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Reduced Functional Connectivity in Brain Networks Underlying Paired Associates Memory Encoding in Schizophrenia

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ABSTRACT

BACKGROUND: Deficits in relational episodic memory encoding are characteristic of schizophrenia (SZ), but whole-brain multivariate analyses of these deficits have been lacking. Open science has provided task-based functional magnetic resonance imaging (fMRI) data investigating paired associate encoding in SZ, but it has not yet been mobilized to address this gap in the literature. Therefore, in this study, we use previously unpublished task fMRI data to conduct the first network-level investigation of impaired relational episodic encoding in SZ.

METHODS: Using fMRI data acquired from 40 healthy control participants and 40 age- and sex-matched persons with SZ, we examined the networks involved in successful versus unsuccessful encoding of verbal paired associates using an associative semantic strategy.

RESULTS: Constrained principal component analysis for fMRI revealed 3 distinct functional networks recruited during encoding: a responding network, a linguistic processing/attention network, and the default mode network. Relative to the healthy control group, the SZ group exhibited aberrant activity in all 3 networks during successful encoding; namely, hypoactivation in the linguistic processing/attention network, lower peak activation in the responding network, and weaker suppression in the default mode network. Independent of group effects, a pattern of stronger anticorrelating linguistic processing/attention–default mode network activity during successful encoding significantly predicted subsequent retrieval of paired associates.

CONCLUSIONS: Together with previous observations of language network hypoactivation during controlled semantic processes, these results suggest that abnormalities in networks representing language and meaning may contribute to difficulties employing deep semantic strategies during relational episodic encoding in SZ.

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Episodic memory (EM) impairments in schizophrenia (SZ) are profound, particularly for verbal information; are related to poorer functional outcomes; and do not respond well to available pharmacological treatments (1–8). Identifying the neural bases of the specific cognitive processes underlying EM impairments in SZ is important for developing novel cognitive remediation and neurostimulation therapies [e.g., (9–11)].

Studies that have contrasted recognition versus cued or free recall over varying delays have indicated that whereas EM storage is largely intact in SZ, encoding is impaired, by some accounts more so than retrieval (8,12–15). Relational (or associative) encoding, which binds the elements of an episode into a cohesive memory, is particularly affected (16,17); over and above memory impairment for individual items, individuals with SZ have impaired recognition of relationships between items (18), such as item pairings (19), object-location associations (20), and stimulus hierarchies (21). Selective relational memory impairments persist even when equating memory load across relational and item-specific conditions, and signal detection methods have linked them with impaired memory discriminability (d-prime), rather than altered response bias (19).

In healthy control (HC) subjects, relational encoding recruits the dorsolateral prefrontal cortex (DLPFC) (Brodmann area [BA] 9 and BA 46), the ventrolateral PFC (VLPFC) (BA 44 and BA 45), and medial temporal structures, including the hippocampus (22,23). Functional neuroimaging studies investigating the basis of relational encoding deficits in SZ have employed mass-univariate, seed-based, and/or region of interest–based analyses, the latter of which have mainly investigated the DLPFC and hippocampus (e.g., 24,25). Across item-specific and relational episodic encoding tasks, the most consistent abnormalities among persons with SZ have been observed in the DLPFC and hippocampus, generally in the direction of hypoactivation (24,26–28).

There is a growing recognition that episodic encoding impairments in SZ are at least partly secondary to abnormalities in other cognitive domains (29). In particular, higher-order deficits in strategy selection and utilization associated with DLPFC hypoactivation (30) account for some, but not all, of the deficits in EM for items in SZ. Behavioral studies indicate that persons with SZ are less likely to spontaneously use effective encoding strategies, such as semantic clustering or

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association, and instead tend to use shallow encoding strategies, such as rote rehearsal (13,31–33). Prompts to use semantic strategies improve subsequent retrieval performance in participants with SZ in the form of faster reaction time (RT) and greater d-prime scores (34–37). While such findings highlight an important role for cognitive training in improving EM deficits in SZ (9,10), neither item recognition performance nor brain activation are fully normalized through use of deep encoding strategies (27,32). With respect to brain activation patterns, deep item encoding has been found to normalize brain activity in individuals with SZ in prefrontal semantic processing areas (VLPFC) (27,32), although residual abnormalities remain, and it is unclear whether this partial normalization extends to relational encoding.

Understanding the residual abnormalities that persist even when persons with SZ employ deep encoding strategies remains an important goal for normalizing EM in the illness. We believe that abnormal representation and processing of meaning in the brain may be a critical factor limiting the efficacy of deep encoding strategies in SZ. Consistent with disrupted frontotemporal semantic networks, an functional magnetic resonance imaging (fMRI) investigation by Kubicki *et al.* (38) found left inferior frontal hypoactivation and left superior temporal gyrus overactivation when persons with SZ encoded words using deep semantic processing. Further, in a verbal paired associates encoding task (25), persons with SZ had hypoactivation in a set of distributed regions, including the left VLPFC, left fusiform and middle temporal gyrus, and midline superior prefrontal gyrus; further, there were significant positive associations between left VLPFC and middle temporal activations during associative encoding with subsequent recall accuracy. Together with evidence that persons with SZ demonstrate reduced frontotemporal connectivity while making controlled semantic associations and decisions (39–43), these studies suggest that disruptions in frontotemporal networks supporting the representation and processing of meaning of words may contribute to difficulties effectively employing semantic strategies in SZ, perhaps particularly during relational EM encoding.

Studies are now needed to elucidate the neural basis of deficits in relational encoding using multivariate techniques, which better reflect the understanding that cognition arises from interactions between brain regions and that SZ involves disordered network connectivity (44–46). Multivariate methods can characterize the multiple overlapping networks activating in parallel during the various stages of learning, from attention to encoding to response execution. To our knowledge, no study has examined relational learning in SZ from a network-level perspective, and this informs the motivation for this study.

The open science movement in neuroimaging [e.g., (47,48)] has resulted in unprecedented access to high-quality, large-sample, task-based fMRI data (49,50). Here, we take advantage of previously unpublished data from the paired associates memory encoding (PAM-enc) paradigm (51), which explicitly prompted participants to use semantic association to learn new item pairings. We used constrained principal component analysis for fMRI (fMRI-CPCA) (52–55) to identify the distinct whole-brain functional networks recruited during PAM-enc and to compare network hemodynamic response shapes between HC subjects and persons with SZ. Whereas network-level analyses typically use resting-state data, fMRI-CPCA specifically analyzes task-based networks and thus enables inferences to be made regarding cognitive function (53,56,57). We used a subsequent memory paradigm, in which brain activation is compared for items later remembered versus forgotten (58,59). We hypothesized that persons with SZ would demonstrate reduced connectivity in semantic (left VLPFC and superior temporal gyrus) regions during relational encoding. Further, we hypothesized that frontotemporal network hypoconnectivity would predict poorer subsequent paired associates retrieval. Additional analyses explored relations of network activation with task performance and symptoms of psychosis.

METHODS AND MATERIALS

Participants

Participants were 40 individuals with a diagnosis of SZ (n = 31) or schizoaffective disorder (n = 9) and 40 age- and sex-matched HC subjects aged 21 to 49 years who performed a paired associates memory fMRI task as part of the larger UCLA Consortium for Neuropsychiatric Phenomics LA5c Study (51). The dataset was obtained from the OpenNeuro database (accession number ds00030). All participants provided written informed consent according to procedures approved by the University of California Los Angeles Institutional Review Board.

All participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I disorders (60) and the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (61). Psychotic symptoms of participants with SZ were measured with the Brief Psychiatric Rating Scale (62) and the Scales for the Assessment of Positive/Negative Symptoms (63,64). Additional inclusion/exclusion criteria are detailed in Poldrack *et al.* (51).

Of the 45 participants with SZ and 80 HC participants with complete fMRI data, 4 (n = 2 SZ, n = 2 HC) were excluded before age and sex matching owing to head motion during fMRI scanning, and 1 participant with SZ was excluded owing to a suspected invalid response set during retrieval testing (giving positive responses to all retrieval pairs). Three participants with SZ could not be matched with HC participants on the basis of age (within 2 years), resulting in the sample sizes reported above.

Table 1 contains demographic and clinical information for the sample. The groups were equivalent in their sex distributions (28 males in each group) and did not differ significantly in age (t_{78} = 0.04, p = .97) or proportion of Caucasian participants ($\chi^2_{1,\ (N\ =\ 80)}$ = 1.00, p = .32). The SZ group had significantly fewer years of education (t_{78} = 7.36, $p < .001$). Of the 39 participants with SZ with available medication history, 36 reported taking at least one atypical antipsychotic, 3 reported taking both an atypical and a typical antipsychotic, and none reported taking only a typical antipsychotic.

Paired Associates Encoding Task

The PAM-enc paradigm (Figure 1) was designed to assess associative memory encoding. Participants received training on the task immediately before scanning. The task consisted of a single run of 64 trials (24 control trials and 40 memory trials). During control trials, pairs of orange and black-and-white

Table 1. Participant Characteristics

Characteristics	Healthy Control Participants, *n* = 40	Persons With Schizophrenia, *n* = 40
Age, Years, Mean (SD)	34.88 (8.66)	34.95 (8.90)
Education, Years, Mean (SD)	15.05 (1.57)	12.55 (1.47)
Sex Distribution, *n*	12 female; 28 male	12 female; 28 male
Handedness (R/L/Mixed), *n*	39/0/1	39/0/1
Race, White, *n* (%)	31 (78%)	27 (68%)
SAPS Total, Mean (SD)	NA	30.98 (20.70)
SANS Total, Mean (SD)	NA	34.53 (20.52)
BPRS Total, Mean (SD)	NA	51.54 (15.36)
CPZ Equivalent Dose, mg, Mean (SD)	NA	523.56 (573.07)

Mean participant age, education, symptom ratings, and medication information, and distributions of sex, race, and handedness in healthy control and schizophrenia samples. Medication information was not available for 1 participant. CPZ equivalent doses were calculated according to guidelines from Procyshyn *et al.* (90).

BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine; L, left-handed; NA, not applicable; R, right-handed; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

squares were presented for 2 seconds. During memory trials, participants viewed sets of semantically unrelated word pairs and their corresponding pictures. First, two words appeared, one on each side of the screen. After 1 second, line-drawing illustrations appeared with their respective words, one in orange and the other in black-and-white, and the word-picture pairs were presented together for an additional 3 seconds. In both the memory and control trials, participants were instructed to press the button corresponding to the location on the screen (left or right) of the orange item. For memory trials, participants were additionally instructed to memorize the word pairs by trying to form meaningful relationships between them and were given specific suggestions to "make a story about the two words, or think about how the two words could go together in real life." These training instructions encouraged the use of semantic encoding strategies. Participants were informed that their memory for the pairings would be tested in a subsequent recognition test.

Paired Associates Retrieval Testing

Participants' memory for previously learned word pairs was assessed in a subsequent in-scanner retrieval task (PAM retrieval); we analyzed only the PAM retrieval behavioral data. In each trial, participants viewed a pair of words with corresponding images. Participants made a right-handed button press to indicate "Sure correct," "Maybe correct," "Maybe incorrect," or "Sure Incorrect," according to their confidence that the pairing had previously been learned. There were 40 target trials, in which items were shown correctly paired as they had been during the encoding phase, and 40 foil trials, in which word pairings were new.

Data Analysis

Task Performance. Retrieval performance was evaluated based on signal detection theory (65). Discriminability (d-prime) was used to assess participants' sensitivity in discriminating between old and reorganized new pairs and was computed as the left-tail z score of the hit rate minus the z score of the false alarm rate. Hit trials were defined as those with a positive response (i.e., "sure correct" or "maybe correct") during target trials, and false alarm trials were those with a negative response during foil trials. Response bias during retrieval was computed as the decision criterion, $C = -0.5 \times (z$ score of the hit rate $+ z$ score of the false alarm rate). Additional performance measures consisted of RT during memory trials and proportion of "sure" responses. Independent-sample *t* tests

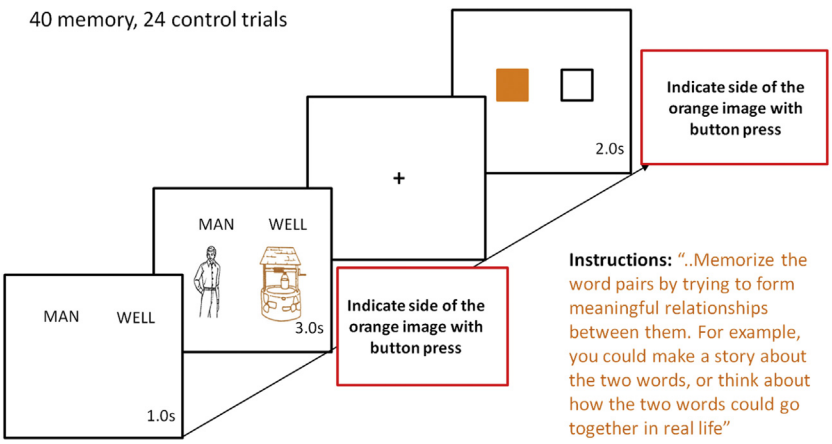

Figure 1. Task diagram for paired associates memory encoding functional magnetic resonance imaging task. Task diagram illustrates an example of a memory trial followed by a control trial. During memory trials, pairs of words with corresponding pictures were presented. Participants were instructed to memorize the word pairs by trying to form meaningful relationships between them. Participants were also instructed to press the first button if the orange image is on the left and the second button if the orange image is on the right. During control trials, instead of viewing word/object pairs, participants saw pairs of squares, and were tasked with pressing the button corresponding to the location of the orange square.

compared performance measures between groups. Participant attentiveness during encoding was verified by examining rates of missed trials, RT, and accuracy indicating the location of the orange object.

PAM-enc memory trials were retrospectively subdivided into successful encoding and unsuccessful encoding trials based on participants' retrieval responses: when participants responded positively to a target trial, the corresponding PAM-enc pairing was considered successfully encoded; when participants responded negatively to a previously presented pairing, the corresponding PAM-enc trial was considered unsuccessfully encoded.

To assess potential confounding effects of medication status, we ran simple regression analyses of the relationship of chlorpromazine equivalents with our primary performance measures.

Functional Connectivity Analysis. Image acquisition and preprocessing are detailed in the Supplement and elsewhere (51). The large-scale brain networks involved in the PAM-enc task were measured using fMRI-CPCA (53,56,66). fMRI-CPCA reveals distinct functional networks and their corresponding poststimulus fluctuations in blood oxygen level–dependent (BOLD) signal through multivariate regression of fMRI BOLD signal onto a task timing model, followed by PCA on the resulting predicted scores (Supplement) (52,67). The fMRI-CPCA application is available online (http://www.nitrc.org/projects/fmricpca).

Effects of group and task condition on hemodynamic response (HDR) were investigated using 10 × 3 × 2 mixed-model analyses of variance on the predictor weights (subject- and condition-specific estimates of BOLD signal) for each network, with within-subjects factors of time (10 poststimulus time points) and encoding (successful encoding, unsuccessful encoding, control) and the between-subjects factor of group (HC vs. SZ). Adjusted degrees of freedom are reported where the assumption of sphericity was violated.

Associations of Network Activation With Performance and Symptoms. Cognitive processes are thought to arise from the balanced and integrated activity of multiple spatially overlapping networks. Pre- and postpeak values can index different task-related cognitive processes (68–71) and were therefore computed separately. For each condition, baseline-to-peak activity was computed as the mean of predictor weights up to and including the peak, discarding the first scan. Return-to-baseline activity was computed as the average of all postpeak predictor weights. CPCA permutation-based significance testing was used to examine how network baseline-to-peak and return-to-baseline values related to 1) clinical symptoms and 2) performance measures independently of and in interaction with group using an α level of 0.01 to control for multiple testing (Supplement) (72).

RESULTS

Task Performance

Accuracy indicating the location of the orange object during encoding exceeded 93% for both the memory and control conditions for both groups; accuracy, RT, and missed trials did not differ between groups, indicating similarly good effort and engagement (p values $>$ .12) (Table 2). During retrieval testing, HC participants had significantly greater recognition sensitivity (d-prime), missed fewer trials, and made significantly more "sure" responses. HC participants had significantly faster RT during control trials; RT for memory trials and response bias criterion c did not differ significantly between HC subjects and participants with SZ (p values $>$ .08). Medication burden (chlorpromazine equivalent doses) did not significantly correlate with performance measures (p values $>$ .50).

Functional Connectivity

After inspection of the scree plot (73,74), 3 components were extracted, accounting for 17.90%, 13.03%, and 8.06% of timing-predictable variance in BOLD signal, respectively. All three networks showed significant effects of poststimulus time (p values $<$ .001). Visual examination of the predictor weights for each network confirmed biologically plausible HDR shapes (Figures 2–4). Each network's anatomical characteristics, overlap with resting-state networks, and overlap with previously published fMRI-CPCA components are detailed in the Supplement.

Component 1: Responding. Component 1 (Figure 2) included task-induced activations in the supplementary motor area, bilateral occipital cortex (BA 18, BA 19), left-dominant somatomotor areas, and bilateral hippocampus and thalamus. Spatially similar functional networks have been observed previously in tasks requiring coordinated responding and sustained visual attention, including our previous investigation of controlled semantic integration (39,75).

There was a significant time × encoding interaction ($F_{18,1404}$ = 7.53, p < .001), caused by an earlier peak for the control condition relative to the memory conditions and more robust modulation (rise to peak and postpeak suppression) in the successful encoding memory condition relative to other conditions. There was a significant interaction of time, group, and encoding ($F_{18,1404}$ = 3.43, p < .001), driven by a significant group × time interaction for the successful encoding condition ($F_{9,702}$ = 5.02, $p \leq$ .001) but not the unsuccessful encoding or the control conditions ($F_{9,702}$ = 0.24 and $F_{9,702}$ = 1.80, respectively; p = .91 and p = .13, respectively). Relative to the SZ group, HC subjects showed significant activation as the network rose to its peak (3–7 seconds) (t_{78} = 2.01, t_{78} = 3.41, and t_{78} = 2.23, respectively; p = .047, p = .001, and p = .029, respectively) in the responding network during successful encoding trials.

Component 2: Language/Attention. Component 2 (Figure 4) included task-induced activations in the left middle temporal gyrus, left fusiform gyrus, left middle and inferior frontal cortex, and dorsal anterior cingulate cortex, consistent with associative learning and language functions (76–78). This network also included robust hippocampal and visual cortex activations, which prior task-based multivariate analyses have demonstrated typically fall onto separate attentional brain networks involved in episodic encoding when experimental manipulations allow task-general functions to be disentangled from linguistic or other task-specific processes (71,75). This network

Table 2. Paired Associates Memory Performance by Group

Task Performance Measure	HC, Mean (SD)	SZ, Mean (SD)	Group Comparison	
			t	*p* Value
PAM-Enc Accuracy—Control Trials, %	93 (16)	95 (7)	$t_{78} = -0.72$	$p = .47$
PAM-Enc Accuracy—Memory Trials, %	94 (17)	98 (3)	$t_{120} = -1.50$	$p = .14$
PAM-Enc Control RT, ms	904 (215)	872 (122)	$t_{78} = 0.82$	$p = .42$
PAM-Enc Memory RT, ms	1207 (373)	1105 (372)	$t_{78} = 1.23$	$p = .22$
PAM-Enc Missed Trials, *n*	0.55 (1.1)	2.08 (6.0)	$t_{78} = -1.58$	$p = .12$
PAM-Ret Hit Rate, %	76 (16)	61 (19)	$t_{78} = 3.94$	$p < .001$[a]
PAM-Ret False Alarm Rate, %	19 (20)	44 (25)	$t_{78} = -5.02$	$p < .001$[a]
PAM-Ret Missed Trials, *n*	0.58 (1.37)	3.65 (5.54)	$t_{78} = -3.41$	$p < .001$[a]
PAM-Ret Rate "Sure" Responses, %	71 (21)	58 (20)	$t_{78} = 2.81$	$p = .005$[b]
PAM-Ret Control RT, ms	1345 (283)	1681 (318)	$t_{78} = -4.99$	$p < .001$[a]
PAM-Ret Memory RT, ms	2050 (289)	2182 (381)	$t_{78} = -1.75$	$p = .08$
d-Prime	1.92 (1.22)	0.55 (0.79)	$t_{78} = 5.93$	$p < .001$[a]
Criterion *C*	−0.47 (0.09)	−0.53 (0.17)	$t_{78} = 1.64$	$p = .11$

Task performance during PAM-enc and PAM-ret tasks, compared between healthy control and schizophrenia groups with independent-sample *t* tests. Means and SD are presented.

HC, healthy control; PAM-enc, paired associates memory encoding; PAM-ret, paired associates memory retrieval; RT, reaction time; SZ, schizophrenia.

[a] $p < .001$.

[b] $p < .01$.

replicated one that we previously observed to activate while passively hearing or internally generating sentences associating visually presented objects with their definitions (49).

There were significant main effects of encoding (successful encoding > control) ($F_{2,156} = 60.27$, $p < .001$) and a significant time × encoding interaction ($F_{18,1404} = 60.81$, $p < .001$), related to minimal activation of this network during the control condition. There was a significant time × encoding × group interaction ($F_{18,1404} = 6.15$, $p < .001$), driven by a significant time × group interaction only in the successful encoding condition ($F_{9,702} = 12.64$, $p < .001$; other p values > .16). During successful encoding, the HC group had a greater degree of language/attention network activation relative to the SZ group 5 to 15 seconds after stimulus onset, around the time of maximal network recruitment (p values < .03).

Component 3: Default Mode Network. Component 3 (Figure 3) was characterized by prominent negative loadings in regions associated with the default mode network (DMN) (79), including the medial cingulate and precuneus cortex and bilateral posterior temporal regions. It also included task-induced activations in the bilateral occipital cortex extending dorsally and rostrally to the superior parietal cortex. Because this component replicates previous work (39,70), we identified this network as visual regions anticorrelating with the DMN. The dominance of primary visual processing in the positive spatial loadings of the network and the early activation of the network relative to components 1 and 2 support this interpretation.

There were significant main effects of encoding (successful > control) ($F_{2,156} = 14.24$, $p < .001$), a significant time × encoding interaction ($F_{18,1404} = 19.37$, $p < .001$), and a significant time × encoding × group interaction ($F_{18,1404} = 2.73$, $p \leq .001$). Follow-up one-way analyses of variance found that group × time interactions reached significance for the successful encoding condition only ($F_{3.19,248.87} = 2.94$, $p = .031$; other p values > .41). During successful encoding, HC subjects had a faster return from DMN suppression relative to the SZ group, with significantly lower estimated HDR (reduced suppression) 11 seconds after stimulus onset as activity was returning to baseline ($t_{78} = -2.02$, $p = .047$).

A supplementary analysis held the number of trials constant across conditions to verify that group differences were not affected by the sample having more successful encoding than unsuccessful encoding trials (Supplement). The only effect that was not replicated was the time × encoding × group interaction in the DMN ($p = .11$) (Supplement).

Associations of Performance With Relationships Among Networks, Group, and Interaction of Group With Network

Permutation testing found that HDR independent of group and group independent of HDR accounted for variance in PAM retrieval performance above chance levels (38.18% and 6.56%, respectively, p values < .001; the interaction between group and network HDR did not reach significance [$p = .12$]). The significant main effect of group indicated that the SZ group had deficits in performance over and above those explained by network HDRs (Supplement).

The main effect of network HDR independent of group revealed a one-component solution, accounting for 29.68% of variance in performance. Table 3 contains all component and predictor loadings and corresponding p values. The component was dominated by RT, d-prime, and certainty ratings, but not response bias, with all significant loadings in the direction of better performance. Predictor loadings indicated that this pattern of memory performance was significantly associated with the degree of anticorrelation of the language/attention network and DMN during successful encoding.

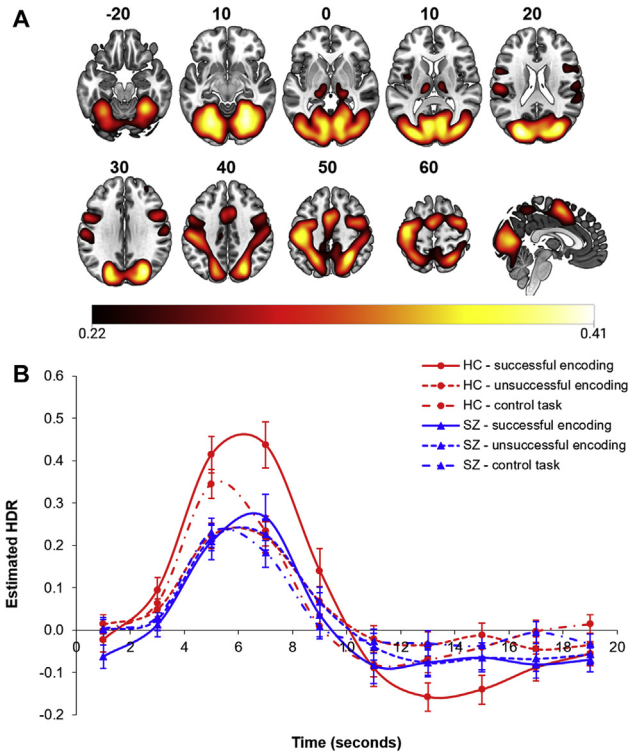

Figure 2. Spatial and temporal characteristics of the responding network. **(A)** Dominant 20% of component loadings for the responding network (component 1: positive loadings, threshold = 0.23, maximum = 0.42; no negative loadings). Slices are displayed in Montreal Neurological Institute coordinates. **(B)** Estimated responding network hemodynamic response for HC subjects and persons with SZ completing recalled and nonrecalled memory trials and control trials of the paired associate memory encoding task. Error bars = standard errors. HC, healthy control; HDR, hemodynamic response; SZ, schizophrenia.

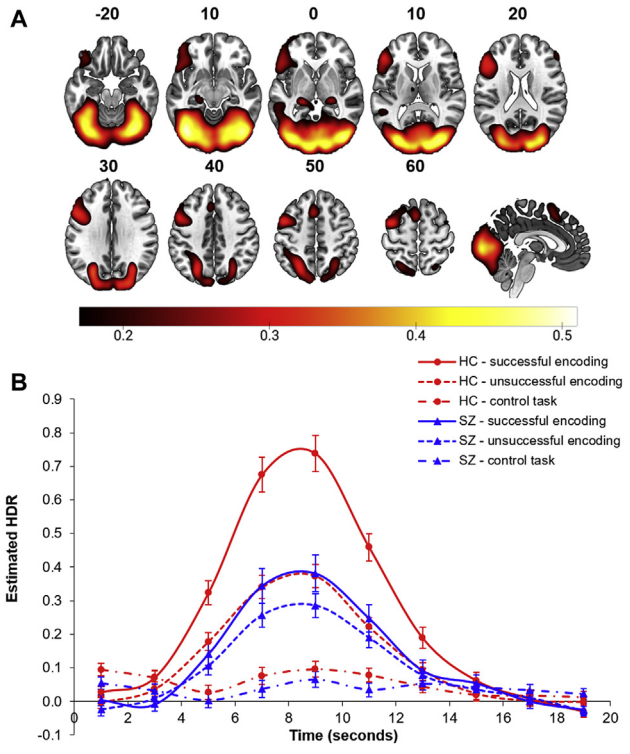

Figure 3. Spatial and temporal characteristics of the linguistic processing/attention network. **(A)** Dominant 20% of component loadings for the linguistic processing/attention network (component 2: positive loadings, threshold = 0.18, maximum = 0.50; no negative loadings). Slices are displayed in Montreal Neurological Institute coordinates. **(B)** Estimated linguistic processing/attention network hemodynamic response for HC subjects and persons with SZ completing recalled and nonrecalled memory trials and control trials of the paired associate memory encoding task. HC, healthy control; HDR, hemodynamic response; SZ, schizophrenia.

Associations of Network Activation and Symptom Ratings

HDR estimates did not account for variance in Brief Psychiatric Rating Scale or Scales for the Assessment of Negative/Positive Symptoms symptoms above chance levels (48.05% and 37.69%, respectively; p = .12 and p = .87, respectively).

DISCUSSION

In a novel investigation of the network-level basis of impaired relational encoding using a deep semantic strategy in SZ, fMRI-CPCA identified 3 distinct whole-brain functional networks recruited during paired associates learning: a responding network, a language/attention network, and the DMN. A pattern of anticorrelating language/attention–DMN activity during successful encoding significantly predicted subsequent retrieval of paired associates, independent of group effects.

Component 1: Responding

The responding network included activations in regions that have been implicated in somatomotor activity and demonstrated postpeak hemodynamic suppression similar to previously published whole-brain networks implicated in response processes (39,66,71,75,80,81). It exhibited greater engagement for successful relative to unsuccessful encoding, had an early peak and return to baseline relative to other networks, and included visual, frontal, and thalamic activations. Together, these temporal and spatial properties suggest that the network supports early attentional processes in addition to responding.

Component 2: Language/Attention

The language/attention network was the only network to specifically engage during the memory encoding conditions. It exhibited minimal engagement during the nonmemory control task and was most active during successful encoding. The language/attention network spatially replicated one that we previously found in a task-merge analysis to activate while internally generating sentences (49) (Figures S5 and S6). This network included activations in VLPFC regions (BA 44, 45) that have been previously been found to normalize in individuals with SZ during item encoding when using semantic strategies (82); these findings therefore suggest that the ability to activate the semantic network may become a limiting factor under relational encoding demands. It is notable that DLPFC regions

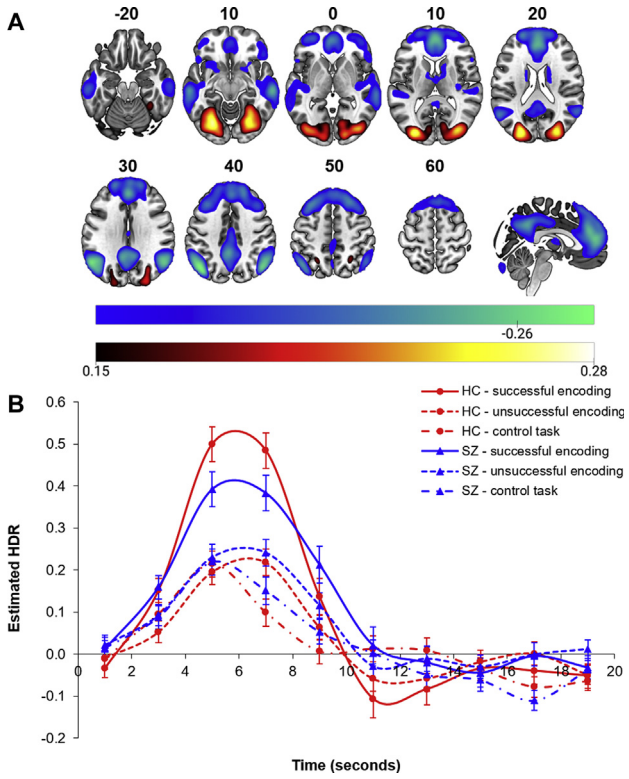

Figure 4. Spatial and temporal characteristics of the DMN. **(A)** Dominant 20% of component loadings for the DMN (component 3: negative loadings, threshold = −0.15, minimum = −0.27; positive loadings, threshold = 0.15, maximum = 0.30). Slices are displayed in Montreal Neurological Institute coordinates. **(B)** Estimated DMN hemodynamic response for HC subjects and persons with SZ completing recalled and nonrecalled memory and control trials of the paired associate memory encoding task. Error bars = standard errors. DMN, default mode network; HC, healthy control; HDR, hemodynamic response; SZ, schizophrenia.

(BA 9, BA 46) were not characteristic of the networks that hypoactivated in persons with SZ and predicted poorer performance; this suggests that a higher-order deficit in implementing the semantic strategy was not a limiting factor.

Hypoactivation of the language/attention network in participants with SZ during successful encoding is consistent with previous findings of frontotemporal hypoactivity during controlled semantic processes (39–43). It is also consistent with previous mass-univariate findings of hypoactive left inferior frontal and temporal cortices during encoding of verbal paired associates in SZ (25) and extends these findings to delineate how these regions are functionally connected within a distributed network.

Component 3: DMN

The DMN network exhibited demand-dependent deactivation, consistent with previous research [e.g., (39,75,81,83,84)]. The greater and more sustained deactivation for the memory conditions relative to the control condition was likely influenced by the shorter trial length (2 vs. 4-s memory trials), and presumably lower demands, of the control trials. Compared with the SZ group, HC subjects may have had an earlier return from suppression in the DMN during successful encoding, possibly

Table 3. Relationship of Network Activation With Retrieval Performance, Independent of Group

Performance Measures	Component Loading	*p* Value
PAM-ret Memory RT	−0.32	<.001[a,b]
Sensitivity d-prime	0.50	<.001[a,b]
Decision Criterion *C*	0.06	.32
Proportion of "Sure" Ratings	0.28	.002[b,c]
Network HDR Measures	**Predictor Loading**	***p* Value**
Responding		
Control BTP	0.16	.10
Control RTB	0.02	.81
Successful encoding BTP	0.13	.19
Successful encoding RTB	−0.06	.54
Unsuccessful encoding BTP	−0.23	.02
Unsuccessful encoding RTB	0.17	.08
Linguistic processing/attention		
Control BTP	0.04	.73
Control RTB	−0.03	.72
Successful encoding BTP	0.54	<.001[a,b]
Successful encoding RTB	0.40	<.001[a,b]
Unsuccessful encoding BTP	−0.23	.02
Unsuccessful encoding RTB	0.06	.57
Default mode network		
Control BTP	−0.02	.87
Control RTB	−0.06	.55
Successful encoding BTP	0.29	<.001[a,b]
Successful encoding RTB	−0.38	<.001[a,b]
Unsuccessful encoding BTP	−0.18	.08
Unsuccessful encoding RTB	−0.24	.01

Component and predictor loadings for constrained principal component analysis analysis exploring relationship of HDR measures, independent of group, with PAM-ret performance. An α level of 0.01 was used to control for multiple testing.

BTP, baseline-to-peak; HDR, hemodynamic response; PAM-ret, paired associates memory retrieval; RT, reaction time; RTB, return-to-baseline.

[a] $p < .001$.
[b] $p < .005$.
[c] $p < .01$.

reflecting greater neural efficiency. However, this should be interpreted cautiously, because it was not replicated in a supplementary analysis using an equal subset of trials per condition.

Associations of Performance and Symptoms With Network Coordination

The degree of language/attention–DMN anticorrelation during successful encoding using semantic association significantly predicted subsequent retrieval performance independent of group effects. This finding is interesting considering previous findings of aberrant coordination between language networks and the DMN among individuals with SZ during passive verbal processes (49,85). Whereas previous research indicates that individuals with SZ have greater activity in language regions and more silencing of the DMN during passive verbal processes (49,85), this study indicates a weaker trade-off between the language/attention network and DMN in the SZ group

during verbal associative encoding, a pattern that predicted poorer retrieval performance. DMN activation during encoding has been shown to predict subsequent forgetting (86), perhaps owing to lapses in attention or mind-wandering (87–89). Network activation was not significantly associated with symptom ratings.

Limitations

Participants' use of semantic encoding strategies was not verified (e.g., through self-report). It could be that groups differed in utilization of the semantic strategy; however, the observation that DLPFC activation did not characterize any of the networks that predicted performance or distinguished groups makes this interpretation less likely. It is also possible that the effects we report here were influenced by medication status. We did not find associations between medication burden and performance, however, and the relationship of language/attention–DMN anticorrelation with retrieval performance was independent of group effects.

This experimental design may also be limited in its ability to separate networks supporting linguistic demands from those supporting task-general processes. Our previous work (49,71,75) has highlighted that when distinct networks have similar time courses, the low temporal resolution of the HDRs often result in the spatial and temporal blurring of multiple networks. The language/attention network reported here and previously (49) may therefore amalgamate several processes that could be separated through careful experimentation—for example, by systematically varying the semantic relatedness of word pairs. fMRI-CPCA offers the significant advantage of allowing networks to be held constant across multiple task designs, enabling future investigations of such questions [see (49,50,57,75) for illustrations of this approach]. Our findings represent an important starting point for describing the neural abnormalities limiting the effectiveness of deep semantic strategies in SZ.

Conclusions

These findings indicate that semantic network hypoactivity and inefficient DMN suppression may limit the ability of persons with SZ to employ deep semantic strategies during relational episodic encoding.

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ARTICLE INFORMATION

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