Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: a multimodal meta-analysis of fMRI and VBM studies

Running title: Familial risk for schizophrenia and alterations in the brain

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Abstract

Objective: Schizophrenia has one of the highest heritability estimates in psychiatry, but the genetically-based underlying neuropathology has mainly remained unclear. We conducted a multimodal coordinate-based meta-analysis (CBMA) to investigate brain structural and functional alterations in individuals with high familial risk for schizophrenia, i.e. in first-degree relatives of schizophrenia patients (FRs). **Methods:** We conducted a systematic literature search from two electronic databases to find studies that examined differences between FRs and healthy controls using whole-brain functional magnetic resonance imaging (fMRI) or voxel-based morphometry (VBM). A CBMA of 30 fMRI (754 FRs; 959 controls) and 11 VBM (885 FRs; 775 controls) datasets were conducted using the anisotropic effect-size version of signed differential mapping. Further, we conducted separate meta-analyses about functional alterations in different cognitive tasks: social cognition, executive functioning, working memory, and inhibitory control. **Results:** When compared to healthy controls, FRs showed higher fMRI activation in the right frontal gyrus during cognitive tasks. In VBM studies, there were no differences in grey matter density between FRs and healthy controls. Furthermore, multi-modal meta-analysis obtained no differences between FRs and healthy controls. Finally, by utilizing the BrainMap database, we showed that the brain region which showed functional alterations in FRs (i) overlapped only slightly with the brain regions that were affected in the meta-analysis of schizophrenia patients and (ii) correlated positively with the brain regions that exhibited increased activity during cognitive tasks in healthy individuals. **Conclusions:** Based on this meta-analysis, FRs may exhibit only minor functional alterations in the brain during cognitive tasks, and the alterations are much more restricted and only slightly overlapping with the regions that are affected in schizophrenia patients. The familial risk did not relate to structural alterations in the grey matter.

Keywords: Schizophrenia; Psychosis; Genetic risk; Familial risk; Brain structure; Brain activity

1 Introduction

The heritability of schizophrenia and psychotic disorders may be as high as 80% (Sullivan et al., 2003), but the genetically-based underlying neuropathology is mostly unknown. First-degree relatives of schizophrenia patients (FRs) compose a particular risk group since their lifetime morbidity risk for schizophrenia is increased ten-fold to 10% (Gottesman et al., 2010; Lichtenstein et al., 2006). Consequently, when evaluating an individual's risk for schizophrenia, the familial risk is among the most important factors (Mäki et al., 2005).

Cognitive impairment is very common in prodromal schizophrenia (Cornblatt et al., 2004; Lencz et al., 2006). Furthermore, large cognitive deficits are present prior to illness onset and represent vulnerability markers for the onset of the disorder (Carrión et al., 2018). Along with this, cognitive impairment is also included as a diagnostic criterion for schizophrenia in the DSM-V classification. Overall, cognitive functioning is shown to be more severely impaired in genetic than clinical high-risk populations (Seidman et al., 2010). The most affected cognitive abilities are executive functioning, such as working memory and inhibitory control (Snitz et al., 2005), and social cognition (Cornblatt et al., 2003; Hans et al., 2010). Consequently, cognitive impairment is a crucial element when aiming to identify predictors for the onset of schizophrenia.

Previous meta-analyses suggest that relatives of schizophrenia patients have increased activity in the right-side parietal, temporal, and frontal regions (Cooper et al., 2014; Scognamiglio et al., 2014; Zhang et al., 2016). Findings on brain regions with decreased activity in FRs have been inconclusive, with findings in the thalamus, cerebellum, cingulate, or frontal lobes (Cooper et al., 2014; Scognamiglio et al., 2014; Zhang et al., 2016; Niu et al., 2017). Regarding structural alterations, FRs seem to have decreased gray matter in the insula and frontal regions, even though the findings have varied somewhat (Cooper et al., 2014; Niu et al., 2017; Boos et al., 2007). Multimodal meta-analyses in FRs have been inconclusive (Cooper et al., 2014; Niu et al., 2017).

An updated meta-analysis on this topic is very much needed for several reasons. Firstly, a growing number of original studies have been conducted on this topic during recent years, so a higher number of participants are available for a meta-analysis. Secondly, previous meta-analyses have not investigated functional alterations in FRs separately in different cognitive tasks. This might be important since there is evidence that different cognitive abilities may be selectively impaired among individuals at risk for schizophrenia (Cornblatt et al., 2003; Hans et al., 2000). Thirdly, there is a possibility that alterations in genetic high-risk individuals are located in overlapping regions but are more subtle than in schizophrenia patients. However, this has remained uninvestigated in the previous meta-analyses. Finally, previous meta-analyses have not examined if the functional alterations during cognitive tasks in FRs are located in the brain regions that exhibit increased activity during cognitive tasks in healthy individuals. This is a crucial question since there is evidence about compensating mechanisms in the brain among individuals at risk for psychosis (Cooper et al., 2014; Fusar-Poli et al., 2010; Pulkkinen et al., 2015). For example, it is possible that before any psychotic symptomatology has emerged, FRs can compensate for mild cognitive impairments by activating more extensive brain networks (i.e. different/additional brain regions than in healthy individuals) during a cognitive task.

Our first aim was to conduct a multimodal meta-analysis in order to investigate the functional and structural alterations in first-degree relatives of schizophrenia patients. We included peer-reviewed functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM) studies with whole-brain scanning. Our second aim was to investigate whether brain regions with structural or functional alterations in FRs overlap with the regions (i) that are affected in schizophrenia patients or (ii) that exhibit increased activity during cognitive tasks in healthy individuals. For this purpose, we utilized the publically available meta-analysis database BrainMap. We did not set a-priori hypotheses in this study.

2 Methods

2.1 Search strategies

The MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist was followed throughout the meta-analysis (https://www.elsevier.com/__data/promis_misc/ISSM_MOOSE_Checklist.pdf). The fulfilled form of the MOOSE Checklist can be found in Supplementary Table 1. A systematic literature search was carried out between August and November 2018 using the electronic databases of PubMed and Web of Science. For fMRI studies, we used the following search terms: “schizophrenia” AND (“genetic risk” OR “familial risk” OR “parental risk” OR “relatives” OR “twins” OR “offspring” OR “siblings”) AND (“fMRI” OR “functional MRI” OR “BOLD”). For VBM studies, the search terms included: “schizophrenia” AND (“genetic risk” OR “familial risk” OR “parental risk” OR “relatives” OR “twins” OR “offspring” OR “siblings”) AND (“VBM” OR “gray matter” OR “gray matter" OR "voxel-based morphometry"). There were no restrictions regarding language, publication date, or publication status, and the search was directed to all fields.

After removing duplicates, all identified studies were screened based on the title and abstract and defined as eligible/ineligible for the meta-analysis. In addition to original research papers, all meta-analyses and reviews identified by our search strategies were scrutinized, and their reference lists were manually checked for any additional eligible studies. After the abstract and title review, the identified full-text articles were screened more precisely on the basis of the exclusion and inclusion criteria (described in the next section). The article selection process is illustrated in Figure 1. In each phase of the article selection process, the eligibility of the inclusion/exclusion was double-checked by another author (A.S./S.H./J.P./L.B./J.L.). The primary reasons for excluding articles are shown in Supplementary Tables 2 and 3.

2.2 Inclusion and exclusion criteria

The inclusion criteria for the identified studies were: a peer-reviewed original article; the study included fMRI or VBM on gray matter; subjects were first-degree relatives of schizophrenia patients; subjects were compared to a healthy control group; whole-brain scanning; T or Z statistics of the observed BOLD response difference between FRs and healthy controls were available; p-values were available; the coordinates were reported using the Talairach Atlas (Tal) or the Montreal Neurological Institute (MNI)

space. The exclusion criteria for the identified studies were as follows: only regions of interest (ROIs) were investigated; a small volume correction (SVC) was used; participants consisted exclusively of individuals with 22q11.2 deletion; the participants with familial risk for schizophrenia expressed psychotic symptomatology or had antipsychotic medications; the group size of the participants with familial risk for schizophrenia was less than 10; or a larger sample of the same population was provided in another included study. We also excluded studies that reported only functional connectivity-based group differences due to the significant variations in these techniques.

2.3 Data collection from the included studies

We collected the following information (if available): publication year, sample size, gender distribution, age, the score of the Global Assessment of Functioning (GAF), intelligence quotient (IQ), the diagnostic classification system that was used for the identification of schizophrenia, smoothing kernel (mm), psychopharmacological treatment of FRs (other than antipsychotic medications), mental disorders of FRs (other than psychotic disorders), used analyzing software package for fMRI/VBM, magnetic field strength (Tesla), the use of correction for multiple comparisons, and the use of covariates. Additionally, when applicable, we collected the x-, y- and z-coordinates (reported using Tal or MNI) of statistically significant findings and the direction of the observed difference between FRs and healthy controls. In case some necessary information was missing, we contacted the authors of the original articles.

2.4 Statistical analyses and meta-analytical models

We performed separate voxel-based meta-analyses of findings in fMRI activation, and regional gray matter volume (VBM) maps in individuals with FRs relative to healthy controls using an anisotropic effect-size version of signed differential mapping (AES-SDM v5.141, see http://www.sdmproject.com). The analytical processes of AES-SDM meta-analysis have been described in detail elsewhere (Radua et al., 2012b, 2014).

For the analysis, we extracted the peak coordinates and *t*-statistics of fMRI activation or gray matter differences between FRs and healthy controls from each included data set. We ensured that the same statistical threshold was used throughout the brain and throughout the study. If multiple thresholds were

used, we selected the most stringent threshold. If *t*-statistics were not available, we used the web-based tool provided by the AES-SDM (https://www.sdmproject.com/utilities/?show=Statistics) to convert *z*-statistics or *p*-values into *t*-statistics. Next, we estimated a standard MNI-map of fMRI activation or gray matter alterations (VBM) for each study separately using an anisotropic Gaussian kernel (full width at half maximum=20 mm). After that, we employed a random-effects model, taking into account the sample size, intra-study variance, and between-study heterogeneity. It has been demonstrated that high statistical stability can be acquired with 20 permutations (Radua et al., 2012b). To ensure the stability of the analyses, we performed these analyses using 50 permutations.

AES-SDM uses the following default statistical threshold: uncorrected voxel *p*-value of 0.005, peak height $Z \geq 1$, and cluster extent ≥ 10 voxels. This thresholding approximates the corrected *p*-value of 0.05 and creates an optimal balance between sensitivity and specificity (Radua et al., 2012b). To avoid spurious findings, we set a more stringent threshold by using the significance level at the uncorrected voxel p-value of 0.0005, peak height Z = 2, and 80 voxels. The robustness of the results was assessed by 1) assessing the level of heterogeneity (using I^2 statistics that refers to the percentage of total variance between studies resulting from rather a heterogeneity than chance); 2) inspecting the funnel plots for publication bias using Egger's test; and 3) implementing a jack-knife sensitivity analysis. Additionally, we conducted meta-regression analyses with age (in FR group), field strength, and sex distribution (in FR group) as a regressor (using even more stringent threshold of p=0.0001).

Regarding fMRI studies, we conducted five separate analyses. The first analysis included all the fMRI studies (regardless of which cognitive tasks had been used). The second analysis included studies with executive functioning tasks. FMRI studies with executive functioning tasks were further classified into working memory tasks (Analysis 3) and inhibitory control tasks (Analysis 4). Analysis 5 included fMRI studies with social cognition tasks. The classification of cognitive tasks was based on the previous models of cognitive functions (Diamond et al., 2013; Miyake et al., 2012).

Finally, since we were interested in both functional and structural abnormalities in FRs, we also performed a multimodal analysis on the fMRI and VBM meta-analytical maps. The multimodal analysis was conducted according to Radua et al. (2013) to investigate potential conjunctions between the

VBM and fMRI modalities. Briefly, this method estimates the significance of the overlap between the actual p-values of the two modalities.

For non-neuroimaging statistical analyses, we used R (http://cran.r-project.org) version R 3.4.3 (R Core Team, 2014) with *psych* (Revelle, 2017) and *metafor* (Viechtbauer, 2010) packages. We conducted random effect models (visualized in forest plots) and analyzed the heterogeneity of the studies.

2.5 Comparison to the meta-analysis of previous fMRI and VBM studies in schizophrenia patients

As an additional analysis, we investigated whether the brain regions which exhibited functional or structural alterations in FRs in the meta-analysis overlapped with brain regions that are affected in schizophrenia patients. This investigation was conducted using the BrainMap database. The data collection methods of the BrainMap database have been described with more detail elsewhere (Laird et al., 2011), and it has also been used in several previous meta-analyses (e.g. Daniel et al., 2016; Vanasse et al., 2018). Specifically, we conducted an additional automatic meta-analysis of the previous VBM and fMRI studies in schizophrenia patients (the search with Sleuth was conducted in August 2018, see http://www.brainmap.org/sleuth/). We identified 50 fMRI studies and 27 VBM studies. In the meta-analysis of fMRI studies, we used contrasts in both directions (i.e. schizophrenia>controls and schizophrenia<controls). This was because schizophrenia patients have exhibited both increased and decreased brain activity patterns in various brain regions. In the meta-analysis of VBM studies, we analyzed only schizophrenia<controls contrast because one of the most robust findings in the previous literature has been the lower gray matter volume in schizophrenia patients when compared to controls (Haijma et al., 2012). GingerALE (Turkeltaub et al., 2002; Eickhoff et al., 2009) with 1000 repetitions was used. The p-values for each meta-analysis were thresholded at a cluster level corrected threshold of $p<0.05$ (cluster-forming threshold at voxel-level $p<0.001$).

2.6 Comparison to the previous fMRI studies in healthy individuals

We investigated whether the brain regions that were found to be affected in FRs (in the fMRI and VBM meta-analysis) overlapped with the brain regions activated during behavioral tasks in healthy individuals. First, we examined the brain activity maps during a wide variety of behavioral tasks (e.g. working memory,

language processing and emotion recognition.) in healthy individuals. This was done by using the BrainMap database (http://www.brainmap.org/taxonomy/behaviors.html) and conducting meta-analyses on the previous fMRI studies in healthy individuals during different behavioral tasks. We included all the behavioral domains that had been investigated in at least 17 previous fMRI studies, as this is suggested to be the minimum number of studies for running a meta-analysis on GingerAle (Eickhoff et al., 2016). Using this criterion, we retained 47 behavioral domains that are listed in Supplementary Table 4. Thereafter, we extracted Z-statistics of the unthresholded activity maps of each behavioral domain using the Automated Anatomical Labeling (AAL) parcellation (Tzourio-Mazoyer et al., 2002). Next, we employed principal component analysis (PCA) on the 47 behavioral domains to reduce the dimensionality of the domains (using *psych* package in R). Behavioral domains that had a loading greater than 0.5 were considered as primary indicators of a specific component. Finally, we correlated the Z-maps of the components with the untresholded Z-maps of the fMRI in FRs.

3 Results

3.1 Description of the included studies

The systematic literature search resulted in 29 fMRI studies (one study included two separate datasets that were analyzed separately, i.e. altogether 30 fMRI datasets) and 10 VBM studies (one study included two separate datasets, i.e. altogether 11 VBM datasets). All the studies were originally published between 2003 and 2018. The descriptive statistics of the included studies are presented in Table 1 (fMRI studies) and Table 2 (VBM studies). In the fMRI studies, there were altogether 754 FRs (sample size weighted mean age=31.9 years; 56.8% female) and 959 healthy controls (sample size weighted mean age=30.5 years; 50.5% female). In the VBM studies, there were altogether 885 FRs (mean age=31.2 years; 51.6% female) and 775 healthy controls (mean age=30.8 years; 49.6% female). IQ was reported only in 15 datasets (11 fMRI and 4 VBM). These 15 datasets indicated that IQ was lower in FRs than in controls (sample size weighted mean=104.2 vs. 108.9, Z=-3.8, p<.0001) (forest plot available in Supplementary Figure 1). There was,

however, significant heterogeneity between the included studies (I^2=71.30%, Q(14)=53, p<.0001) but no indication of publication bias (Egger's test, p=.62).

Regarding cognitive tasks in the fMRI studies, there were 19 studies with executive functioning tasks that were further classified into two categories: 11 datasets with working memory tasks (the N-back working memory task; the Sternberg working memory task; Spatial delayed-response task) and 8 datasets with inhibitory control tasks (the Continuous Performance Task, Stop-Signal Anticipation Task; Dot Probe Expectancy Task; Hayling Sentence Completion Task; Pro- and Antisaccades Task). Additionally, there were seven studies with social cognition tasks (including Theory of Mind Task; Irony comprehension task; Facial processing tasks; Self-referential task).

There were 6 fMRI studies with such cognitive tasks that could not be classified into the previous categories. The cognitive tasks assessed reward anticipation (1 dataset), early visual processing (2 datasets), visual memory (1 dataset), auditory comprehension (1 dataset), and cognitive skills learning (1 dataset). These datasets were included in the first fMRI meta-analysis (with the full set of cognitive tasks).

3.2 Meta-analysis of the fMRI studies

The results of the fMRI meta-analysis are presented in Table 3. In the first analysis with the full set of cognitive tasks, FRs had increased activity in the right inferior frontal gyrus (opercular part) when compared to healthy controls. Supplementary Figure 2 provides the individual study estimates and an overall estimate of the activation difference in the right inferior frontal gyrus between FRs and healthy controls. The results remained basically the same when excluding studies that possibly included a few second-degree relatives of schizophrenia patients (two studies) (see Supplementary Table 5). However, when we excluded studies that did not employ any correction for multiple comparisons (eight studies), we found no group differences in the BOLD response. The field strength, mean age of the FR group or the gender distribution in the familial risk group did not relate to fMRI findings as analyzed with meta-regression. In the fMRI meta-analysis, we detected no significant between-study heterogeneity in the right inferior frontal gyrus (I^2=0.1%). Additionally, the jackknife sensitivity analysis confirmed that the findings in the right inferior frontal gyrus

were reproducible (27/30). Moreover, there was no indication of publication bias in the right inferior frontal gyrus (Egger's test p=0.34) (see funnel plots in Supplementary Figure 3).

During executive functioning tasks and working memory tasks, FRs had increased activity in the right inferior frontal gyrus when compared to healthy controls. No other group differences during these tasks were detected. Further, no findings were observed in social cognition and inhibition control studies in BOLD response in FR vs. controls.

3.3 Meta-analysis of the VBM studies

The meta-analysis of the VBM studies showed that there were no differences in gray matter volume between FRs and healthy controls. No findings were also found when excluding studies that possibly included a few second-degree relatives of schizophrenia patients (two studies). In addition, there were no group differences in grey matter density when excluding studies that did not employ any correction for multiple comparisons (three studies).

3.4 Multimodal meta-analysis of the fMRI and VBM studies

In the multimodal analyses, we included both fMRI and VBM studies in the same meta-analysis, in order to assess whether some brain regions exhibited both functional and structural alterations. Multimodal analyses obtained no differences between FRs and healthy controls.

3.5 Comparison to the meta-analysis of previous fMRI and VBM studies in schizophrenia patients

We investigated whether brain regions that exhibited functional in FRs overlapped with brain regions that showed both functional and structural alterations in schizophrenia. The results are shown in Figure 2. In the full set of fMRI studies, FRs had increased activity in the right inferior frontal gyrus. This region was slightly overlapping with the brain regions that were affected in schizophrenia patients.

3.6 Comparison to the meta-analysis of previous behavioral fMRI studies in healthy individuals

Principal component analysis of the brain activity patterns of different behavioral domains resulted in a two-component solution (76% of the variance explained). The component structure was further promax rotated. The loadings of all the 47 behavioral domains on the two components are shown in Figure 3a. The first component had factor loadings from the domains of executive functioning, inhibition, attention, working memory, spatial reasoning, and language processing. The second component included factor loadings from processing negative and positive affect, interoceptive processing, and sensory processing. Consequently, the first component was named as "cognitive component" and the second component as "affect/sensory component".

Next, we investigated whether the untresholded FR vs. control map might correlate with the cognition- or affect/sensory-related brain activity maps in healthy individuals. The results are shown in Figures 3b and 3c. Specifically, the brain activity maps of cognitive domains (in healthy individuals) correlated positively with the untresholded FR vs. controls meta-analysis map. In contrast, the brain activity maps of affect/sensory-related domains (in healthy individuals) did not correlate with the untresholded FR vs. controls meta-analysis map. Taken together, the brain region that exhibited functional alterations in FRs seemed to correlate with the brain activity maps that are activated during cognitive tasks in healthy individuals.

4 Discussion

To the best of our knowledge, this is the largest multimodal coordinate-based meta-analysis on first-degree relatives of schizophrenia patients (754 FRs in fMRI studies and 885 FRs in VBM studies). We found that FRs exhibit very restricted and only slightly overlapping functional alterations with those seen in schizophrenia patients. We also found that the brain regions that exhibited altered functioning in FRs correlated positively with the brain regions that exhibit increased activity during cognitive tasks in healthy individuals. The VBM meta-analysis and multimodal analyses obtained no differences between FRs and healthy controls.

4.1 fMRI meta-analyses on different cognitive tasks

In the full set of cognitive tasks, FRs had higher activity in the right frontal gyrus when compared to healthy controls. This difference was also obtained during working memory tasks and executive functioning tasks. Previously, the right frontal gyrus is found to response inhibition and attentional control (Aron et al., 2003; Chikazoe et al., 2007; Hampshire et al., 2010). These abilities, in turn, are known to be impaired in schizophrenia patients (Enticott et al., 2008; Wang et al., 2005). Hence, the findings suggest that some impairments in the neurobiological basis of these abilities may familial risk of psychosis.

Previously, single studies have suggested that during executive functioning tasks, FRs might exhibit altered activity in regions that are not generally related to executive functioning, such as anterior cingulate gyrus (Filbey et al., 2008) or corpus callosum (Karch et al., 2009). However, this meta-analysis did not support these findings. Specifically, we obtained functional alterations in FRs during cognitive tasks only in the right frontal gyrus, and the untresholded group comparison map correlated positively with those brain regions that exhibit increased activity during cognitive tasks in healthy individuals.

We found that the right frontal gyrus exhibited higher activity in FRs (vs. controls) during cognitive tasks. We speculate that this finding might relate to the neural compensatory mechanism, where individuals with FR compensate for the difficulty of the task via hyperactivation. Similar conclusions have been made in previous studies (Cooper et al., 2014; Fusar-Poli et al., 2010; Pulkkinen et al., 2015). This conclusion is in line with a previous meta-analysis that found the activity of the right inferior frontal gyrus decreasing in FRs during rest (Niu et al., 2017).

The brain regions with increased activity in FRs during cognitive tasks appeared to be mostly located in the right hemisphere. This may be related to the lateralization hypothesis of schizophrenia (Crow et al., 1989), postulating that schizophrenia is linked to weaker lateralization of the brain functioning. For example, schizophrenia patients have an abnormal right hemisphere dominance during language processing tasks (Li et al., 2009). Additionally, schizophrenia patients have a higher prevalence of left-handedness, indicating a dominance of the right brain hemisphere in motor functioning (Dragovic et al., 2005). In line with this, we found that FRs had increased activity in the right hemisphere during cognitive tasks.

It has been suggested that the differences between FRs and healthy controls may be at least partially explained by differences in IQ (de Zwarte et al., 2018). In this meta-analysis, we found that IQ was lower in FR when compared with controls. Note, nonetheless, that the average IQ in FRs was 104, which is even slightly above the average IQ. Overall, we suggest that future studies should extend the neuroimaging research on intelligence and psychosis risk.

4.2 VBM meta-analysis

The VBM meta-analysis showed that there were no differences between FRs and healthy controls in gray matter density in the brain. This finding may be related to a variety of issues. Firstly, population-based studies have demonstrated that the gray matter volume steadily decreases from middle childhood or early adolescence onwards (Sowell et al., 2003). Along with this, the previous findings of greater gray matter volume in high-risk individuals are suggested to be explained by study sampling: in several samples, the participants with prodromal syndromes have been younger than healthy controls (Hirayasu et al., 2001). The results of our meta-analysis are in line with this since the mean age of the FRs, and healthy controls was approximately the same (31.9 years in FRs and 30.5 years in healthy controls), and no structural differences were obtained.

Secondly, it has been suggested that some of the alterations in FRs may be present only in those FRs who will develop psychosis later in life (Fusar-Poli et al., 2012). Further, the structural alterations are found to correlate with the duration of the illness and the use of medications (van Erp et al., 2018). In our meta-analysis, we excluded those studies that included FRs with psychotic symptomatology and obtained no structural alterations in FRs. Hence, it is possible that only those FRs who will convert later into psychosis have structural alterations in the brain. However, no firm conclusions can be made about converters vs. non-converters because the data did not provide possibilities to analyze structural differences between converters vs. non-converters.

Previous ENIGMA studies have shown that schizophrenia patients have smaller volumes in a variety of subcortical regions (e.g. in the hippocampus, amygdala, thalamus, and nucleus accumbens, and larger lateral ventricle) and cortical regions (e.g. thinner cortex and smaller surface area especially in the

frontal and temporal regions) (van Erp et al., 2016, 2018). Regarding FRs, however, it has been suggested that genetically-based abnormalities in the brain structure among FRs are “neither severe nor always specific” and more restricted by location in FRs than in schizophrenia patients (Lieberman et al., 2001). Along with this, our findings suggest that FRs exhibit no similar alterations in gray matter volume compared to schizophrenia patients. The observed modest activation differences in FRs vs. controls are in line with a recent ENIGMA study (1228 FRs and 2246 controls) that found relatively weak effect sizes for the structural brain differences between FR and controls (de Zwarte et al., 2019). Overall, it appears that the possible FR-related neural alterations are subtle and large sample sizes are required to observe the effect of FR on brain structures.

Overall, the VBM meta-analyses among FRs have resulted in inconclusive findings. For example, in Cooper et al. (2014) meta-analysis, FRs were found to have larger grey matter volume in the left medial frontal gyrus and smaller grey matter volume in left thalamus/putamen, right superior frontal gyrus, and left insula, when compared to controls. In our meta-analysis, however, we obtained no structural differences between FRs and healthy controls. The divergent findings of the VBM meta-analyses in FRs may be related to differences in the sample size. Although we had a larger sample size compared to Cooper et al. (2014), however, it is possible that our study was still underpowered, since previous large ENIGMA study in FRs found subtle structural alterations in FRs vs. controls. Additionally, the definition of "familial risk for schizophrenia" has been varying: for example, contrary to our meta-analysis, a first-degree relationship with schizophrenia patients was not required in Cooper's et al. (2014) meta-analysis. Finally, in recent years, there has been an increasing concern about false positives in neuroimaging studies.

4.3 Multimodal meta-analysis

In the multimodal analyses, we included both fMRI and VBM studies in the same meta-analysis, in order to see whether some brain regions exhibited both functional and structural alterations. No differences were obtained between FRs and healthy controls. This is in line with the previous meta-analysis that also obtained no differences between FRs and healthy controls in the multimodal analyses (Niu et al., 2017). Among patients with first episode psychosis, it has been found that the use of antipsychotics correlates with

alterations in the regions that exhibit conjoint structural and functional alterations (Radua et al., 2012a). Hence, it may be that multimodal alterations may be obtained only after the onset of psychosis.

4.4 Methodological considerations

The number of fMRI studies investigating social cognition was comparatively low (7 studies), whereas the optimal number of studies for meta-analysis is likely higher (Eickhoff et al., 2016). In the case of such a low number of studies, also differences in fMRI tasks may be a source of heterogeneity. However, this same challenge has also been present in other coordinate-based meta-analyses. For example, in the previous VBM meta-analysis investigating the functional changes during cognitive tasks in individuals at genetic risk for schizophrenia, there were only 6 VBM studies (Cooper et al., 2014). Thus, it appears that more research reporting voxel-wise results are needed in order to be able to conduct a reliable coordinate-based meta-analysis on different behavioral tasks in the future. Overall, future meta-analyses should investigate social cognition-related alterations in FRs when a larger number of studies are available.

Secondly, it could be argued that the reason for investigating alterations in FRs is that they are known to have an elevated risk for psychotic symptoms and for the use of antipsychotic medications. In this meta-analysis, however, we excluded studies where FRs had psychotic symptoms or had used antipsychotic medications. This is because there is evidence that the onset of psychosis is characterized by decreases of gray matter in a variety of brain regions (e.g. temporal and frontal regions) (Fusar-Poli et al., 2011). Additionally, exposure to antipsychotic drugs is shown to be related to structural alterations in the brain (e.g. insula and anterior cingulate) (Radua et al., 2012a; van Erp et al., 2018). Moreover, individuals with psychotic symptoms or antipsychotic medications have also been excluded in several previous meta-analyses (e.g. Cooper et al., 2014; Scognamiglio et al., 2014; Zhang et al., 2016). Consequently, antipsychotic medications or psychotic symptoms could potentially have confounded the association of familial risk for schizophrenia with structural and functional alterations in the brain.

Thirdly, this meta-analysis included studies that had investigated participants with at least one first-degree relative with schizophrenia. This methodological choice has also been used in the previous meta-analyses (Cooper et al., 2014; Scognamiglio et al., 2014). We did not conduct separate analyses among

different types of first-degree relatives (i.e. offspring, parents, siblings). It has been shown that there may not exist significant structural differences in the brain between different types of first-degree relatives (de Zwarte et al., 2018). Generally, it has been demonstrated that cognitive deficits are more severe in relatives with higher genetic risk for schizophrenia (Byrne et al., 2003; Faraone et al., 2000). Hence, the neural alterations in FRs may be even more evident in FRs with two first-degree relatives with schizophrenia.

Fourthly, after conducting the article search for this meta-analysis, two more recent studies have been published. The studies suggested that FRs may have a smaller total volume of the cortical and cerebellar gray matter and smaller volume in the thalamus, putamen, amygdala, and nucleus accumbens (de Zwarte et al., 2018, 2019). Hence, the continuous accumulation of new research is necessary to take into consideration. Additionally, it is necessary to consider is that we utilized different software for the comparison of our findings to previous schizophrenia studies and behavioral domains. Thus, these analyses should be considered as supplementary analyses.

This meta-analysis had a variety of strengths. Firstly, we had a substantially higher number of studies and a higher total number of FRs (41 datasets, 1638 FRs) than in the largest previous meta-analysis (25 datasets, 1065 FRs) (Boos et al., 2007) that was published before the conduction of our analyses. A recently published ENIGMA study (de Zwarte et al., 2019), however, included more participants than our meta-analysis (1228 FR and 2246 controls). Secondly, we also performed a multimodal meta-analysis to investigate whether the functional and structural alterations occur in overlapping brain regions. Thirdly, to the best of our knowledge, this meta-analysis was the first to investigate functional alterations in FRs separately in various cognitive tasks. Finally, we investigated whether the brain regions with structural or functional alterations in FRs are overlapping with the brain regions (i) that are affected among schizophrenia patients and (ii) that exhibit increased activity during cognitive tasks in healthy individuals.

4.6 Conclusions

In summary, the fMRI meta-analysis showed that during cognitive tasks, FRs had increased activity in the right inferior frontal gyrus when compared to healthy controls. Overall, the functional alterations in FRs were very restricted and only slightly overlapping with the affected brain regions in schizophrenia patients.

The functional alterations in FRs correlated positively with the brain regions that exhibited increased activity during cognitive tasks in healthy individuals. The VBM meta-analysis or multimodal analyses obtained no differences between FRs and healthy controls. It is necessary to consider that due to the comparatively low number of studies with some types of cognitive tasks (e.g. social cognition tasks), no firm conclusions about task-specific alterations in FRs can be made. Consequently, more research is needed about functional alterations on a broader range of different cognitive tasks. In conclusion, our findings suggest that there may exist minor functional alterations in the brain in FRs (vs. controls) in various cognitive domains that have a role in the pathogenesis of schizophrenia. Instead, we did not find any structural alterations in FRs.

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Table 1. Description of the fMRI studies included in the meta-analysis.

		FRs			Healthy controls						
First author	Publication year	*N*	Female (%)	Mean age (years)	*N*	Female (%)	Mean age (years)	Software package	Tesla	Smoothing kernel (mm)	Cognitive task
Working memory											
Callicott, J.H.[a]	2004a	23	74	34	18	39	30	SPM	1.5	10	N-back working memory task
Callicott, J.H.[a]	2004b	25	56	37	15	60	28	SPM	1.5	10	N-back working memory task
Choi, J.S.	2011	17	47	21	16	44	21	SPM	1.5	8	Spatial delayed-response task (spatial working memory)
De Leeuw, M.	2013	23	39	30	24	50	28	SPM	3	8	Sternberg Working Memory Task
Jiang, S.	2015	20	45	51	20	50	52	SPM	3	8	N-back working memory task
Karch, S.	2009	11	64	34	11	64	34	Brainvoyager	1.5	8	N-back working memory task
Li, X.	2016	43	71	25	32	59	25	FSL	3	8	Visual and verbal 1-back working memory task
Loeb, F.F.	2018	30	43	19	39	46	20	AFNI	3	8	1- and 2-back working memory tasks
Meda, S.A.	2008	23	61	51	43	53	43	SPM	3	12	Sternberg Working Memory Task
Stäblein, M.	2018	22	64	43	25	52	35	BrainVoyager	3	NA	Visual working memory task (a masked change detection task)
Zandbelt, B.B.	2011	24	46	30	24	38	32	SPM5	3.0	6	Sternberg Working Memory Task; Stop-Signal Anticipation Task (inhibitory control)
Inhibitory control											
Becker, T.M.	2008	17	65	33	17	41	33	AFNI	3	8	Stroop task
Delawalla, Z.	2008	30	53	21	92	58	20	NA	1.5	8	Continuous performance task (the AX-CPT)
Lopez-Garcia, P.	2016	16	44	57	20	60	33	SPM	3	8	Dot Probe Expectancy Task (context processing)
Raemaekers, M.	2006	16	50	34	16	50	33	IDL	1.5	8	Pro- and antisaccades task (eye movement control)
Sepede, G.	2009	11	55	34	11	55	32	BrainVoyager	1.5	NA	Continuous Performance Test (sustained attention)
Whalley, H.C.	2004	69	57	26	21	38	27	SPM99	1.5	6	Hayling Sentence Completion Task (response intiation and suppression)

Zandbelt, B.B.	2011	24	46	30	24	38	32	SPM5	3.0	6	Sternberg Working Memory Task; Stop-Signal Anticipation Task (inhibitory control)
Social cognition											
Dodell-Feder, D.	2014	19	74	27	18	78	26	SPM	3	6	Theory of mind tasks (Person-Description task; False-Belief Task)
Herold, R.	2018	12	50	43	12	58	37	FSL	3	5	Irony comprehension task
Li, X.	2012	12	66	31	12	50	29	SPM	3	6	Facial emotional valence discrimination
Park, H.Y.	2016	20	65	24	17	53	23	SPM	3	8	Facial emotion processing task
Pirnia, T.	2015	14	64	40	30	20	29	FSL	3	6	Facial memory task (face-name encoding and retrieval)
Spilka, M.J.	2017	27	63	41	27	52	41	FSL	3	7	Facial emotion and age recognition task
Van Buuren, M.	2012	25	56	28	25	56	28	SPM5	3.0	8	Self-referential task (social cognition)
Other tasks											
Grimm, O.	2014	54	57	34	80	51	34	SPM	3	9	Monetary reward anticipation paradigm
Lee, J.	2010	21	52	36	19	26	43	FSL	3	5	Visual backward masking task
Rajarethinam, R.	2011	15	53	15	17	47	15	SPM	4	8	Auditory comprehension task
Rasetti, R.	2014	65	58	36	181	52	35	SPM	3	8	Declarative memory task (visual encoding)
Stolz, E.	2012	16	63	23	28	68	27	SPM	3	8	Visual episodic memory encoding and retrieval task
Wagshal, D.	2013	10	50	13	25	40	13	FSL	3	5	Weather Prediction Task (cognitive skill learning task)

[a] Callicott et al. (2004) study included two datasets that were treated separately in the meta-analysis.
NA = Information not available. AFNI = Analysis of Functional NeuroImages. SPM = Statistical parametric mapping. FSL = The FMRIB Software Library. IDL = The Interactive Data Language.

Table 2. Description of the VBM studies included in the meta-analysis.

First author	Publication year	FRs			Healthy controls			Software package	Tesla	Smoothing kernel (mm)
		N	Female (%)	Age (years)	*N*	Female (%)	Age (years)			
Boos, H.B.M.	2011	186	54	28	122	50	28	Other	1.5	8
Guo, W.	2015	46	37	23	46	50	23	SPM	3.0	8
Guo, W.	2014	25	32	23	43	42	24	SPM	3.0	8
Honea, R.A.	2008	213	58	36	212	51	33	SPM2	1.5	6
Job, D.E.	2003	146	49	21	36	53	21	SPM99	1.0	12
Lei, W.[a]	2015a	25	48	44	40	55	43	SPM8	3.0	6
Lei, W.[a]	2015b	42	55	43	40	55	43	SPM8	3.0	6
McIntosh, A.M.	2004	24	54	39	49	53	35	SPM	1.5	8
Tian, L.	2011	55	51	50	29	52	52	SPM5 / VBM5	3.0	6
Van der Velde, J.	2015	89	54	32	69	45	34	SPM	3.0	8
Wagshal, D.	2015	14	43	12	46	46	13	FSL	3.0	3

[a] The study included two datasets that were treated separately in the meta-analysis.
SPM = Statistical parametric mapping. FSL = The FMRIB Software Library.

Table 3. Brain regions with altered activation in FRs (fMRI studies) and altered gray matter volume in FRs (VBM studies) in the multimodal meta-analysis, when compared to healthy controls.

	Coordinates (MNI)	Test statistic of SDM	*p*	Voxels	Description
fMRI studies					
Full set of cognitive tasks					
FRs > Controls	46, 12, 32	2.158	0.000001967	616	Right inferior frontal gyrus, opercular part, BA 44
Executive functioning					
FRs > Controls	50,16,28	2. 485	0.000003099	553	Right inferior frontal gyrus, opercular part, BA 48
Working memory					
FRs > Controls	50, 12, 26	2.443	0.000003219	913	Right inferior frontal gyrus, opercular part, BA 44

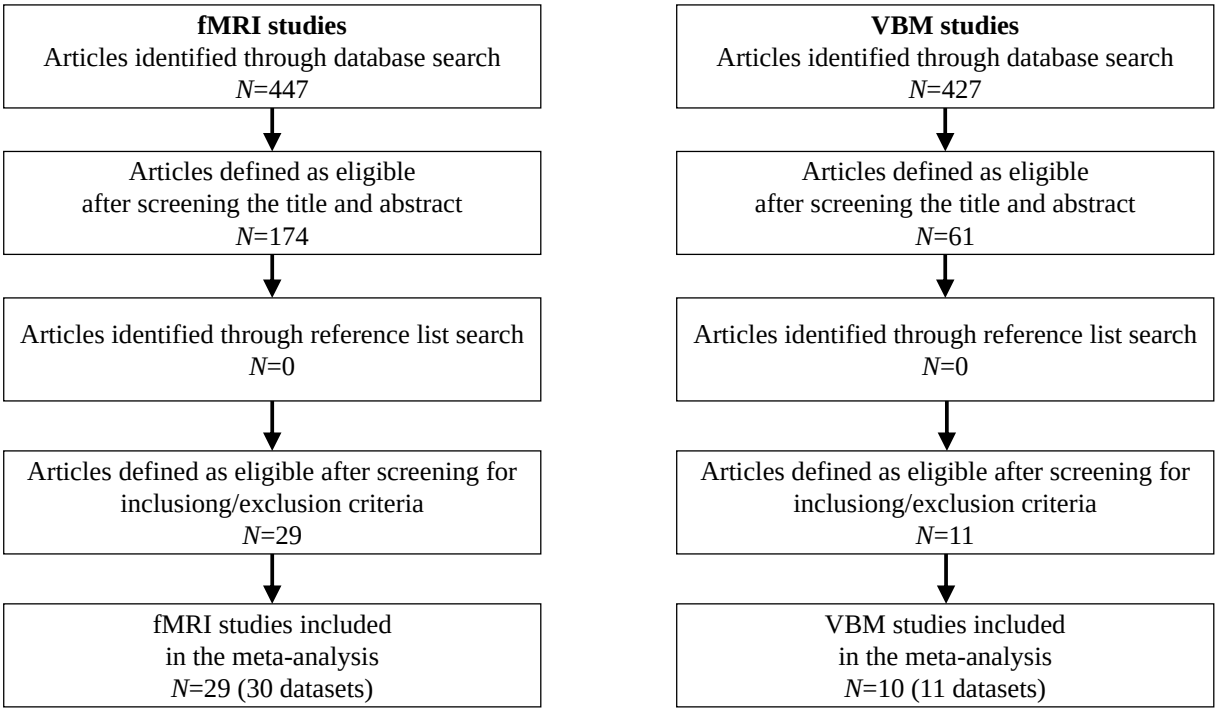


Figure 1. The selection process of the fMRI and VBM studies that were included in the meta-analysis.

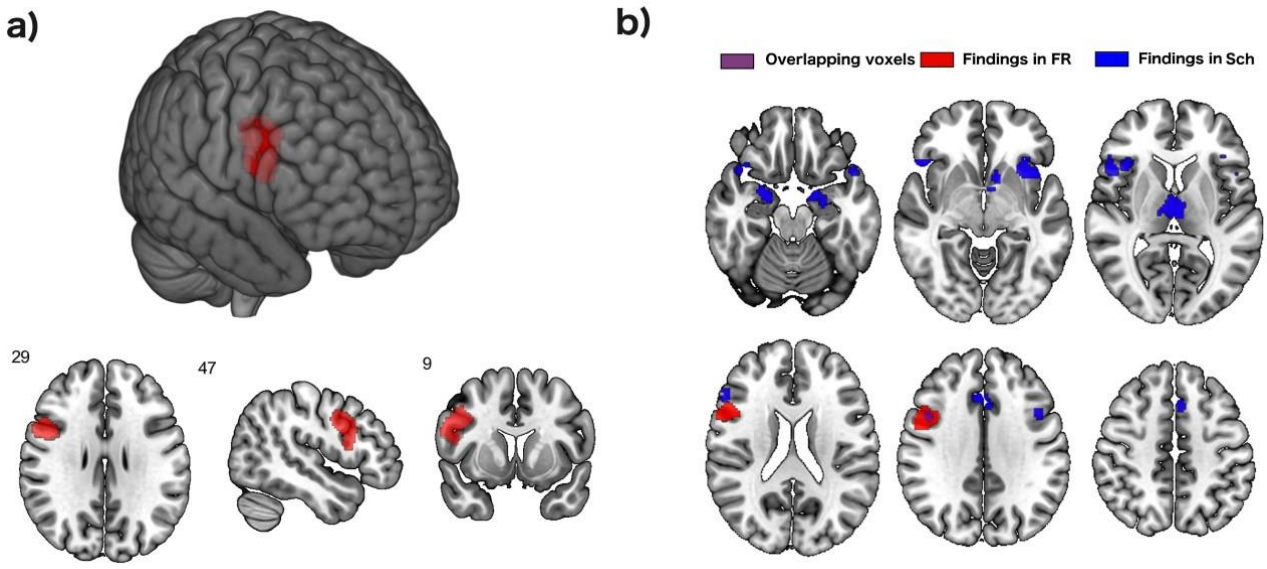


Figure 2. (a) Brain regions with increased (red) or decreased (blue) activity (fMRI) or volume (VBM) (in blue color) in FRs during different types of cognitive tasks, when compared to healthy controls. (b) Brain regions with overlap between meta-analyses in FRs and schizophrenia patients (Sch).

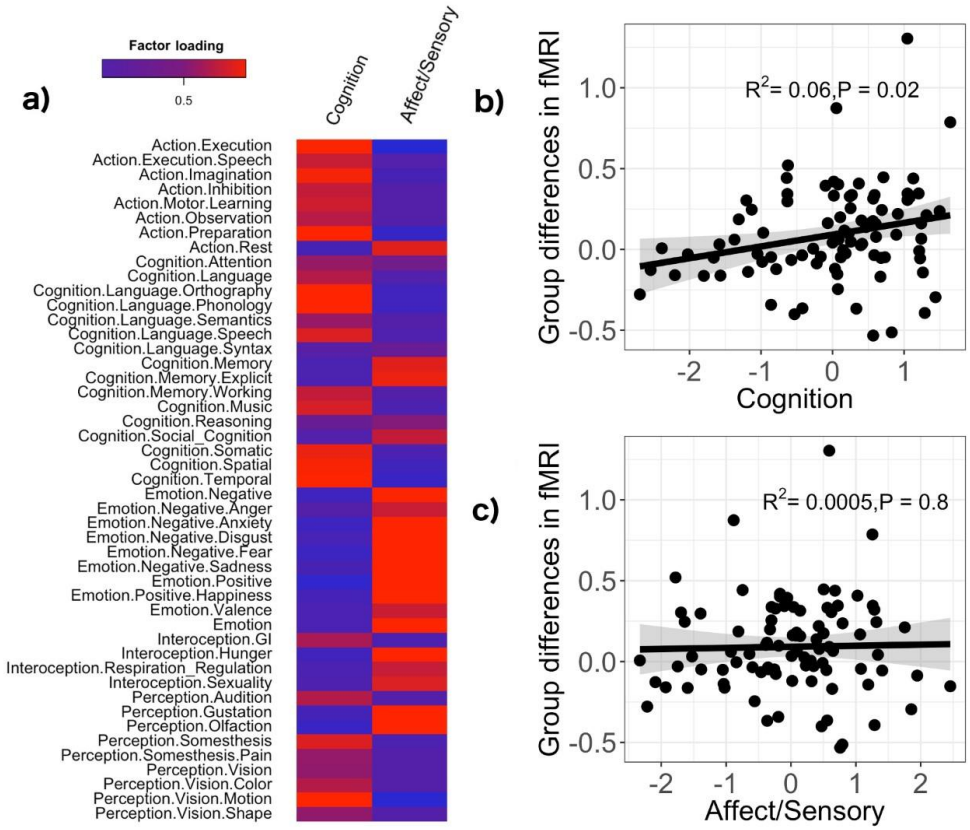
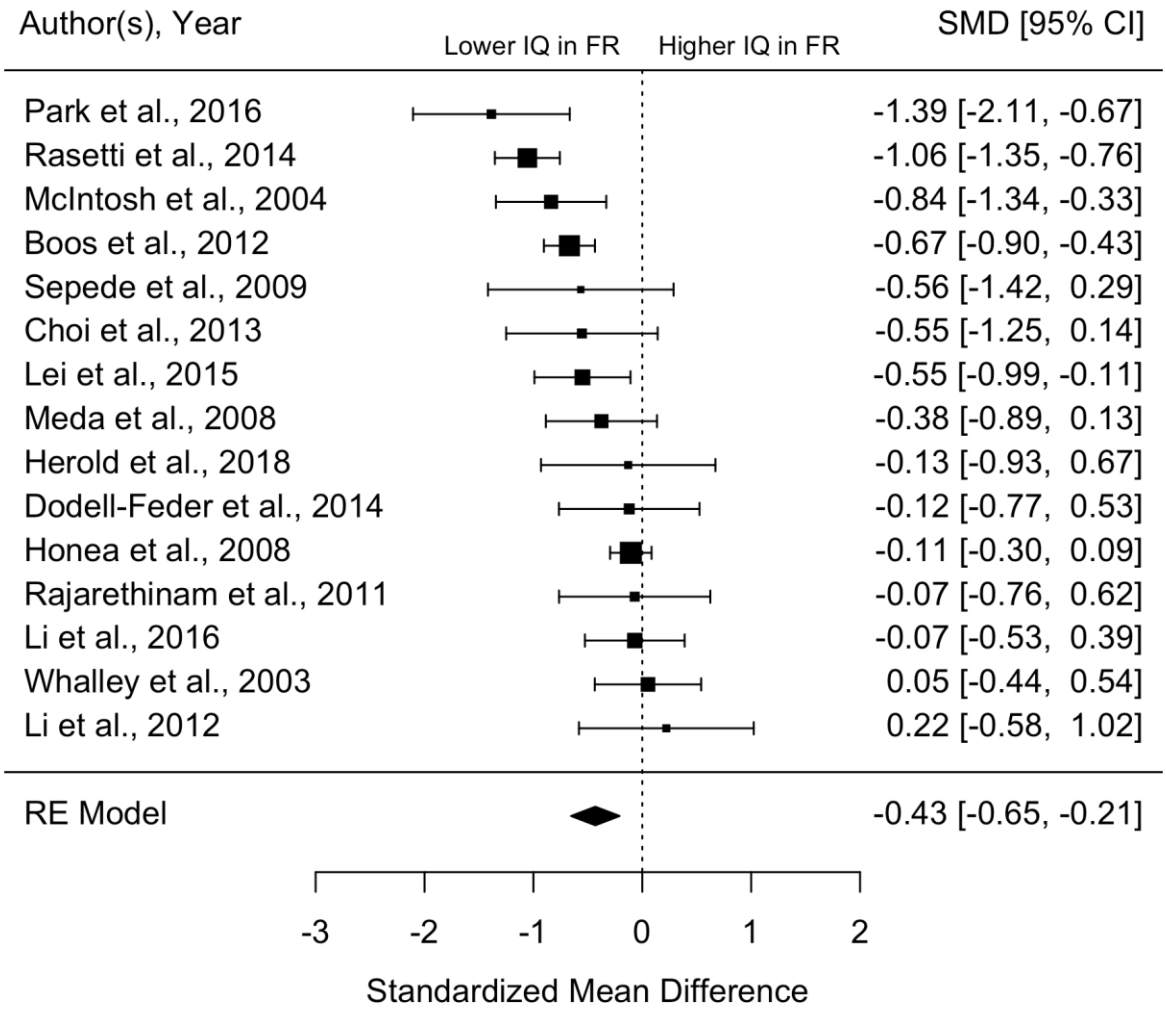
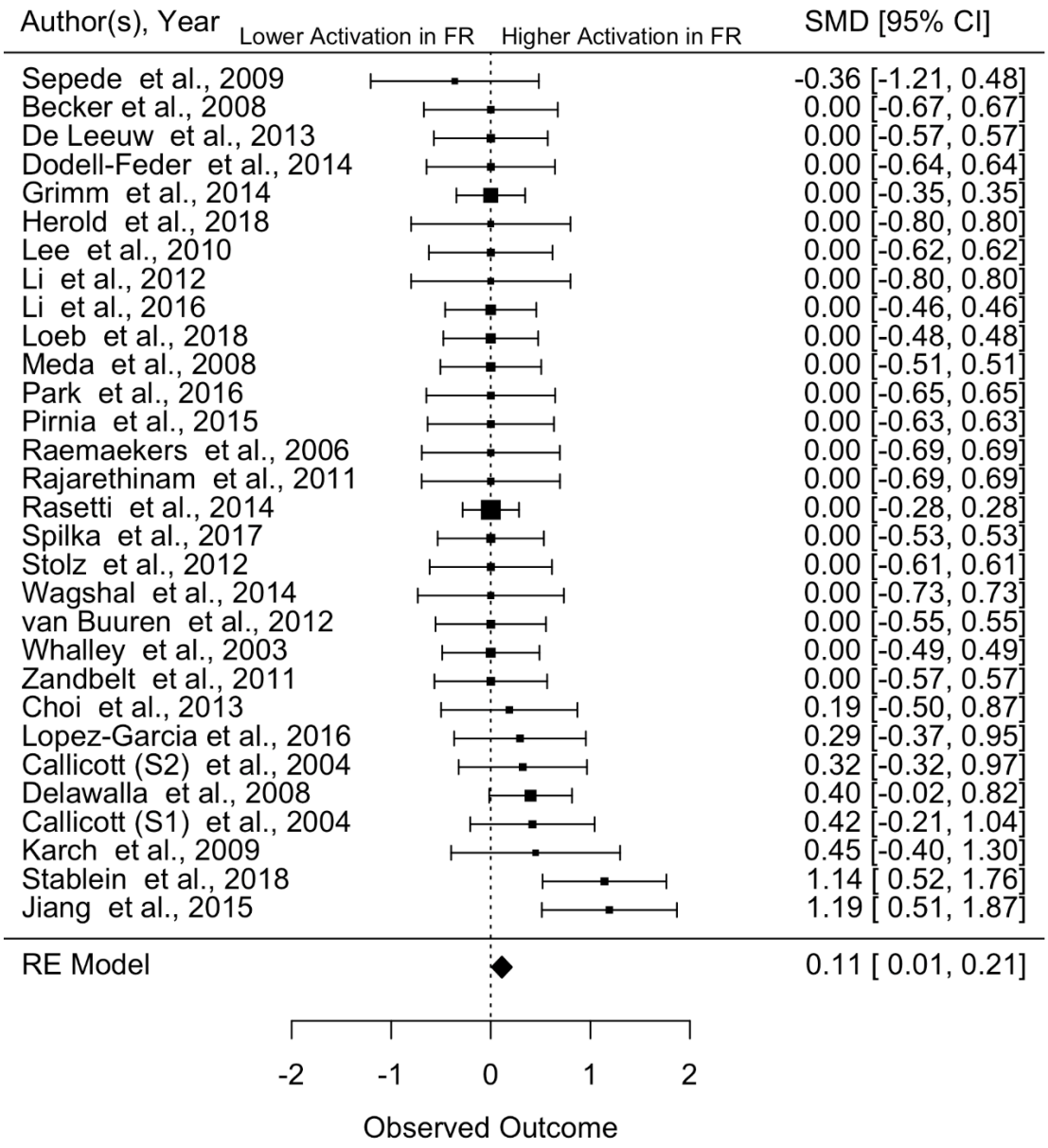


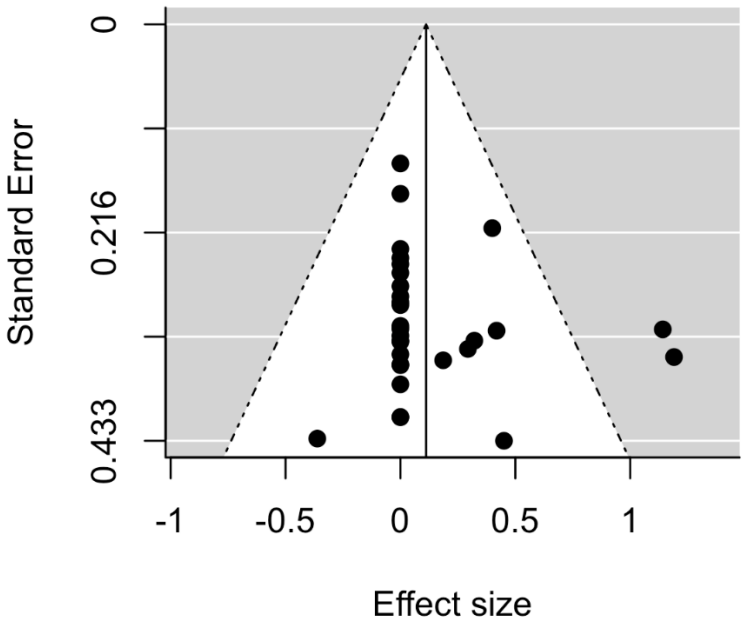
Figure 3. (a) The results of the principal component analysis: the loadings of the brain activity patterns of different behavioral domains to the cognition- and affect/sensory-related components in healthy individuals. (b) The correlations of the brain activation patterns during cognition- and affect/sensory-related processing (in healthy individuals) with the brain regions that showed altered fMRI activity in FRs. (c) The correlations of the brain activation patterns during cognition and affect/sensory-related processing (in healthy individuals) with the brain regions that showed structural alterations in FRs.



Supplementary Figure 1. Forest plot of the standardized mean differences in the level of IQ between FRs and healthy controls (in the 15 datasets of this meta-analysis that reported IQ). *Note*: RE=random effect, SMD=standardized mean difference.



Supplementary Figure 2. Forest plot depicting the individual study estimates and the overall estimate of the activation difference in the right inferior frontal gyrus (MNI coordinate: 46,12,32) between FRs and healthy controls. *Note*: RE=random effect, SMD=standardized mean difference.



Supplementary Figure 3. Funnel plot for the differences in the right inferior frontal gyrus (MNI coordinates: 46,12, 32). In Egger's test, p-value=0.34.

Supplementary Table 1. The fulfilled form of the MOOSE Checklist for Meta-analyses of Observational Studies.

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	Page 4
2	Hypothesis statement	Page 4
3	Description of study outcome(s)	Page 4
4	Type of exposure or intervention used	Page 4
5	Type of study designs used	Page 4
6	Study population	Page 4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	Pages 4-5
9	Effort to include all available studies, including contact with authors	Pages 4-6
10	Databases and registries searched	Page 4
11	Search software used, name and version, including special features used (eg, explosion)	Pages 4-5
12	Use of hand searching (eg, reference lists of obtained articles)	Page 5
13	List of citations located and those excluded, including justification	Figure 1, Supplementary Tables 1 and 2
14	Method of addressing articles published in languages other than English	Page 5
15	Method of handling abstracts and unpublished studies	Pages 4-5
16	Description of any contact with authors	Page 6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Pages 9-10
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Pages 5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Page 6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Pages 10-11
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Pages 9-11
22	Assessment of heterogeneity	Page 7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Pages 6-9
24	Provision of appropriate tables and graphics	Pages 6-9
Reporting of results should include		

25	Graphic summarizing individual study estimates and overall estimate	Supplementary figure 2
26	Table giving descriptive information for each study included	Tables 1 and 2
27	Results of sensitivity testing (eg, subgroup analysis)	Pages 10-11
28	Indication of statistical uncertainty of findings	Pages 10-11

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Pages 13-14
30	Justification for exclusion (eg, exclusion of non-English language citations)	Page 16
31	Assessment of quality of included studies	Pages 15-17
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Page 17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 17-18
34	Guidelines for future research	Page 17-18
35	Disclosure of funding source	(Reported in another document)

Source: Stroup, D.F., Berlin, J.A., Morton, S.C., et al., 2000. For the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA 283, 2008-2012.

Supplementary Table 2. The fMRI studies that were identified in literature search on the basis of title and abstract and that were excluded in the later phase.

First author	Published	Title	Reason for exclusion
Altamura, M.	2012	Abnormal functional motor lateralization in healthy siblings of patients with schizophrenia	ROI-based analyses
Antonucci L. A.	2016	Association of familial risk for schizophrenia with thalamic and medial prefrontal functional connectivity during attentional control	ICA was used
Barbour, T.	2012	fMRI responses to emotional faces in children and adolescents at genetic risk for psychiatric illness share some of the features of depression	Coordinates or Z/T-statistics not available
Barbour, T.	2010	Reduced intra-amygdala activity to positively valenced faces in adolescent schizophrenia offspring	ROI-based analyses
Bedwell, J. S.	2006	Schizophrenia and red light: fMRI evidence for a novel biobehavioral marker	ROI-based analyses
Bonner-Jackson, A.	2007	Levels-of-processing effects in first-degree relatives of individuals with schizophrenia	High-risk individuals and healthy controls not compared
Brahmbhatt, S. B.	2006	Neural correlates of verbal and nonverbal working memory deficits in individuals with schizophrenia and their high-risk siblings	High-risk individuals and healthy controls not compared
Braun, U.	2016	Dynamic brain network reconfiguration as a potential schizophrenia genetic risk mechanism modulated by NMDA receptor function	Only brain network analyses
Brent, B.	2014	Neural responses during social reflection in relatives of schizophrenia patients: Relationship to subclinical delusions	ROI-based analyses
Chahine, G.	2017	Disruptions in the left frontoparietal network underlie resting state endophenotypic markers in schizophrenia	Only brain network analyses
Chang, X.	2014	Altered default mode and fronto-parietal network subsystems in patients with schizophrenia and their unaffected siblings	ICA used
Collin, G.	2011	Impaired cerebellar functional connectivity in schizophrenia patients and their healthy siblings	Only functional connectivity analyses
Dauvermann, M. R.	2013	The application of nonlinear Dynamic Causal Modelling for fMRI in subjects at high genetic risk of schizophrenia	ROI-based analyses
de Achaval, D.	2013	Activation of brain areas concerned with social cognition during moral decisions is abnormal inschizophrenia patients and unaffected siblings	Coordinates or Z/T-statistics not available
de Achával, D.	2012	Decreased activity in right-hemisphere structures involved in social cognition in siblings discordant for schizophrenia	Coordinates or Z/T-statistics not available

Di Giorgio, A.	2013	Evidence that hippocampal-parahippocampal dysfunction is related to genetic risk for schizophrenia	Coordinates or Z/T-statistics not available
Dodell-Feder, D.	2014	The relationship between default mode network connectivity and social functioning in individuals at familial high-risk for schizophrenia	ROI-based analyses
Egan, M. F.	2001	Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia	High-risk individuals and healthy controls not compared
Fahim, C.	2004	Genes and memory: the neuroanatomical correlates of emotional memory in monozygotic twin discordant for schizophrenia	High-risk group size < 10
Falkenberg, I.	2015	Failure to deactivate medial prefrontal cortex in people at high risk for psychosis	Not peer-reviewed original article
Ganella, E. P.	2018	Risk and resilience brain networks in treatment-resistant schizophrenia	Only functional connectivity analysis
Goghari, V. M.	2011	Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimation meta-analysis	Not peer-reviewed original article
Goghari, V. M.	2017	Task-Related Functional Connectivity Analysis of Emotion Discrimination in a Family Study of Schizophrenia	Only functional connectivity analysis
Goldberg, T. E.	2006	The G72/G30 gene complex and cognitive abnormalities in schizophrenia	High-risk individuals and healthy controls not compared
Guo, S.	2018	The instability of functional connectivity in patients with schizophrenia and their siblings: A dynamic connectivity study	Only functional connectivity analysis
Guo, W.	2014	Decreased default-mode network homogeneity in unaffected siblings of schizophrenia patients	ROI-based analyses
Guo, W.	2014	Decreased regional activity of default-mode network in unaffected siblings of schizophrenia patients at rest	ICA was used
Guo, W.	2014	Decreased resting-state interhemispheric functional connectivity in unaffected siblings of schizophrenia patients	Only functional connectivity analysis
Guo, W.	2015	Dissociation of functional and anatomical brain abnormalities in unaffected siblings of schizophrenia patients	Resting-state
Guo, W.	2017	Family-based case-control study of homotopic connectivity in first-episode, drug-naive schizophrenia at rest	Only functional connectivity analysis
Guo, W.	2015	Resting-state cerebellar-cerebral networks are differently affected in first-episode, drug-naïve schizophrenia patients and unaffected siblings	Only functional connectivity analysis
Guo, W.	2017	Hyperactivity of the default-mode network in first-episode, drug-naive schizophrenia at rest revealed by family-based case-control and traditional case-control designs	Resting-state
Guo, W.	2017	Using short-range and long-range functional connectivity to identify schizophrenia with a family-based case-control design	Only functional connectivity analysis

Guo, W.	2015	Increased Cerebellar Functional Connectivity With the Default-Mode Network in Unaffected Siblings ofSchizophrenia Patients at Rest	Only functional connectivity analysis
Habel, U.	2004	Genetic load on amygdala hypofunction during sadness in nonaffected brothers of schizophrenia patients	ROI-based analyses
Hager, B.	2017	Neural complexity as a potential translational biomarker for psychosis	Brain activation levels not investigated
Hanssen, E.	2015	Neural correlates of reward processing in healthy siblings of patients with schizophrenia	Coordinates or Z/T-statistics not available
Harms, M. P.	2013	Structure-function relationship of working memory activity with hippocampal and prefrontal cortex volumes	High-risk individuals and healthy controls not compared
Hart, S. J.	2013	Altered fronto-limbic activity in children and adolescents with familial high risk for schizophrenia	Antipsychotic medications among high-risk individuals
Hart, S. J.	2015	Measurement of Fronto-limbic Activity Using an Emotional Oddball Task in Children with Familial High Risk for Schizophrenia	Antipsychotic medications among high-risk individuals
Hass, J.	2015	Complexin2 modulates working memory-related neural activity in patients with schizophrenia	High-risk individuals and healthy controls not compared
Jang, J. H.	2011	Reduced prefrontal functional connectivity in the default mode network is related to greater psychopathology in subjects with high genetic loading for schizophrenia	Only functional connectivity analyses
Jukuri, T.	2015	Central executive network in young people with familial risk for psychosis--the Oulu Brain and Mind Study	Resting-state
Jukuri, T.	2015	Cerebellar activity in young people with familial risk for psychosis--The Oulu Brain and Mind Study	Resting-state
Jukuri, T.	2013	Default mode network in young people with familial risk for psychosis--the Oulu Brain and Mind study	Resting-state
Karbasforoushan, H.	2012	Resting-state networks in schizophrenia	Not peer-reviewed original article
Karlsgodt, K. H.	2007	The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects	ROI-based analyses
Keshavan, M. S.	2002	A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents	High-risk individuals and healthy controls not compared
Kim, D.	2015	Shared and Distinct Neurocognitive Endophenotypes of Schizophrenia and Psychotic Bipolar Disorder	Not fMRI study
Landin-Romero, R.	2015	Failure of deactivation in the default mode network: a trait marker for schizophrenia?	High-risk individuals and healthy controls not compared
Langbein, K.	2011	Functional MRI in twins discordant for schizophrenia during a working memory task: preliminary results from the Eutwinss Study	Not peer-reviewed original article

Langbein, K.	2010	Functional MRI of working memory related activation in monozygotic wtins discordant for schizophrenia: preliminary results from the Eutwinss Study	Not peer-reviewed original article
Lawrie, S. M.	2008	Brain structure and function changes during the development of schizophrenia: The evidence from studies of subjects at increased genetic risk	Not peer-reviewed original article
Lawrie, S. M.	2003	Structural and functional abnormalities of the amygdala in schizophrenia	ROI-based analyses
Lerner, Y.	2017	Abnormal neural hierarchy in processing of verbal information in patients with schizophrenia	Not brain activation levels investigated
Li, X.	2007	An fMRI study of language processing in people at high genetic risk for schizophrenia	High-risk individuals and healthy controls not compared
Li, X.	2010	Disturbed Functional Connectivity of Cortical Activation during Semantic Discrimination in Patients with Schizophrenia and Subjects at Genetic High-risk	Not brain activation levels investigated
Li, X.	2007	fMRI study of language activation in schizophrenia, schizoaffective disorder and in individuals genetically at high risk	ROI-based analyses
Li, X.	2009	Language pathway abnormalities in schizophrenia: a review of fMRI and other imaging studies	Not peer-reviewed original article
Liao, H.	2012	A resting-state functional magnetic resonance imaging study on the first-degree relatives of persons with schizophrenia	Resting-state study
Lindberg, P. G.	2016	Altered cortical processing of motor inhibition in schizophrenia	ROI-based analyses
Liu, J.	2007	A novel approach to analyzing fMRI and SNP data via parallel independent component analysis	High-risk individuals and healthy controls not compared
Liu, M.	2012	Potential risk for healthy siblings to develop schizophrenia: evidence from pattern classification with whole-brain connectivity	High-risk individuals and healthy controls not compared
Liu, M.	2011	Schizophrenic Patients and Their Unaffected Siblings Show Similar Abnormalities in Resting-State Functional Connectivity	ROI-based analyses
Lo, C. Y.	2015	Randomization and resilience of brain functional networks as systems-level endophenotypes of schizophrenia	Coordinates or Z/T-statistics not available
Lui, S.	2015	Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives	Not brain activation levels investigated
MacDonald, A. W.	2003	Context processing deficits associated with hypofrontality in the healthy relatives of schizophrenia patients: An event-related fMRI study	No access to full-text version
MacDonald, A. W.	2006	Functional magnetic resonance imaging study of cognitive control in the healthy relatives of schizophrenia patients	High-risk individuals and healthy controls not compared
Marjoram, D.	2006	A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia	High-risk individuals and healthy controls not compared

Meda, S.	2012	Differences in Resting-State Functional Magnetic Resonance Imaging Functional Network Connectivity Between Schizophrenia and Psychotic Bipolar Probands and Their Unaffected First-Degree Relatives	Not brain activation levels investigated
Meda, S.	2015	Frequency-Specific Neural Signatures of Spontaneous Low-Frequency Resting State Fluctuations in Psychosis: Evidence From Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium	Not brain activation levels investigated
Mohnke, S.	2016	Theory of mind network activity is altered in subjects with familial liability for schizophrenia	ROI-based analyses
Niu, Y.	2017	Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: a multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies	Not peer-reviewed original article
Nook, E. C.	2018	Weak dorsolateral prefrontal response to social criticism predicts worsened mood and symptoms following social conflict in people at familial risk for schizophrenia	ROI-based analyses
Oertel-Knöchel, V.	2014	Association between symptoms of psychosis and reduced functional connectivity of auditory cortex	Only functional connectivity analysis
Oertel-Knöchel, V.	2013	Reduced functional connectivity and asymmetry of the planum temporale in patients with schizophrenia and first-degree relatives	Only functional connectivity analysis
Pearlson, G. D.	2017	Applications of Resting State Functional MR Imaging to Neuropsychiatric Diseases	Not peer-reviewed original article
Pearlson, G. D.	2011	Exploring connectivity differences among low-frequency resting-state fMRI networks between schizophrenia and psychotic bipolar subject and their unaffected first-degree relatives	Not peer-reviewed original article
Pearlson, G. D.	2009	Resting State and Default Mode fMRI Data in Schizophrenia, Bipolar Disorder, and Relatives	No access to full-text version
Pearlson, G. D.	2005	Working memory deficits and aberrant prefrontal cortex activation in first-degree relatives ofschizophrenia patients: An fMRI study	No access to full-text version
Peeters, S.	2015	Semi-metric analysis of the functional brain network: Relationship with familial risk for psychotic disorder	Only functional network analysis
Pettersson-Yeo, W.	2011	Dysconnectivity in schizophrenia: Where are we now?	Not peer-reviewed original article
Picchioni, M. M.	2010	Genetic and non-genetic influences on brain function in schizophrenia: an fMRI study in twins	Not peer-reviewed original article
Picchioni, M. M.	2001	Verbal fluency in twins with schizophrenia: An fMRI study	High-risk individuals and healthy controls not compared
Poppe, A. B.	2015	Task-based functional connectivity as an indicator of genetic liability to schizophrenia	Only functional connectivity analysis
Pruitt, P.	2009	Disordered functional maturation of the amygdala during adolescence: fMRI studies of affective judgment in schizophrenia offspring	Not peer-reviewed original article
Pulkkinen, J.	2015	Functional mapping of dynamic happy and fearful facial expressions in young adults with familial risk for psychosis - Oulu Brain and Mind Study	Not necessarily 1st degree relatives

Rasetti, R.	2009	Evidence that altered amygdala activity in schizophrenia is related to clinical state and not genetic risk	ROI-based analyses
Repovs, G.	2011	Brain Network Connectivity in Individuals with Schizophrenia and Their Siblings	Only network connectivity analysis
Sambataro, F.	2010	Abnormal Cognitive Control Processing in Unaffected Siblings of Patients with Schizophrenia: An fMRI Intermediate Phenotype for Schizophrenia?	Not peer-reviewed original article
Schmidt, A.	2015	Approaching a network connectivity-driven classification of the psychosis continuum: a selective review and suggestions for future research	Not peer-reviewed original article
Schneider, M.	2017	Altered DLPFC-Hippocampus Connectivity During Working Memory: Independent Replication and Disorder Specificity of a Putative Genetic Risk Phenotype for Schizophrenia	Coordinates or Z/T-statistics not available
Scognamiglio, C.	2014	A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia	Not peer-reviewed original article
Seidman, L. J.	2006	Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: an fMRI study of working memory	ROI-based analyses
Seidman, L. J.	2007	Auditory verbal working memory load and thalamic activation in nonpsychotic relatives of persons with schizophrenia: an fMRI replication	ROI-based analyses
Seidman, L. J.	2014	Medial temporal lobe default mode functioning and hippocampal structure as vulnerability indicators for schizophrenia: a MRI study of non-psychotic adolescent first-degree relatives	ROI-based analyses
Sommer, I. E.	2004	Language activation in monozygotic twins discordant for schizophrenia	ROI-based analyses
Spaniel, F.	2007	Language lateralization in monozygotic twins discordant and concordant for schizophrenia: A functional MRI pilot study.	ROI-based analyses
Spilka, M. J.	2015	Functional activation abnormalities during facial emotion perception in schizophrenia patients and nonpsychotic relatives	Larger sample of the same population provided elsewhere
Su, J.	2016	Heredity characteristics of schizophrenia shown by dynamic functional connectivity analysis of resting-state functional MRI scans of unaffected siblings	Resting-state study
Tang, Y.	2015	Neural activity changes in unaffected children of patients with schizophrenia: A resting-state fMRI study	Not activation investigated
Thermenos, H. W.	2013	Altered language network activity in young people at familial high-risk for schizophrenia	Relatives expressed psychotic
Thermenos, H. W.	2007	Elaborative verbal encoding and altered anterior parahippocampal activation in adolescents and young adults at genetic risk for schizophrenia using FMRI	ROI-based analyses
Thermenos, H. W.	2004	Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: a pilot study	ROI-based analyses
Tian, L.	2011	Convergent evidence from multimodal imaging reveals amygdala abnormalities in schizophrenic patients and their first-degree relatives	Not activation investigated

van Buuren, M.	2011	Exaggerated Brain Activation During Emotion Processing in Unaffected Siblings of Patients with Schizophrenia	Larger sample of the same population provided elsewhere
van der Meer, L.	2014	Neural correlates of emotion regulation in patients with schizophrenia and non-affected siblings	Larger sample of the same population provided elsewhere
van Leeuwen, J. M. C.	2018	At-risk individuals display altered brain activity following stress	Larger sample of the same population provided elsewhere
Wang, J.	2015	Three dysconnectivity patterns in treatment-resistant schizophrenia patients and their unaffected siblings	Only functional connectivity analysis
Wang, Z.	2015	Large-Scale Fusion of Gray Matter and Resting-State Functional MRI Reveals Common and Distinct Biological Markers across the Psychosis Spectrum in the B-SNIP Cohort	Resting-state study
Watsky, R. E.	2016	Attenuated Resting-State Functional Connectivity in Patients with Childhood- and Adult-OnsetSchizophrenia, Not in Their Siblings	Resting-state study
Watsky, R. E.	2018	Attenuated resting-state functional connectivity in patients with childhood- and adult-onset schizophrenia	Resting-state study
Whalley, H. C.	2012	Effects of a mis-sense DISC1 variant on brain activation in two cohorts at high risk of bipolar disorder orschizophrenia	High-risk individuals and healthy controls not compared
Whalley, H. C.	2012	Impact of a microRNA MIR137 Susceptibility Variant on Brain Function in People at High Genetic Risk of Schizophrenia or Bipolar Disorder	First-degree relatives and healthy controls not compared
Whalley, H. C.	2009	fMRI changes over time and reproducibility in unmedicated subjects at high genetic risk of schizophrenia	Coordinates or Z/T-statistics not available
Whalley, H. C.	2005	Functional disconnectivity in subjects at high genetic risk of schizophrenia	Not necessarily 1st degree relatives
Whalley, H. C.	2006	Functional imaging as a predictor of schizophrenia	
Whitfield-Gabrieli, S.	2009	Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia	High-risk individuals and healthy controls not compared
Whyte, M. C.	2006	Event-related fMRI of word classification and successful word recognition in subjects at genetically enhanced risk of schizophrenia	Larger sample of the same population provided elsewhere
Villarreal, M. F.	2014	Pattern of brain activation during social cognitive tasks is related to social competence in siblingsdiscordant for schizophrenia	High-risk individuals and healthy controls not compared
Windemuth, A.	2008	Physiogenomic analysis of localized FMRI brain activity in schizophrenia	ROI-based analyses
Vink, M.	2016	DRD2 Schizophrenia-Risk Allele Is Associated With Impaired Striatal Functioning in Unaffected Siblings of Schizophrenia Patients	ROI-based analyses
Woodward, N. D.	2007	An FMRI investigation of procedural learning in unaffected siblings of individuals with schizophrenia	High-risk group size < 10

Woodward, N. D.	2009	Abnormal prefrontal cortical activity and connectivity during response selection in first episode psychosis, chronic schizophrenia, and unaffected siblings of individuals with schizophrenia	High-risk group size < 10
Woodward, N. D.	2007	An fMRI investigation of procedural learning in unaffected siblings of individuals with schizophrenia	ROI-based analyses
Xi, Y. B.	2016	Anterior Cingulate Cortico-Hippocampal Dysconnectivity in Unaffected Relatives of Schizophrenia Patients: A Stochastic Dynamic Causal Modeling Study	Only functional connectivity analysis
Xiao, B.	2017	Abnormalities of localized connectivity in schizophrenia patients and their unaffected relatives: a meta-analysis of resting-state functional magnetic resonance imaging studies	Resting-state study
Yu, Y.	2013	Functional connectivity-based signatures of schizophrenia revealed by multiclass pattern analysis of resting-state fMRI from schizophrenic patients and their healthy siblings	Resting-state study
Zhang, R.	2016	Working Memory in Unaffected Relatives of Patients With Schizophrenia: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies	Not peer-reviewed original article
Mitchell, R. L. C.	2001	fMRI and cognitive dysfunction in schizophrenia	Not peer-reviewed original article
Ceaser, A.	2013	COMT influences on prefrontal and striatal blood oxygenation level-dependent responses during working memory among individuals with schizophrenia, their siblings, and healthy controls	Coordinates or Z/T-statistics not available
Diwadkar, V. A.	2011	Fronto-parietal hypo-activation during working memory independent of structural abnormalities: conjoint fMRI and sMRI analyses in adolescent offspring of schizophrenia patients	ROI-based analyses
Diwadkar, V. A.	2011	Hypo-activation in the executive core of the sustained attention network in adolescent offspring of schizophrenia patients mediated by premorbid functional deficits	ROI-based analyses
Diwadkar, V. A.	2012	The neural correlates of performance in adolescents at risk for schizophrenia: inefficiently increased cortico-striatal responses measured with fMRI	Coordinates or Z/T-statistics not available
Habel, U.	2002	Neuronal substratum for emotional impairments in patients with schizophrenia - results of neuroimaging	Not peer-reviewed original article
Bakshi, N.	2011	Inefficiently increased anterior cingulate modulation of cortical systems during working memory in young offspring of schizophrenia patients	ROI-based analyses
Dauvermann, M. R.	2012	Relationship Between Gyrification and Functional Connectivity of the Prefrontal Cortex in Subjects at High Genetic Risk of Schizophrenia	ROI-based analyses
Diwadkar, V. A.	2014	Dysfunction and Dysconnection in Cortical-Striatal Networks during Sustained Attention: Genetic Risk for Schizophrenia or Bipolar Disorder and its Impact on Brain Network Function	Only functional connectivity analysis
Jamadar, S. D.	2013	Semantic association fMRI impairments represent a potential schizophrenia biomarker	High-risk individuals and healthy controls not compared

Whalley, H. C.	2008	Hypofrontality in subjects at high genetic risk of schizophrenia with depressive symptoms	High-risk individuals and healthy controls not compared
Wolf, D. H.	2011	Amygdala abnormalities in first-degree relatives of individuals with schizophrenia unmasked by benzodiazepine challenge	Coordinates or Z/T-statistics not available

Supplementary Table 3. The VBM studies that were identified in literature search on the basis of title and abstract and that were excluded in the later phase.

First author	Published	Title	Reason for exclusion
Bois, C.	2015	Cortical Surface Area Differentiates Familial High Risk Individuals Who Go on to Develop Schizophrenia	Not VBM study
Borgwardt, S.J.	2010	Regional gray matter volume in monozygotic twins concordant and discordant for schizophrenia	High-risk group size < 10
Cannon, T.D.	1998	Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls	Not VBM study
Cannon, T.D.	2002	Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia	Not VBM study
Cannon, T.D.	2005	Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory	High-risk individuals and healthy controls not compared
Cao, H.	2016	Altered Functional Subnetwork During Emotional Face Processing: A Potential Intermediate Phenotype for Schizophrenia	Not VBM study
Chang, M.	2016	Voxel-Based Morphometry in Individuals at Genetic High Risk for Schizophrenia and Patients with Schizophrenia during Their First Episode of Psychosis	Statistical test/reporting of findings not applicable
Chen, Y.H.	2018	Associations and Heritability of Auditory Encoding, Gray Matter, and Attention in Schizophrenia	Not VBM study
Deng, W.	2006	Voxel-based morphometric analysis of gray matter in first-episode schizophrenia and their unaffected relatives: A 3T MR investigation	Statistical test/reporting of findings not applicable
Diwadkar, V.A.	2006	Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia?	High-risk individuals and healthy controls not compared
Diwadkar, V.A.	2011	Fronto-parietal hypo-activation during working memory independent of structural abnormalities: conjoint fMRI and sMRI analyses in adolescent offspring of schizophrenia patients	Not VBM study
Fan, Y.	2008	Unaffected family members and schizophrenia patients share brain structure patterns: A high-dimensional pattern classification study	Statistical test/reporting of findings not applicable
Goghari, V.M.	2014	Relationship between prefrontal gray matter volumes and working memory performance in schizophrenia: a family study	Not VBM study
Gogtay, N.	2007	Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia	Not VBM study

Goldman, A.L.	2008	Heritability of brain morphology related to schizophrenia: a large-scale automated magnetic resonance imaging segmentation study	Not VBM study
Gong, Q.	2018	A transdiagnostic neuroanatomical signature of psychiatric illness	Not VBM study
Ho, B.C.	2007	MRI brain volume abnormalities in young, nonpsychotic relatives of schizophrenia probands are associated with subsequent prodromal symptoms	Not VBM study
Hu, M.	2013	Decreased left middle temporal gyrus volume in antipsychotic drug-naive, first-episode schizophrenia patients and their healthy unaffected siblings	Statistical test/reporting of findings not applicable
Huang, L.	2016	The impact of CACNA1C allelic variation on regional gray matter volume in Chinese population	High-risk individuals and healthy controls not compared
Ivleva, E.I.	2013	Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)	High-risk individuals and healthy controls not compared
Ivleva, E.I.	2017	Brain Structure Biomarkers in the Psychosis Biotypes: Findings From the Bipolar-Schizophrenia Network for Intermediate Phenotypes	High-risk individuals and healthy controls not compared
Knöchel, C.	2016	Shared and distinct gray matter abnormalities in schizophrenia, schizophrenia relatives and bipolar disorder in association with cognitive impairment	Not VBM study
Lee, P.H.	2013	Neural correlate of impulsivity in subjects at ultra-high risk for psychosis	High-risk individuals and healthy
Lee, T.Y.	2016	Partitioning heritability analysis reveals a shared genetic basis of brain anatomy and schizophrenia	High-risk individuals and healthy controls not compared
Lui, S.	2009	Neuroanatomical differences between familial and sporadic schizophrenia and their parents: An optimized voxel-based morphometry study	Statistical test/reporting of findings not applicable
Lymer, G.K.S.	2006	Brain - behaviour relationships in people at high genetic risk of schizophrenia	Not VBM study
Marcelis, M.	2003	Searching for a structural endophenotype in psychosis using computational morphometry	Statistical test/reporting of findings not applicable
Mattai, A.A.	2011	Normalization of cortical gray matter deficits in nonpsychotic siblings of patients with childhood-onset schizophrenia	Not VBM study
McDonald, C.	2004	Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes	High-risk individuals and healthy controls not compared
Nenadic, I.	2015	Brain structure in people at ultra-high risk of psychosis, patients with first-episode schizophrenia, and healthy controls: a VBM study	Statistical test/reporting of findings not applicable
Oertel-Knöchel, V.	2012	Cortical-basal ganglia imbalance in schizophrenia patients and unaffected first-degree relatives	High-risk individuals and healthy controls not compared
Orešič, M.	2012	Phospholipids and insulin resistance in psychosis: a lipidomics study of twin pairs discordant for schizophrenia	Not VBM study

Pietiläinen, O.P.	2009	Association of AKT1 with verbal learning, verbal memory, and regional cortical gray matter density in twins	High-risk individuals and healthy controls not compared
Pol, H.E.H.	2004	Gray and white matter density abnormalities in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry	Statistical test/reporting of findings not applicable
Raznahan, A.	2011	Catechol-o-methyl transferase (COMT) val158met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls	Not VBM study
Schneider-Axmann, T.	2006	Relation between cerebrospinal fluid, gray matter and white matter changes in families with schizophrenia	Not VBM study
Shi, F.	2012	Altered structural connectivity in neonates at genetic risk for schizophrenia: a combined study using morphological and white matter networks	Not VBM study
Soh, P.	2015	Joint Coupling of Awake EEG Frequency Activity and MRI Gray Matter Volumes in the Psychosis Dimension: A BSNIP Study	Not VBM study
Sprooten, E.	2013	Cortical thickness in first-episode schizophrenia patients and individuals at high familial risk: A cross-sectional comparison	Not VBM study
Solé-Padullés, C.	2016	Altered Cortico-Striatal Connectivity in Offspring of Schizophrenia Patients Relative to Offspring of Bipolar Patients and Controls	Not VBM study
Sugranyes, G.	2015	Gray Matter Volume Decrease Distinguishes Schizophrenia From Bipolar Offspring During Childhood and Adolescence	Statistical test/reporting of findings not applicable
Sugranyes, G.	2017	Clinical, Cognitive, and Neuroimaging Evidence of a Neurodevelopmental Continuum in Offspring of Probands With Schizophrenia and Bipolar Disorder	Not VBM study
Tijms, B.M.	2015	Grey matter networks in people at increased familial risk for schizophrenia	Not VBM study
Turner, J.A.	2012	Heritability of multivariate gray matter measures in schizophrenia	Not VBM study
Van der Auwera, S.	2017	Predicting brain structure in population-based samples with biologically informed genetic scores for schizophrenia	High-risk individuals and healthy controls not compared
van Haren, N.E.	2012	The genetic and environmental determinants of the association between brain abnormalities and schizophrenia: the schizophrenia twins and relatives consortium	Not VBM study
Watsky, R.E.	2016	Severity of Cortical Thinning Correlates With Schizophrenia Spectrum Symptoms	Not VBM study
Wei, Q.	2012	The effect of DISC1 on regional gray matter density of schizophrenia in Han Chinese population	High-risk individuals and healthy controls not compared
Wright, C.	2016	Polymorphisms in MIR137HG and microRNA-137-regulated genes influence gray matter structure in schizophrenia	High-risk individuals and healthy controls not compared
Yang, Y.	2010	The contributions of disease and genetic factors towards regional cortical thinning in schizophrenia: the UCLA family study	Not VBM study

Supplementary Table 4. Data from the BrainMap database (http://www.brainmap.org/taxonomy/behaviors.html).

Behavioral domain	N of publications	Description
Action: Execution	309	The state or process of executing an overt movement of the body (other than speech).
Action: Execution, Speech	93	The state or process of overtly speaking.
Action: Imagination	50	The state or process of imagining an overt movement of the body.
Action: Inhibition	148	The state or process of inhibiting an overt movement of the body.
Action: Motor Learning	26	The state or process of learning how to execute an overt movement of the body.
Action: Observation	45	The state or process of observing an overt movement of the body.
Action: Preparation	21	The state or process of preparing for an overt movement of the body.
Action: Rest	76	The state or process of resting from overt movements of the body.
Cognition: Attention	646	The act or state of attending by applying the mind to any object of sense or thought.
Cognition: Language	43	The mental faculty associated with knowledge of a system of objects or symbols, such as sounds or character sequences, that can be combined in various ways following a set of rules, especially to communicate thoughts, feelings, or instructions.
Cognition: Language, Orthography	84	The mental faculty associated with the part of language study concerned with letters and spelling.
Cognition: Language, Phonology	91	The mental faculty associated with knowledge of the distribution and patterning of speech sounds in a language and of the tacit rules governing pronunciation.
Cognition: Language, Semantics	311	The mental faculty associated with knowledge of meaning in language forms.
Cognition: Language, Speech	230	The mental faculty associated with knowledge of overtly or covertly speaking.
Cognition: Language, Syntax	38	The mental faculty associated with knowledge of the rules for the formation of grammatical sentences in a language.
Cognition: Memory, Other	24	The mental faculty of retaining and reviving facts, events, or impressions, or of recalling or recognizing previous experiences.
Cognition: Memory.Explicit	260	The memory that consists of information stored and retrieved explicitly from the external world.
Cognition: Memory, Working	291	The memory for intermediate results that must be held during thinking.
Cognition: Music	34	The mental faculty associated with the art of sound in time that expresses ideas and emotions in significant forms through the elements of rhythm, melody, harmony, and color.
Cognition: Reasoning	264	The mental faculty of forming conclusions, judgments, or inferences from facts or premises.
Cognition: Social Cognition	122	The mental faculty associated with how people process social information, especially its encoding, storage, retrieval, and application to social situations.
Cognition: Somatic	22	The mental faculty associated with knowledge of one's body.
Cognition: Spatial	62	The mental faculty associated with awareness of the three-dimensional expanse in which all material objects are located and all events occur.

Cognition: Temporal	30	The mental faculty associated with the system of sequential relations that any event has to any other as past, present, or future.
Emotion: Negative	37	The experience of negative emotion subsumes a variety of emotions including anger, contempt, disgust, guilt, fear, anxiety, hate, etc.
Emotion: Negative, Anger	41	An emotion of wrath or ire characterized by displeasure and belligerence aroused by a wrong.
Emotion: Negative, Anxiety	52	An emotion characterized by distress or uneasiness of mind caused by fear of danger or misfortune.
Emotion: Negative, Disgust	50	An emotion characterized by a strong distaste, nausea, or loathing.
Emotion: Negative, Fear	103	An emotion of being afraid aroused by distress, impending danger, evil, pain, etc.
Emotion: Negative, Sadness	72	An emotion of sorrow or mourning characterized by unhappiness or grief.
Emotion: Positive	21	The experience of positive emotion subsumes a variety of emotions including joy, happiness, contentment, love, etc.
Emotion: Positive, Happiness	88	An emotion of well-being ranging from contentment to intense joy (excluding humor).
Emotion: Valence	24	The intrinsic attractiveness/"good"-ness (positive valence) or averseness/"bad"-ness (negative valence) of an event, object, or situation.
Emotion	219	Any affective processes that qualify as Emotion, but do not fit into any of the other Emotion sub-domains.
Interoception: Gastrointestinal-Genitourinary	17	Awareness of pressure or distension in gastrointestinal or genitourinary systems, including the mouth, esophagus, stomach, bladder, anus, rectum.
Interoception: Hunger	17	The need for food.
Interoception: Respiration Regulation	21	The need for respiration.
Interoception: Sexuality	50	The need for sexual activity.
Perception: Audition	155	The sense of hearing.
Perception: Gustation	45	The sense of tasting.
Perception: Olfaction	42	The sense of smelling.
Perception: Somesthesis	109	The sensory systems associated with the skin, including touch, pressure, temperature and position.
Perception: Somesthesis, Pain	117	The senses of bodily perception associated with an unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder.
Perception: Vision	170	The sense of sight.
Perception: Vision, Color	35	The visual perception of the quality of an object or substance with respect to light reflected by the object, usually determined visually by measurement of hue, saturation, and brightness of the reflected light.

Perception: Vision, Motion	92	The visual perception of the action or process of moving or of changing place or position.
Perception: Vision, Shape	158	The visual perception of the quality of a distinct object in having an external surface or outline of specific form or figure.

Supplementary Table 5. The results of the meta-analyses on the fMRI (28 datasets) and VBM (9 datasets) studies that included only first-degree relatives of schizophrenia patients.

	Coordinates (MNI)	Test statistic of SDM	*p*	Voxels	Description
fMRI studies					
FRs > Controls	46, 6, 34	2.078	0.000007	418	Right precentral gyrus, BA 44