



Altered language network activity in young people at familial high-risk for schizophrenia

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ABSTRACT

Background: Abnormalities in language and language neural circuitry are observed in schizophrenia (SZ). Similar, but less pronounced language deficits are also seen in young first-degree relatives of people with SZ, who are at higher familial risk (FHR) for the disorder than the general population. The neural underpinnings of these deficits in people with FHR are unclear.

Methods: Participants were 43 people with FHR and 32 comparable controls. fMRI scans were collected while participants viewed associated and unrelated word pairs, and performed a lexical decision task. fMRI analyses conducted in SPM8 examined group differences in the modulation of hemodynamic activity by semantic association.

Results: There were no group differences in demographics, IQ or behavioral semantic priming, but FHR participants had more schizotypal traits than controls. Controls exhibited the expected suppression of hemodynamic activity to associated versus unrelated word pairs. Compared to controls, FHR participants showed an opposite pattern of hemodynamic modulation to associated versus unrelated word pairs, in the left inferior frontal gyrus (IFG), right superior and middle temporal gyrus (STG) and the left cerebellum. Group differences in activation were significant, FWE-corrected for multiple comparisons ($p < 0.05$). Activity within the IFG during the unrelated condition predicted schizotypal symptoms in FHR participants.

Conclusions: FHR for SZ is associated with abnormally increased neural activity to semantic associates within an inferior frontal/temporal network. This might increase the risk of developing unusual ideas, perceptions and disorganized language that characterize schizotypal traits, potentially predicting which individuals are at greater risk to develop a psychotic disorder.

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1. Introduction

Schizophrenia (SZ) has been characterized as a disorder of language, thought and communication since its earliest inception (Bleuler, 1950; Andreasen, 1979). Deficits range from the single word to whole discourse level (Goldberg et al., 1998; Titone et al., 2000; Kuperberg and Goldberg, 2006; Kuperberg, 2010a,b) and have been detected prior to or during the first episode (Hoff et al., 1999; Fuller et al., 2002; Hoff et al., 2005). It has been suggested that language deficits in SZ arise from an abnormal spread of activity across semantic networks, due to

abnormalities in both automatic and controlled mechanisms of semantic retrieval (Manschreck et al., 1988; Spitzer et al., 1994; Kuperberg and Goldberg, 2006; Kreher et al., 2008).

One way of examining the spread of activity across semantic networks is through semantic priming (Meyer and Schvaneveldt, 1971; Neely, 1991). Semantic priming describes the faster response to a target word when it is preceded by a semantically associated word compared to an indirectly associated or unrelated word. There is some inconsistency in results of semantic priming experiments in patients with SZ. While some behavioral (Manschreck et al., 1988; Spitzer et al., 1994; Moritz et al., 2001b) and electrophysiological studies (Kreher et al., 2008) have shown an exaggerated semantic priming effect in patients with SZ (Maher et al., 2005; Kuperberg et al., 2007), other studies reveal normal or reduced priming (Kuperberg et al., 2008a; Kreher et al., 2009).

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Two factors that affect the direction of findings in priming studies of SZ are the presence of thought disorder in study participants, and the experimental design. Increased semantic priming effects (including priming responses to indirectly-related as well as directly-related primes) are generally reported when the patients with SZ have formal thought disorder (Manschreck et al., 1988; Spitzer et al., 1994; Moritz et al., 2001a, 2001b; Kreher et al., 2008), and/or when the experiment is designed to probe automatic semantic retrieval mechanisms (Neely, 1991; Spitzer et al., 1993, 1994; Moritz et al., 2001a, 2001b; Lecardeur et al., 2006; Pomarol-Clotet et al., 2008; Kreher et al., 2009). In the latter case, the effect of strategy, expectancy and general executive function on performance is circumvented using a number of techniques, including use of a short interval between the prime and target word (Stimulus Onset Asynchrony, or SOA). Alternatively, when participants are not selected based on the presence of thought disorder, or when the experiment is designed to probe controlled, strategic aspects of semantic prediction or retrieval, patients with SZ show normal or reduced priming effects relative to controls (Vinogradov et al., 1992; Barch et al., 1996; Ober et al., 1997; Besche-Richard et al., 2005; Kreher et al., 2009).

The neural basis of lexico-semantic processing is fairly well understood. Broadly, middle and inferior temporal cortices have been implicated in lexico-semantic storage and access (Van Petten and Luka, 2006; Lau et al., 2008; Lau et al., in press) while the left inferior frontal cortex (Broca's area) is thought to mediate controlled semantic retrieval and/or selection (Thompson-Schill et al., 1997, 1999; Wagner et al., 2001; Gold et al., 2006). fMRI studies of semantic priming in healthy individuals have demonstrated reduced activity to semantically associated versus unrelated word pairs within both temporal and inferior frontal regions ('association-induced suppression') (Kotz et al., 2002; Copland et al., 2003; Rissman et al., 2003; Matsumoto et al., 2005; Wheatley et al., 2005; Kuperberg et al., 2008b). Because fMRI is sensitive to the relatively slow hemodynamic response (integrating activity over seconds), it is not possible to distinguish neural responses to the prime vs. the target using this method alone. However, a recent study combining fMRI with event-related potentials (ERPs) and magnetoencephalography (MEG) suggests that automatic priming can lead to neural suppression within the left anterior temporal cortex between 300 and 500 ms (the N400 time window) following target onset (Lau et al., in press).

Consistent with altered semantic processing in SZ, fMRI studies of semantic priming in SZ have reported less association-induced suppression in left frontal and temporal regions (Han et al., 2007; Kuperberg et al., 2007), and sometimes even the opposite pattern of modulation, with more activity to semantically associated relative to unrelated pairs ('association-induced enhancement') (Kuperberg et al., 2007). These abnormalities were seen even when behavioral semantic priming was normal. In inferior temporal cortices, the degree of association-induced enhancement in SZ predicted severity of positive thought disorder (Kuperberg et al., 2007).

There is considerable debate about what drives hemodynamic response suppression versus enhancement in priming paradigms (Segaert et al., 2013). Kuperberg et al. (2007) speculated that the abnormal hemodynamic response enhancement in patients arose from a failure to inhibit activity within the temporal cortex to the related words, perhaps as a result of an inefficiency of left frontal cortex-mediated controlled processing. fMRI concatenates neural activity over a number of time scales, and thus, it may be that both inefficiency in frontal function and prolonged residual activation in the temporal cortex were captured by the overall increase in BOLD activity to the related (versus unrelated) words in patients. Results were interpreted to be consistent with associative hyperactivity and possible frontotemporal dysconnection in SZ (Kuperberg et al., 2007).

Altered frontotemporal responses during semantic priming in SZ are consistent with other neuroimaging data implicating frontotemporal alterations in SZ (Petty et al., 1995; Li et al., 2007a; Oertel et al., 2010). These include altered frontotemporal connectivity (Skudlarski et al.,

2010; Voineskos et al., 2010; Wang et al., 2011), abnormalities in the structure of Broca's and other frontal regions (Sanfilippo et al., 2000; Shenton et al., 2001; Wible et al., 2001; Bartzokis et al., 2003; Kuperberg et al., 2003; Wisco et al., 2007), abnormalities within white matter tracts to and from the temporal lobe (Honer et al., 1995; Shenton et al., 2001; Kubicki et al., 2002; Burns et al., 2003; Hubl et al., 2004; Jones et al., 2006; Cui et al., 2010; Whitford et al., 2010; Cui et al., 2011; Kubicki et al., 2011) and altered fMRI activation during performance on a wide variety of language tasks (Sommer et al., 2001; Kubicki et al., 2003; Sommer et al., 2003; Weiss et al., 2003; Ragland et al., 2004; Sommer et al., 2004; Li et al., 2007a; Kuperberg et al., 2008c; Li et al., 2009; Oertel et al., 2010). It has been suggested that these abnormalities may result from early, possibly genetically-mediated alterations in the development of language circuits (Wyatt, 1996; Crow, 1997; Woolf, 1997; Crow, 2008) that occur prior to disease onset (Pantelis et al., 2003). Indeed, retrospective analysis of clinical data indicates early language and reading delays in people who later developed SZ (DeLisi et al., 1991; Hoff et al., 1999, 2005).

Language and frontotemporal alterations may also be a marker of disease risk. There is increasing evidence of language (Hallett et al., 1986; Ott et al., 2001; Cannon et al., 2002; Whalley et al., 2004; Bhojraj et al., 2009) and frontotemporal alterations in first-degree biological relatives of persons with SZ, who are at elevated or familial high-risk (FHR) to develop a psychotic disorder. Neuroimaging studies of participants with FHR reveal structural alterations, and in some cases, altered lateralization (Sommer et al., 2004; Li et al., 2009) in frontal and temporal regions. Structural abnormalities have been described in the posterior sylvian fissure (Honer et al., 1995), inferior frontal (McIntosh et al., 2004; Bhojraj et al., 2009, 2011; Li et al., 2012) and several temporal regions (McIntosh et al., 2004; Oertel et al., 2010; Goghari et al., 2011; Li et al., 2012) [e.g., Heschl's gyrus (Bhojraj et al., 2009, 2011), superior temporal gyrus (STG) (Rajarethinam et al., 2004) and the planum temporale (Oertel et al., 2010)]. Some fMRI studies of language in FHR participants (using diverse language tasks) have reported increased right inferior frontal activity (Sommer et al., 2004; Li et al., 2007b) (or decreased left-sided activity) (Li et al., 2007a), as well as abnormalities in temporal, parietal and cerebellar regions (Sommer et al., 2004; Whalley et al., 2004; Whyte et al., 2006; Rajarethinam et al., 2011). In one study, a functional connectivity analysis revealed reduced connectivity from inferior frontal to visual language processing regions (Li et al., 2010). Taken together, these results suggest that abnormalities of frontotemporal pathways might increase vulnerability to develop SZ in FHR participants. What remains unclear, however, is whether participants with FHR show the more specific abnormalities in semantic associative activity that are thought to be central to SZ itself.

To address this question, we carried out a semantic priming fMRI study in young adult participants with FHR and low-risk controls, using the same set of stimuli and task that has previously been used to examine semantic activity in SZ (Kuperberg et al., 2007). We examined how the semantic association between prime and target word-pairs modulated lexical decision reaction times and hemodynamic activity in language-related brain regions. Analyses were carried out across the whole brain and in language-specific regions of interest, derived from previous studies of language in participants with FHR and studies of semantic priming in healthy controls and patients with SZ (inferior frontal gyrus and superior, middle and inferior temporal gyrus). We also examined the relationship between language-related brain activity, behavioral semantic priming and schizotypal symptoms. Based on previous work in SZ, we predicted that participants with FHR would exhibit association-induced enhancement (with more activity to the associated relative to unrelated word pairs) in inferior frontal and temporal regions (where controls exhibit association-induced suppression). We predicted that differences in semantic association-induced brain activity in FHR participants would be associated with increased schizotypal symptoms.

2. Methods and Materials

2.1. Participants

Participants were 43 non-psychotic people with FHR (having at least one first-degree relative with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, and one 1st, 2nd or 3rd degree relative with a history of psychosis, suicide, psychiatric hospitalization or Axis I disorder), and 32 controls (with no family history of a psychosis in 1st, 2nd or 3rd degree relatives), who were group-matched in age (mean age 25, range 19–32), gender, ethnicity and handedness (all right-handed). FHR participants were recruited from Massachusetts and neighboring New England regions through brochures and advertisements and through the National Alliance on Mental Illness (NAMI). Controls were recruited from the same communities as the FHR participants via advertisement. Exclusion criteria for all participants were: lifetime history of DSM-IV psychotic disorder, English not the participant's native language, non-right-handedness (Annett, 1970), neurological illness, and IQ below 80. Control participants were excluded if they had a family history of psychotic disorder, other major psychiatric illness or suicide. The Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; First et al., 1996) indicated the following diagnoses in the participants with FHR: 16 with major depression, 8 with anxiety disorder, 8 with attention deficit hyperactivity disorder, 6 with substance abuse, 4 with an eating disorder, and 2 with schizotypal personality disorder. The study was approved by the Human Participants Investigation Committee at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts Institute of Technology, Brigham and Women's Hospital and Veterans Administration Boston Healthcare System, Brockton, Massachusetts. All participants provided written informed consent and were paid for their participation.

2.2. Psychiatric and neuropsychological assessments

A medical and substance use history and family pedigree were obtained via interview. The Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; First et al., 1996) was administered by an experienced, trained interviewer, to establish the lifetime presence of any Axis I or II psychiatric disorder. Diagnoses based on the DIGS were made by the study Principal Investigator (L.E.D.). Schizotypal traits (magical thinking, ideas of reference, illusions, suspiciousness, psychotic-like symptoms, restricted emotion, social isolation/introversion, schizotypal social anxiety, and anger to slights) were assessed using the Structured Interview for Schizotypy (SIS) (Kendler et al., 1989). This interview provides an indication of attenuated psychotic symptoms which may be observed on a continuum, and to varying degrees in non-psychotic people at FHR for SZ. Subjects are given a score on each schizotypal trait ranging from 0 to 6, with scores over 2 indicative of psychopathology. For each subject, scores were quantified as: 1) the number of schizotypal trait scores with a non-zero value, and 2) the number of schizotypal traits with a global score over 2. Mood on the day of scanning was assessed with the Profile of Mood States (POMS) (McNair et al., 1992). General intellectual ability (IQ) was prorated from Vocabulary and Block Design subtests of the Wechsler Adult Scale of Intelligence (WASI) (Wechsler, 1999). Relative hand preference was assessed using the Annett 23 item scale (Annett, 1970).

2.3. Semantic priming paradigm

During scanning, participants carried out a semantic priming paradigm with a lexical decision task, using stimuli developed for Kuperberg et al. (2007) and Kreher et al. (2006). These consisted of target words (e.g., stripes) that were paired with associated primes (tiger) or unrelated primes (truck) (methods used to establish the associative strength between prime-target word pairs in studies of controls are further

detailed in Kreher et al. (2006) and Kuperberg et al. (2007)). In a third condition, targets were paired with indirectly related primes. In this study, however, we focus on the contrast between associated and unrelated word pairs as this provides the most robust measure of association-induced hemodynamic activity. All nonword targets were phonologically permissible strings in English and they were all derived from words that were unrelated to their primes (e.g., lion-soble). Stimuli were counterbalanced across the three lists.

During each of three 6 minute and 10 second fMRI runs, participants viewed a list of 200 stimulus pair trials: 50 associated, 50 unrelated and 50 indirectly related prime-target word-pairs, and 50 word-nonword trials. Each trial began with the prime (500 ms), a blank screen (300 ms), a target (500 ms), and then another blank screen (300 ms) [thus, we used a fixed 800 millisecond stimulus onset asynchrony (SOA) between the onset of the prime and the onset of the target]. Between each word pair, a question mark appeared (1100 ms) followed by a blank screen (300 ms). The trial types appeared in pseudorandom order, interspersed among 100 visual fixation trials (where participants fixated on a plus sign for variable durations of 1000–8000 ms; mean, 3000 ms). The random interleaving of these fixation or null-events among the word-pairs enabled the efficient estimation and deconvolution of the entire hemodynamic response (Burock et al., 1998).

During the lexical decision task, participants decided as quickly and as accurately as possible whether the target was a real English word or a nonword, indicating their decisions by button press. Participants were trained on the task prior to scanning. Their accuracy and reaction times (RTs) were recorded.

2.4. Neuroimaging

Imaging was conducted on a Siemens TRIO TIM 3.0 Tesla full body MR scanner at the A.A. Martinos Imaging Center in the McGovern Institute for Brain Research at the Massachusetts Institute of Technology (MIT), using a 32 channel head coil. A localizer sequence was performed for placement of slices, followed by a coronal T2-weighted sequence to rule out unexpected neuropathology. During each of the three semantic priming task runs, whole-brain T2* weighted gradient echo EPI was acquired (TR/TE/Flip = 2000 ms/30 ms/90°, 32 contiguous 4 mm thick slices, positioned parallel to anterior commissure–posterior commissure line, echo spacing = 0.5, bandwidth = 2300, FOV = 200 × 200, matrix size = 64 × 64). To accelerate fMRI acquisitions and minimize distortions, GRAPPA (Generalized Autocalibrating Partially Parallel Acquisition) with an acceleration factor of 2 was used. The fMRI sequences included prospective acquisition correction (PACE) for head motion (Thesen et al., 2000).

2.5. Statistical analysis

All (non-fMRI) variables were compared using ANOVAS and independent sample t-tests performed in the Statistical Package for the Social Sciences (SPSS) software. Accuracy (with which nonwords and words were correctly classified) was calculated as the percentage of items answered correctly. RTs were entered into a 2 × 2 ANOVA (with Group as the between-subjects factor and Association as the within-subjects factor).

Pre-processing of fMRI data [motion correction, co-registration, spatial normalization (using nonlinear volume-based techniques) and smoothing (with an 8 mm Gaussian filter)] and statistical analysis of semantic priming related modulation of blood-oxygen level dependent (BOLD) signal (activation and suppression) was examined using SPM8 (Department of Imaging Neuroscience, London, UK) (www.fil.ion.ucl.ac.uk/spm/) and in-house software (<http://web.mit.edu/swg/software.html>) running in the MATLAB environment (Mathworks, Inc.). Data were inspected for artifacts and motion using custom software ART (<http://web.mit.edu/swg/software.html>).

Table 1
Demographic, neuropsychological and clinical characteristics of controls (CON) and young people at familial high-risk for schizophrenia (FHR).

| Variable | CON (n = 32) | FHR (n = 43) | CON v. FHR |
|---|----------------|----------------|-----------------------|
| | Mean (SD) or % | Mean (SD) or % | t (p) or χ^2 (p) |
| <i>Matching variables</i> | | | |
| Age at MRI | 24.6 (2.8) | 25.2 (3.1) | .93 (.36) |
| Gender (% male) | 41% | 29% | .88 (.35) |
| Ethnicity (% cauc.) | 78% | 69% | 2.33 (.80) |
| Handedness (% right) | 100% | 100% | – |
| WRAT-IV ^a reading | 109.6 (12.8) | 110.9 (12.5) | .41 (.69) |
| <i>Education & IQ</i> | | | |
| Education (years) | 16.0 (1.7) | 15.6 (2.3) | .99 (.32) |
| IQ estimate ^b | 117.7 (14.7) | 116.8 (11.4) | .24 (.81) |
| | Mean (SD) | Mean (SD) | t (p) |
| <i>Lexical decision task (in-scanner)</i> | | | |
| Associated cond. (% hits) | 98.9% | 96.3% | 0.84 (.41) |
| Unrelated cond. (% hits) | 98.3% | 95.1% | 1.05 (.30) |
| Associated cond. RT ^c | 844 (227) | 857 (206) | .26 (.80) |
| Unrelated cond. RT ^c | 857 (216) | 875 (203) | .37 (.71) |
| <i>POMS^d T scores</i> | | | |
| Tension/anxiety | 30.9 (4.9) | 34.4(7.3) | 2.32 (.02) |
| Depression | 36.8 (6.1) | 39.5 (7.7) | 1.67 (.10) |
| Anger/hostility | 41.1 (4.9) | 44.7 (7.3) | 2.37 (.02) |
| Vigor | 64.1 (9.5) | 61.4 (9.1) | 1.26 (.21) |
| Fatigue | 41.4 (4.5) | 46.2 (8.8) | 2.98 (.009) |
| Confusion | 33.7 (4.6) | 36.2 (9.4) | 1.39 (.17) |
| <i>SIS^e scores</i> | | | |
| No. of positive scores | 2.2 (2.2) | 7.8 (7.6) | 4.40 (.00004) |
| No. of scores > 2 | 1.1 (1.5) | 5.5 (7.0) | 3.83 (.0002) |

^a WRAT-3, Wide Range Achievement Test—Third Edition.

^b Full Scale IQ assessed using the Wechsler Adult Intelligence Scale-III prorated from eight sub-tests.

^c Milliseconds.

^d Profile of mood states.

^e Structured Interview for Schizotypy.

2.5.1. Semantic association-induced modulation of brain activity

First-level analysis was implemented in SPM8. Estimated motion parameters, artifact-indicator covariates, and low-frequency components were explicitly modeled and their effects removed from the estimation of effects of interest. Contrasts of interest (Unrelated > Associated; Associated > Unrelated) were defined for each subject and entered into second-level group analyses. Group differences in activation were assessed using a 2 (Group) × 2 (Association) ANOVA. Group differences in activation can be driven by differences in the Associated condition, the Unrelated condition, or both. Thus, to further characterize between-group differences, parameter estimates were extracted from the functional clusters that significantly differentiated the groups for the Associated and Unrelated conditions separately (with level of

Table 2
Significant differences in suppression of hemodynamic activity to associated versus unrelated word pairs in controls (CON) compared to young people at familial high-risk for schizophrenia (FHR).

| Difference in fMRI response between groups | Peak coordinate (MNI) ^a | | | | | | | | | |
|--|------------------------------------|------|-------------------------|-----|-----|-----|----------------|----------------|-----------------|--------------------|
| | Region | L/R | Cluster extent (voxels) | x | y | z | Group contrast | t ^b | Effect size (d) | p |
| <i>Whole-brain analysis^c</i> | | | | | | | | | | |
| Inferior frontal and dorsolateral prefrontal cortex (BA 44–46) | L | 2384 | | –54 | 20 | 16 | CON > FHR | 3.47 | 0.81 | 0.002 ^c |
| Cerebellum (posterior lobe) | L | 2058 | | –18 | –64 | –41 | CON > FHR | 3.08 | 0.72 | 0.004 ^c |
| <i>Region-of-interest analysis^d</i> | | | | | | | | | | |
| Superior and middle temporal cortex (BA 21, 22) | R | 24 | | 66 | –25 | –2 | CON > FHR | 3.61 | 0.84 | 0.051 ^d |

^a MNI = Montreal Neurological Institute Coordinate System.

^b Maximum voxel-wise t-value within the cluster of interest.

^c Whole-brain analysis: cluster-wise family-wise error (FWE)-corrected statistic (p < 0.05).

^d Region-of-interest analysis: for regions of interest defined a priori, the voxel-wise statistic was FWE-corrected for multiple comparisons within the a priori region.

activity in each separate condition calculated relative to the baseline fixation). Parameter estimates for each condition relative to fixation baseline were then depicted in the graphs. In addition, we tested for effects of Association within the control and FHR participant groups separately across the whole brain using one-sample t tests on the contrast images. Results were corrected for multiple comparisons across the whole brain or across a priori regions of interest, using the family-wise error correction, cluster-level significance of p < 0.05. Bilateral language task-specific regions of interest were created using the Wakeforest University Pickatlas Tool (<http://www.fmri.wfubmc.edu>) and cortical parcellation methods developed at the Center for Morphometric Analysis (<http://www.cma.mgh.harvard.edu/>), and defined as follows: inferior frontal gyrus (BA 44, 45, 47), orbitofrontal gyrus (BA 10, 11), lateral temporal cortex (including STG and MTG; BA 22, 42, 21) and temporal fusiform cortex (BA 37, 20).

To test a priori hypotheses about relationships between brain activity, task performance and schizotypal symptoms, we carried out bivariate Pearson's correlations (or Spearman's, where appropriate) between the fMRI parameter estimates, behavioral semantic priming and schizotypal traits. For these analyses, parameter estimates for each condition (Unrelated > Fixation; Associated > Fixation) were extracted from predicted functional regions that distinguished the two groups (inferior frontal and temporal regions). Parameter estimates were correlated with 1) a behavioral semantic priming (quantified as the Unrelated condition mean RT–Associated condition mean RT) and 2) schizotypal traits [quantified as number of global SIS scores with a value in the abnormal range (>2)]. Correlations were examined within the control and FHR participant groups separately. Correlations with a p-value < 0.05 were reported as significant.

3. Results

3.1. Demographic, neuropsychological and clinical characteristics

There were no group differences in demographic variables, education or IQ (Table 1). Participants with FHR exhibited significantly greater scores on the tension/anxiety, anger/hostility and fatigue subscales of the POMS, and a significantly higher number of positive SIS scores and number of global SIS scores > 2.

3.2. Behavioral semantic priming

There was a significant main effect of Association on RTs ($F(1,73) = 12.17$, $p = 0.001$), reflecting shorter RTs to directly associated than unrelated targets, i.e., a semantic priming effect. There was no difference in semantic priming between FHR and control participants, as reflected by the absence of a Group by Association interaction ($F(1,73) = 0.31$, $p = 0.58$), and there were no overall differences in RTs between FHR and control participants ($F(1,73) = 0.10$, $p = 0.76$). There were no

effects of Association or Group, and no Association by Group interaction effect on accuracy (all $F_s < 2.7$, $p_s > 0.10$).

3.3. The modulation of hemodynamic activity by semantic association

A 2×2 ANOVA revealed a significant interaction between Group and Association within the left inferior frontal gyrus (IFG), right superior

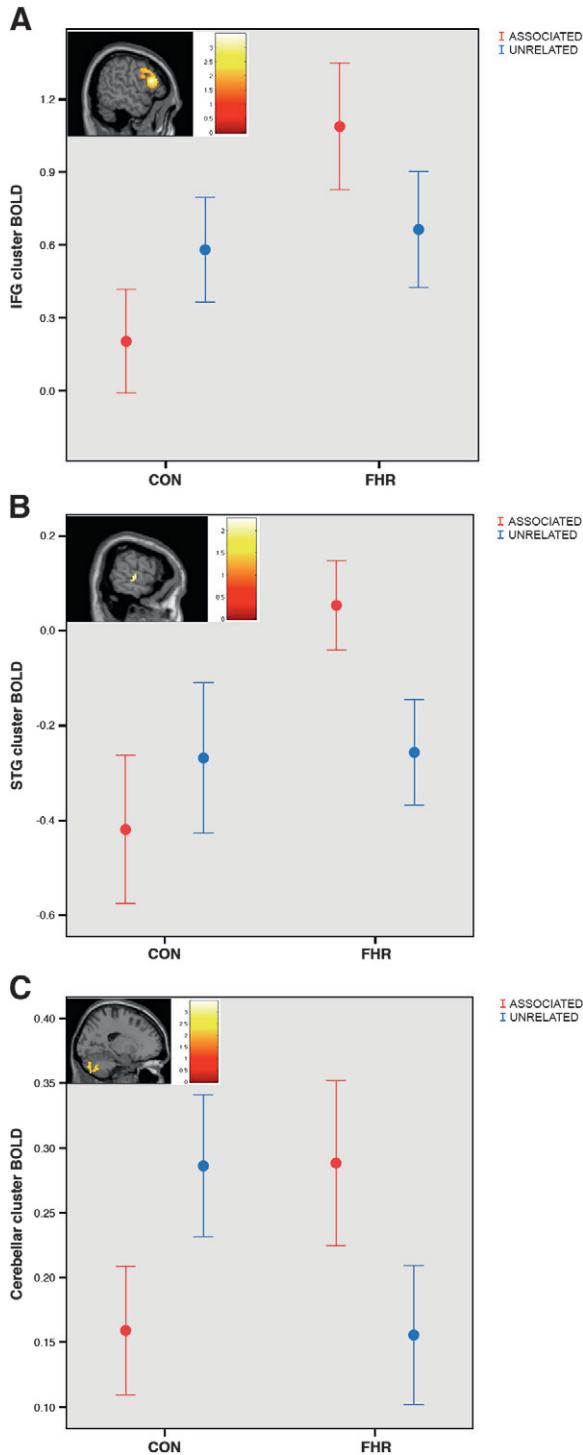


Fig. 1. Compared to controls, participants with FHR showed an opposite pattern of hemodynamic modulation to associated versus unrelated word pairs, in the (A) left inferior frontal gyrus (IFG), (B) right superior and middle temporal gyrus (STG) and (C) left cerebellum (group differences $p < 0.05$, family-wise error cluster-level corrected for multiple comparisons). Color bar = t-value. Bar graphs depict parameter estimates extracted from the significant inferior frontal gyrus, superior/middle temporal gyrus and cerebellar clusters for the Associated (red) and Unrelated (blue) word pair conditions, relative to the baseline fixation.

and middle temporal gyrus (STG) and left cerebellum (Table 2, Fig. 1). Follow-up analyses to determine the source of this interaction were carried out in each of these regions by extracting the parameter estimates and examining each group separately (Fig. 1). In the left inferior frontal and left cerebellar regions, controls showed less activity to the associated than the unrelated word pairs, i.e. association-induced suppression. Participants with FHR, however, showed the opposite pattern in both these regions: more activity to the associated than the unrelated pairs, or association-induced enhancement. In the right superior and middle temporal gyrus (STG), controls showed no significant modulation of activity but, once again, FHR participants exhibited association-induced enhancement.

In addition to extracting parameter estimates from the groups separately, we also carried out within-group analyses in control and FHR participants separately, across the whole brain. Controls exhibited significantly reduced activity in the inferior frontal and dorsolateral prefrontal regions (BA 44–46) and cerebellar regions bilaterally (with larger spatial extent of suppression on the left side) to the associated than the unrelated word pairs ($p < 0.05$). In contrast, FHR participants exhibited significant association-induced suppression in the frontomedial cortex (bilaterally) and the cerebellum, and association-induced enhancement in the superior temporal gyrus (STG) bilaterally ($p < 0.05$).

3.4. Correlation between brain activity with behavioral priming and schizotypal traits

In controls only, the extent of association-induced suppression in the left IFG cluster (or the difference between parameter estimates extracted from the Unrelated vs. Associated condition) was correlated with the semantic priming effect on lexical decision reaction times (Unrelated condition mean RT–Associated condition mean RT) (Fig. 2A). In

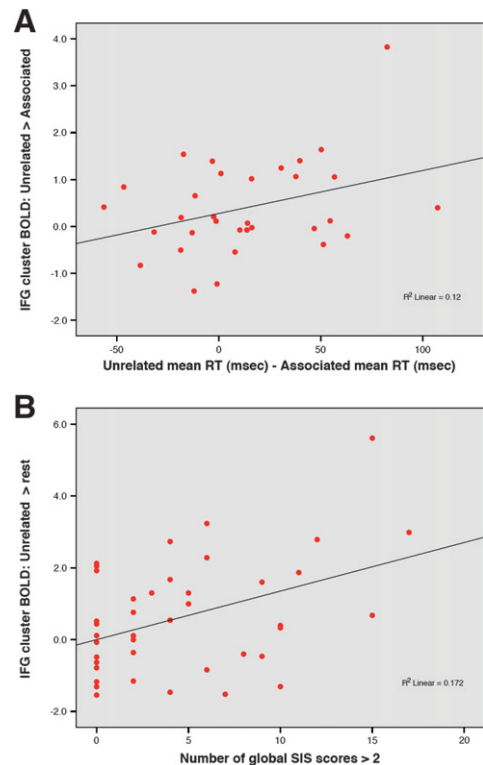


Fig. 2. (A) Significant correlation ($p < 0.05$) between association-induced suppression of left inferior frontal gyrus (IFG) activity and semantic priming effect on lexical decision reaction times (RTs) in control participants; (B) Significant correlation ($p < 0.05$) between left inferior frontal gyrus (IFG) activity (to Unrelated word pairs relative to baseline fixation) and the number of global Structured Interview for Schizotypy (SIS) scores over 2 in FHR participants.

participants with FHR only, parameter estimates extracted from the left IFG cluster (Unrelated condition compared to baseline fixation) were correlated with the number of global SIS scores >2 (Fig. 2B). Other correlations between fMRI parameter estimates and behavioral variables (behavioral priming or schizotypal traits) were not significant.

4. Discussion

In this study, we demonstrate that people at FHR for SZ (FHR) show abnormal hemodynamic response enhancement in regions that were expected to show suppression in response to semantic association (a reverse priming effect). Participants with FHR showed association-induced enhancement in the left inferior frontal, right superior/middle temporal and left cerebellar regions, while controls showed the expected association-induced suppression of activity in frontal and cerebellar regions. The groups were comparable in behavioral semantic priming, demographic variables and IQ, suggesting that group differences in brain activity were not driven by differences in task performance or potentially confounding factors.

4.1. Reversed priming effect in participants with FHR

In controls, the majority of semantic priming studies report association-induced suppression in frontal and/or temporal cortices (Kotz et al., 2002; Copland et al., 2003; Rissman et al., 2003; Matsumoto et al., 2005; Wheatley et al., 2005; Kuperberg et al., 2008b). An associated prime is thought to pre-activate semantic features that are shared by the target (Neely, 1991), leading to reduced activity within temporal cortices where such semantic features and lexical representations are thought to be accessed (Martin, 2007; Patterson et al., 2007; Lau et al., *in press*). This, in turn, imposes fewer demands on actively retrieving the semantic features of the target, and there is also less need to suppress irrelevant semantic features activated by an unrelated prime, leading to reduced activity within frontal cortices.

Kuperberg et al. (2007) suggested that the reverse priming effect seen in SZ stemmed from an abnormal increase in lexico-semantic activity. On this account, rather than facilitate recognition of the target, semantic features activated by the associated prime competed with features activated by the target, placing more selection demands on the frontal cortices in the Associated condition than in the Unrelated condition (for further discussion of how different degrees of lexical activity can lead to either facilitation or interference, see Chen and Mirman, 2012). Also of potential relevance, reverse priming effects have been observed in studies of controls when stimulus perception is impaired (Turk-Browne et al., 2007), and when attention to the stimulus, the perceived task-relevance of stimuli, and self-monitoring play important roles (Brown and Aggleton, 2001; Kouider et al., 2007; Nakamura et al., 2007; Segaert et al., 2013).

The present findings indicate that similar mechanisms may be at play in FHR. Here, we again saw evidence of increased temporal activity (interestingly on the right), as well as increased frontal activity in the Associated (versus Unrelated) condition. Prefrontal hyperactivity in FHR has been reported in a wide variety of tasks with executive demands (even when participants with FHR perform tasks at levels comparable to controls) (reviewed in (Thermenos et al., 2013)). More generally, abnormal frontal-temporal activity (including altered lateralization of function) has been observed in several previous fMRI studies of this group using diverse language tasks (Kubicki et al., 2003; Sommer et al., 2004; Whalley et al., 2004; Li et al., 2007a, 2007b, 2009; Rajarethinam et al., 2011) sometimes in association with symptoms or cognitive decline (Lymer et al., 2006; Bhojraj et al., 2009; Whalley et al., 2009; Oertel et al., 2010; Bhojraj et al., 2011). Our findings are also broadly consistent with structural studies reporting gray (Bhojraj et al., 2009; Gohari et al., 2011; Li et al., 2012) as well as white matter (McIntosh et al., 2004) alterations in frontal and temporal regions in participants with FHR.

4.2. Relationship of altered brain activity to symptoms in participants with FHR

In the inferior frontal gyrus (IFG), participants with FHR showed hyperactivity in response to both unrelated and associated words, and the extent of IFG hyperactivity to unrelated words was associated with the number of clinically meaningful scores on the Structured Interview for Schizotypy (SIS) in participants with FHR. While the precise functional interpretation of this observation is somewhat unclear, it may reflect a neural basis of risk for developing unusual ideas, perceptions and disorganized language (Grimshaw et al., 2010). Previous studies have also reported relationships between abnormal frontal modulation during language processing and clinical symptoms in participants with FHR and SZ (Whyte et al., 2006; Han et al., 2007), (including a relationship between reduced IFG suppression during semantic priming and clinical symptoms in SZ) (Han et al., 2007). The extent of IFG non-suppression during semantic priming could potentially reflect a continuum of risk for SZ, with moderate levels of non-suppression associated with attenuated positive symptoms, and higher levels, with frank psychosis.

4.3. Future research

Our findings raise important questions for future research. To further understand the temporal and spatial architecture of reverse priming deficits in participants with FHR, future studies can combine the spatial resolution of fMRI with the temporal resolution of ERP and/or MEG, using SOAs of different lengths to test different hypotheses. Examination of frontotemporal functional connectivity during associative processing (as well as its relationship to the structure of underlying white matter tracts) will also be an important area for further study. The extent of frontotemporal enhancement in participants with FHR could potentially predict which individuals are at greater risk to develop a psychotic disorder, as suggested by previous work (Lymer et al., 2006; Bhojraj et al., 2009; Whalley et al., 2009; Oertel et al., 2010; Bhojraj et al., 2011). Future longitudinal studies are needed to test this hypothesis and to determine precisely which abnormalities predict which individuals go on to develop symptoms of and/or functional deficits.

4.4. Limitations

The semantic priming effect itself is quite subtle, and there was only a modest difference in brain activity in control and FHR participants (even with a relatively large sample size). There were several other brain regions exhibiting marginal group differences that did not meet criteria for statistical significance in this study. Indeed, effects in FHR participants tend to be subtle, as subjects in the study were non-psychotic (with a small percentage expected to eventually develop a psychotic disorder).

Another limitation of study was the lack of fine-grained quantitative measures of schizotypal traits and positive and negative symptoms, for use in covariance analyses. Finally, due to the close temporal proximity of the prime and target stimuli in our semantic priming task, it is not possible to differentiate neural responses to primes vs. targets using fMRI. Thus, the differential modulation observed between FHR and control participants reflects a combination of responses to the prime and target. Future studies should employ multi-modal technologies (MRI, ERPs and MEG) to improve our understanding of the neural responses to primes and targets in risk for SZ.

In summary, this was the first fMRI study, to our knowledge, to examine semantic priming in non-psychotic participants with FHR. We demonstrated altered semantic association-induced modulation of frontotemporal activity in a relatively large sample of participants with FHR, as well as a relationship of IFG activity to schizotypal traits in this group. This suggests that 1) semantic association-induced frontotemporal enhancement is a potential marker of neurobiological

risk for SZ, and 2) this abnormal modulation of brain activity might increase risk to develop unusual ideas and perceptions that characterize schizotypal disorders (Grimshaw et al., 2010).

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Contributors

H.W. Thermenos developed the study design, collected and analyzed the data, and composed the manuscript. S. Whitfield-Gabrieli developed the study design, supervised statistical analyses and assisted in manuscript composition. L.J. Seidman consulted on study design, supervised data collection and assisted in manuscript composition. G. Kuperberg developed the study design and assisted in manuscript composition. R.J. Juelich coordinated the study, collected the data and assisted in manuscript composition. S. Divatia assisted in statistical analysis of the data and manuscript composition. C. Riley assisted in statistical analysis of the data and manuscript composition. G.A. Jabbar coordinated the study, collected the data and assisted in manuscript composition. M. E. Shenton consulted on study design and assisted in manuscript composition. M. Kubicki consulted on study design and assisted in manuscript composition. T. Manschreck consulted on study design and assisted in manuscript composition. M. S. Keshavan consulted on study design, supervised data collection and assisted in manuscript composition. L.E. DeLisi wrote the grant that funded the study, developed the study design, supervised data collection, and assisted in manuscript composition.

Conflict of interest

Dr. Thermenos reports no financial disclosures or conflicts of interest.
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