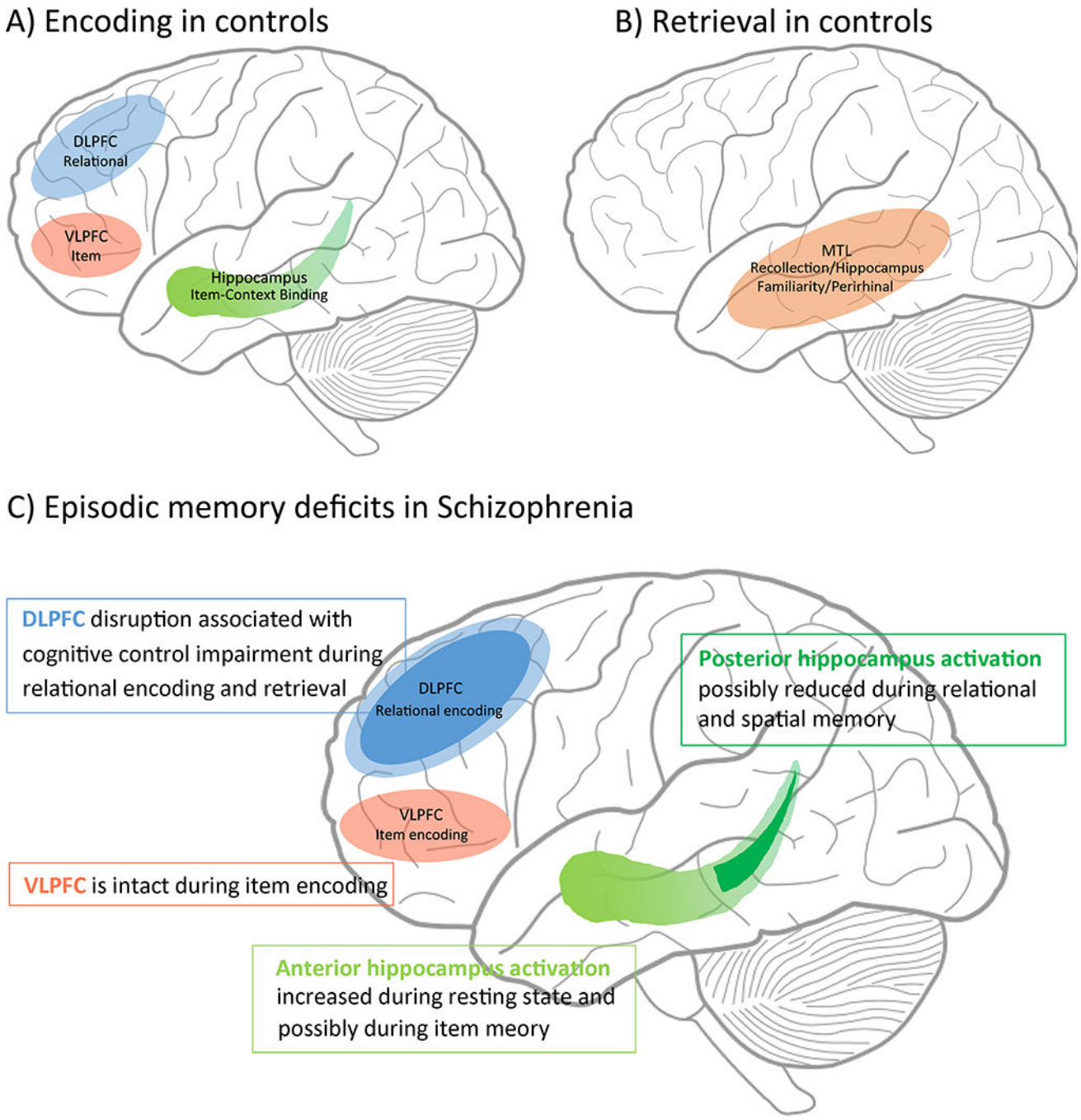

Figure 2:

In controls, DLPFC provides control of relational encoding and VLPFC controls item-specific semantic processing, and hippocampus binds associations between item and context information during encoding (panel A). At retrieval, recollection engages the hippocampus and familiarity engages mainly perirhinal cortex, with little hippocampal engagement (See [30, 33, 118] for theoretical models) (panel B). Panel C illustrates disrupted DLPFC (blue) activation during encoding and retrieval in Sz, while VLPFC (orange) remains intact during item encoding, suggesting an important role for cognitive control deficits underlying

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episodic memory impairment in Sz. On the other hand, relational and spatial memory dysfunction in Sz is associated with reduced posterior hippocampal activation in Sz, whereas increased anterior hippocampal activation has been associated with item memory.