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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References

Aron, A.R., Fletcher, P.C., Bullmore, E.T. et al., 2003. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 6, 115. https://doi.org/10.1038/nn1003

Becker, T.M., Kerns, J.G., MacDonald, III A.W. et al., 2008. Prefrontal dysfunction in first-degree relatives of schizophrenia patients during a Stroop task. Neuropsychopharmacology 33, 2619–2625. https://doi.org/10.1038/sj.npp.1301673

Boos, H.B., Aleman, A., Cahn, W. et al., 2007. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch Gen Psychiatry 64, 297-304. https://doi.org/10.1001/archpsyc.64.3.297

Boos, H.B., Cahn, W., van Haren, N.E. et al., 2011. Focal and global brain measurements in siblings of patients with schizophrenia. Schizophr Bull 38, 814-825. https://doi.org/10.1093/schbul/sbq147

Byrne, M., Clafferty, B.A., Cosway, R. et al., 2003. Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. J Abnorm Psychol 112, 38.

Callicott, J.H., Egan, M.F., Mattay, V.S. et al., 2004. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry 160, 709–719. https://doi.org/10.1176/appi.ajp.160.4.709

Carrión, R.E., Walder, D.J., Auther, A.M. et al., 2018. From the psychosis prodrome to the first-episode of psychosis: No evidence of a cognitive decline. J Psychiatr Res 96, 231–238. https://doi.org/10.1016/j.jpsychires.2017.10.014

Chikazoe, J., Konishi, S., Asari, T., Jimura, K., Miyashita, Y., 2007. Activation of right inferior frontal gyrus during response inhibition across response modalities. Journal of Cognitive Neuroscience 19, 69-80.

Choi, J.S., Park, J.Y., Jung, M.H. et al., 2011. Phase-specific brain change of spatial working memory processing in genetic and ultra-high risk groups of schizophrenia. Schizophr Bull 38, 1189–1199. https://doi.org/10.1093/schbul/sbr038

Cooper, D., Barker, V., Radua, J. et al., 2014. Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia. Psychiatry Res Neuroimaging 221, 69–77. https://doi.org/10.1016/j.pscychresns.2013.07.008

Cornblatt, B.A., Lencz, T., Smith, C.W. et al., 2003. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr Bull 29, 633–651. https://doi.org/10.1093/oxfordjournals.schbul.a007036

Crow, T.J., Ball, J., Bloom, S.R. et al., 1989. Schizophrenia as an anomaly of development of cerebral asymmetry: a postmortem study and a proposal concerning the genetic basis of the disease. Arch Gen Psychiatry 46, 1145-1150. https://doi.org/10.1001/archpsyc.1989.01810120087013

Daniel, T.A., Katz, J.S., Robinson, J.L., 2016. Delayed match-to-sample in working memory: A BrainMap meta-analysis. Biological Psychology 120, 10-20.

De Leeuw, M., Kahn, R.S., Zandbelt, B.B. et al., 2013. Working memory and default mode network abnormalities in unaffected siblings of schizophrenia patients. Schizophr Res 150,555–562. https://doi.org/10.1016/j.schres.2013.08.016

Delawalla, Z., Csernansky, J.G., Barch, D.M., 2008. Prefrontal cortex function in nonpsychotic siblings of individuals with schizophrenia. Biol Psychiatry 63, 490–497. https://doi.org/10.1016/j.biopsych.2007.05.007

de Zwarte, S., Brouwer, R.M., Tsouli, A., Cahn, W., Hillegers, M.H., Pol, H., ..., van Haren, N.E., 2018. Running in the Family? Structural Brain Abnormalities and IQ in Offspring, Siblings, Parents, and Co-twins of Patients with Schizophrenia. Schizophrenia Bulletin.

de Zwarte, S.M., Brouwer, R.M., Agartz, I., Alda, M., Aleman, A., Alpert, K.I., ..., Bramon, E., 2019. The association between familial risk and brain abnormalities is disease-specific: an ENIGMA–Relatives study of schizophrenia and bipolar disorder. Biological Psychiatry 86, 545-556.

Diamond, A., 2013. Executive functions. Annu Rev Psychol 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dodell-Feder, D., DeLisi, L.E., Hooker, C.I., 2014. Neural disruption to theory of mind predicts daily social functioning in individuals at familial high-risk for schizophrenia. Soc Cogn Affect Neurosci 9, 1914-1925.

Dragovic, M., Hammond, G., 2005. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatr Scand 111, 410–419. https://doi.org/10.1111/j.1600-0447.2005.00519.x

Eickhoff, S.B., Laird, A.R., Grefkes, C. et al., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 30, 2907–2926. https://doi.org/10.1002/hbm.20718

Eickhoff, S.B., Nichols, T.E., Laird, A.R. et al., 2016. Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. Neuroimage 137, 70–85. https://doi.org/10.1016/j.neuroimage.2016.04.072

Enticott, P.G., Ogloff, J.R., Bradshaw, J.L., 2008. Response inhibition and impulsivity in schizophrenia. Psychiatry Research 157, 251-254.

Faraone, S.V., Seidman, L.J., Kremen, W.S. et al., 2000. Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. Biol Psychiatry 48, 120-126. https://doi.org/10.1016/S0006-3223(99)00263-2

Filbey, F.M., Russell, T., Morris, R.G. et al., 2008. Functional magnetic resonance imaging (fMRI) of attention processes in presumed obligate carriers of schizophrenia: preliminary findings. Ann Gen Psychiatry 7, 18. https://doi.org/10.1186/1744-859X-7-18

Fusar-Poli, P., Broome, M.R., Matthiasson, P. et al., 2010. Spatial working memory in individuals at high risk for psychosis: longitudinal fMRI study. Schizophr Res 123, 45–52. https://doi.org/10.1016/j.schres.2010.06.008

Fusar-Poli, P., Deste, G., Smieskova, R. et al., 2012. Cognitive functioning in prodromal psychosis: a meta-analysis. Arch Gen Psychiatry 69, 562–571. https://doi.org/10.1001/archgenpsychiatry.2011.1592

Fusar-Poli, P., Radua, J., McGuire, P., & Borgwardt, S., 2011. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. Schizophrenia Bulletin 38, 1297-1307.

Gottesman, I.I., Laursen, T.M., Bertelsen, A. et al., 2010. Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch Gen Psychiatry 67, 252–257. https://doi.org/10.1001/archgenpsychiatry.2010.1

Guo, W., Song, Y., Liu, F. et al., 2015. Dissociation of functional and anatomical brain abnormalities in unaffected siblings of schizophrenia patients. Clin Neurophysiol 126, 927–932. https://doi.org/10.1016/j.clinph.2014.08.016

Guo, W., Hu, M., Fan, X. et al., 2014. Decreased gray matter volume in the left middle temporal gyrus as a candidate biomarker for schizophrenia: a study of drug naive, first-episode schizophrenia patients and unaffected siblings. Schizophr Res 159, 43–50. https://doi.org/10.1016/j.schres.2014.07.051

Grimm, O., Heinz, A., Walter, H. et al., 2014. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. JAMA Psychiatry 71, 531–539. https://doi.org/10.1001/jamapsychiatry.2014.9

Haijma, S.V., Van Haren, N., Cahn, W. et al., 2012. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull 39, 1129–1138. https://doi.org/10.1093/schbul/sbs118

Hampshire, A., Chamberlain, S.R., Monti, M.M., Duncan, J., Owen, A.M., 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50, 1313-1319.

Hans, S.L., Auerbach, J.G., Asarnow, J.R. et al., 2000. Social adjustment of adolescents at risk for schizophrenia: the Jerusalem Infant Development Study. J Am Acad Child Adolesc Psychiatry 39, 1406–1414. https://doi.org/10.1097/00004583-200011000-00015

Herold, R., Varga, E., Hajnal, A. et al., 2018. Altered Neural Activity during Irony Comprehension in Unaffected First-Degree Relatives of Schizophrenia Patients—An fMRI Study. Front Psychol 8, 2309. https://doi.org/10.3389/fpsyg.2017.02309

Hirayasu, Y., Tanaka, S., Shenton, M.E. et al., 2001. Prefrontal gray matter volume reduction in first episode schizophrenia. Cereb Cortex 11, 374–381. https://doi.org/10.1093/cercor/11.4.374

Honea, R.A., Meyer-Lindenberg, A., Hobbs, K.B. et al., 2008. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. Biol Psychiatry 63, 465–474. https://doi.org/10.1016/j.biopsych.2007.05.027

Jiang, S., Yan, H., Chen, Q. et al., 2015. Cerebral inefficient activation in schizophrenia patients and their unaffected parents during the n-back working memory task: a family fMRI Study. PloS One 10, e0135468. https://doi.org/10.1371/journal.pone.0135468

Job, D.E., Whalley, H.C., McConnell, S. et al., 2003. Voxel-based morphometry of gray matter densities in subjects at high risk of schizophrenia. Schizophr Res 64, 1–13. https://doi.org/10.1016/S0920-9964(03)00158-0

Kambeitz, J., Kambeitz-Ilankovic, L., Leucht, S. et al., 2015. Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. Neuropsychopharmacology 40, 1742–1751. https://dx.doi.org/10.1038%2Fnpp.2015.22

Karch, S., Leicht, G., Giegling, I. et al., 2009. Inefficient neural activity in patients with schizophrenia and nonpsychotic relatives of schizophrenic patients: evidence from a working memory task. J Psychiatr Res 43, 1185–1194. https://doi.org/10.1016/j.jpsychires.2009.04.004

Khandaker, G.M., Barnett, J.H., White, I.R. et al., 2011. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophr Res 132, 220–227. https://doi.org/10.1016/j.schres.2011.06.017

Laird, A.R., Eickhoff, S.B., Fox, P.M., Uecker, A.M., Ray, K.L., Saenz, J.J., ..., Turner, J.A., 2011. The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. BMC Research Notes 4, 349.

Lee, J., Cohen, M.S., Engel, S.A. et al., 2010. Regional brain activity during early visual perception in unaffected siblings of schizophrenia patients. Biol Psychiatry 68, 78–85. https://doi.org/10.1016/j.biopsych.2010.03.028

Lei, W., Deng, W., Li, M. et al., 2015. Gray matter volume alterations in first-episode drug-naive patients with deficit and nondeficit schizophrenia. Psychiatry Res Neuroimaging 234, 219–226. https://doi.org/10.1016/j.pscychresns.2015.09.015

Lencz, T., Smith, C.W., McLaughlin, D. et al., 2006. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry 59, 863–871. https://doi.org/10.1016/j.biopsych.2005.09.005

Li, X., Alapati, V., Jackson, C. et al., 2012. Structural abnormalities in language circuits in genetic high-risk subjects and schizophrenia patients. Psychiatry Res Neuroimaging 201, 182–189. https://doi.org/10.1016/j.pscychresns.2011.07.017

Li, X., Branch, C.A., DeLisi, L.E., 2009. Language pathway abnormalities in schizophrenia: a review of fMRI and other imaging studies. Curr Opin Psychiatry 22, 131–139. https://doi.org/10.1097/YCO.0b013e328324bc43

Li, X., Thermenos, H.W., Wu, Z. et al., 2016. Abnormal interactions of verbal-and spatial-memory networks in young people at familial high-risk for schizophrenia. Schizophr Res 176, 100–105. https://doi.org/10.1016/j.schres.2016.07.022

Lichtenstein, P., Björk, C., Hultman, C.M. et al., 2006. Recurrence risks for schizophrenia in a Swedish national cohort. Psychol Med 36, 1417–1425. https://doi.org/10.1017/S0033291706008385

Lieberman, J.A., Perkins, D., Belger, A. et al., 2001. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry 50, 884–897. https://doi.org/10.1016/S0006-3223(01)01303-8

Loeb, F.F., Zhou, X., Craddock, K.E. et al., 2018. Reduced functional brain activation and connectivity during a working memory task in childhood-onset schizophrenia. J Am Acad Child Adolesc Psychiatry 57, 166–174. https://doi.org/10.1016/j.jaac.2017.12.009

Lopez-Garcia, P., Cristobal-Huerta, A., Espinoza, L.Y. et al., 2016. The influence of the COMT genotype in the underlying functional brain activity of context processing in schizophrenia and in relatives. Prog Neuropsychopharmacol Biol Psychiatry 71, 176–182. https://doi.org/10.1016/j.pnpbp.2016.07.005

McIntosh, A.M., Job, D.E., Moorhead, T.W.J. et al., 2004. Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biol Psychiatry 56, 544–552. https://doi.org/10.1016/j.biopsych.2004.07.020

Meda, S.A., Bhattarai, M., Morris, N.A. et al., 2008. An fMRI study of working memory in first-degree unaffected relatives of schizophrenia patients. Schizophr Res 104, 85–95. https://doi.org/10.1016/j.schres.2008.06.013

Miyake, A., Friedman, N.P., 2012. The nature and organization of individual differences in executive functions: Four general conclusions. Curr Dir Psychol Sci 21, 8–14. https://doi.org/10.1177%2F0963721411429458

Mäki, P., Veijola, J., Jones, P.B. et al., 2005. Predictors of schizophrenia—a review. Br Med Bull 73, 1-15. https://doi.org/10.1093/bmb/ldh046

Niu, Y., Li, Z., Cheng, R., et al., 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. Int J Clin Exp Med 10, 1866-1878.

Park, H.Y., Yun, J.Y., Shin, N.Y. et al., 2016. Decreased neural response for facial emotion processing in subjects with high genetic load for schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 71, 90–96. https://doi.org/10.1016/j.pnpbp.2016.06.014

Pirnia, T., Woods, R.P., Hamilton, L.S. et al., 2015. Hippocampal dysfunction during declarative memory encoding in schizophrenia and effects of genetic liability. Schizophr Res 161, 357–366. https://doi.org/10.1016/j.schres.2014.11.030

Pulkkinen, J., Nikkinen, J., Kiviniemi, V. et al., 2015. Functional mapping of dynamic happy and fearful facial expressions in young adults with familial risk for psychosis - Oulu Brain and Mind Study. Schizophr Res 164, 242–249. https://doi.org/10.1016/j.schres.2015.01.039

Radua, J., Borgwardt, S., Crescini, A., Mataix-Cols, D., Meyer-Lindenberg, A., McGuire, P. K., Fusar-Poli, P., 2012a. Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. Neuroscience & Biobehavioral Reviews 36, 2325-2333.

Radua, J., Mataix-Cols, D., Phillips, M.L. et al., 2012b. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur Psychiatry 27, 605–611. https://doi.org/10.1016/j.eurpsy.2011.04.001

Radua, J., Romeo, M., Mataix-Cols, D., Fusar-Poli, P., 2013. A general approach for combining voxel-based meta-analyses conducted in different neuroimaging modalities. Current Medicinal Chemistry 20, 462-466.

Radua, J., Rubia, K., Canales, E.J. et al., 2014. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. Front Psychiatry 5, 13. https://doi.org/10.3389/fpsyt.2014.00013

Raemaekers, M., Ramsey, N.F., Vink, M. et al., 2006. Brain activation during antisaccades in unaffected relatives of schizophrenic patients. Biol Psychiatry 59, 530–535. https://doi.org/10.1016/j.biopsych.2005.07.030

Rajarethinam, R., Venkatesh, B.K., Peethala, R. et al., et al., 2011. Reduced activation of superior temporal gyrus during auditory comprehension in young offspring of patients with schizophrenia. Schizophr Res 130, 101–105. https://doi.org/10.1016/j.schres.2011.05.025

Rasetti, R., Mattay, V.S., White, M.G. et al., 2014. Altered hippocampal-parahippocampal function during stimulus encoding: a potential indicator of genetic liability for schizophrenia. JAMA Psychiatry 71, 236–247. https://doi.org/10.1001/jamapsychiatry.2013.3911

Revelle, W.R., 2017. Psych: Procedures for personality and psychological research. https://CRAN.R-project.org/package=psych

Scognamiglio, C., Houenou, J., 2014. A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia. Aust N Z J Psychiatry 48, 907–916. https://doi.org/10.1177%2F0004867414540753

Seidman, L.J., Giuliano, A.J., Meyer, E.C. et al., 2010. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Arch Gen Psychiatry 67, 578–588. https://doi.org/10.1001/archgenpsychiatry.2010.66

Sepede, G., Ferretti, A., Perrucci, M.G. et al., 2010. Altered brain response without behavioral attention deficits in healthy siblings of schizophrenic patients: an event-related fMRI study. Neuroimage 49, 1080–1090. https://doi.org/10.1016/j.neuroimage.2009.07.053

Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. Science 283, 1657–1661. https://doi.org/10.1126/science.283.5408.1657

Snitz, B.E., MacDonald, III A.W., Carter, C.S., 2005. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull 32, 179–194. https://doi.org/10.1093/schbul/sbi048

Sowell, E.R., Peterson, B.S., Thompson, P.M. et al., 2003. Mapping cortical change across the human life span. Nat Neurosci 6, 309–315. https://doi.org/10.1038/nn1008

Spilka, M.J., Goghari, V.M., 2017. Similar patterns of brain activation abnormalities during emotional and non-emotional judgments of faces in a schizophrenia family study. Neuropsychologia 96, 164–174. https://doi.org/10.1016/j.neuropsychologia.2017.01.014

Stolz, E., Pancholi, K.M., Goradia, D.D. et al., 2012. Brain activation patterns during visual episodic memory processing among first-degree relatives of schizophrenia subjects. Neuroimage 63, 1154–1161. https://doi.org/10.1016/j.neuroimage.2012.08.030

Stäblein, M., Storchak, H., Ghinea, D. et al., 2019. Visual working memory encoding in schizophrenia and first-degree relatives: neurofunctional abnormalities and impaired consolidation. Psychol Med 49, 75–83. https://doi.org/10.1017/S003329171800051X

Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 60, 1187–1192. https://doi.org/10.1001/archpsyc.60.12.1187

Tian, L., Meng, C., Yan, H. et al., 2011. Convergent evidence from multimodal imaging reveals amygdala abnormalities in schizophrenic patients and their first-degree relatives. PloS One 6, e28794. https://doi.org/10.1371/journal.pone.0028794

Turkeltaub, P.E., Eden, G.F., Jones, K.M. et al., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16, 765–780. https://doi.org/10.1006/nimg.2002.1131

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D. et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289. https://doi.org/10.1006/nimg.2001.0978

Vanasse, T.J., Fox, P.M., Barron, D.S., Robertson, M., Eickhoff, S.B., Lancaster, J.L., Fox, P.T., 2018. BrainMap VBM: An environment for structural meta-analysis. Human Brain Mapping 39, 3308-3325.

Van Buuren, M., Vink, M., Kahn, R.S., 2012. Default-mode network dysfunction and self-referential processing in healthy siblings of schizophrenia patients. Schizophr Res 142, 237–243. https://doi.org/10.1016/j.schres.2012.09.017

Van der Velde, J., Gromann, P.M., Swart, M. et al., 2015. Gray matter, an endophenotype for schizophrenia? A voxel-based morphometry study in siblings of patients with schizophrenia. J Psychiatry Neurosci 40, 207. https://doi.org/10.1503/jpn.140064

van Erp, T.G., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., ..., Melle, I. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Molecular Psychiatry 21, 547.

Van Erp, T. G., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., ..., Okada, N., 2018. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. Biological Psychiatry 84, 644-654.

Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum Brain Mapp 30, 829–858. https://doi.org/10.1002/hbm.20547

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J Stat Softw 36, 1-48.

Wagner, S., Sebastian, A., Lieb, K. et al., 2014. A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci 15, 19. https://doi.org/10.1186/1471-2202-15-19

Wagshal, D., Knowlton, B.J., Cohen, J.R., et al., 2015. Cognitive correlates of gray matter abnormalities in adolescent siblings of patients with childhood-onset schizophrenia. Schizophr Res 161, 345–350. https://doi.org/10.1016/j.schres.2014.12.006

Wagshal, D., Knowlton, B.J., Suthana, N.A., et al., 2013. Evidence for corticostriatal dysfunction during cognitive skill learning in adolescent siblings of patients with childhood-onset schizophrenia. Schizophr Bull 40, 1030–1039. https://doi.org/10.1093/schbul/sbt147

Wang, K., Fan, J., Dong, Y., Wang, C.Q., Lee, T.M., Posner, M.I., 2005. Selective impairment of attentional networks of orienting and executive control in schizophrenia. Schizophrenia Research 78, 235-241.

Whalley, H.C., Simonotto, E., Flett, S. et al., 2004. fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. Brain 127, 478–490. https://doi.org/10.1093/brain/awh070

Zandbelt, B.B., van Buuren, M., Kahn, R.S. et al., 2011. Reduced proactive inhibition in schizophrenia is related to corticostriatal dysfunction and poor working memory. Biol Psychiatry 70, 1151–1158. https://doi.org/10.1016/j.biopsych.2011.07.028

Zhang, R., Picchioni, M., Allen, P. et al., 2016. Working memory in unaffected relatives of patients with schizophrenia: a meta-analysis of functional magnetic resonance imaging studies. Schizophr Bull 42, 1068-1077. https://doi.org/10.1093/schbul/sbv221

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

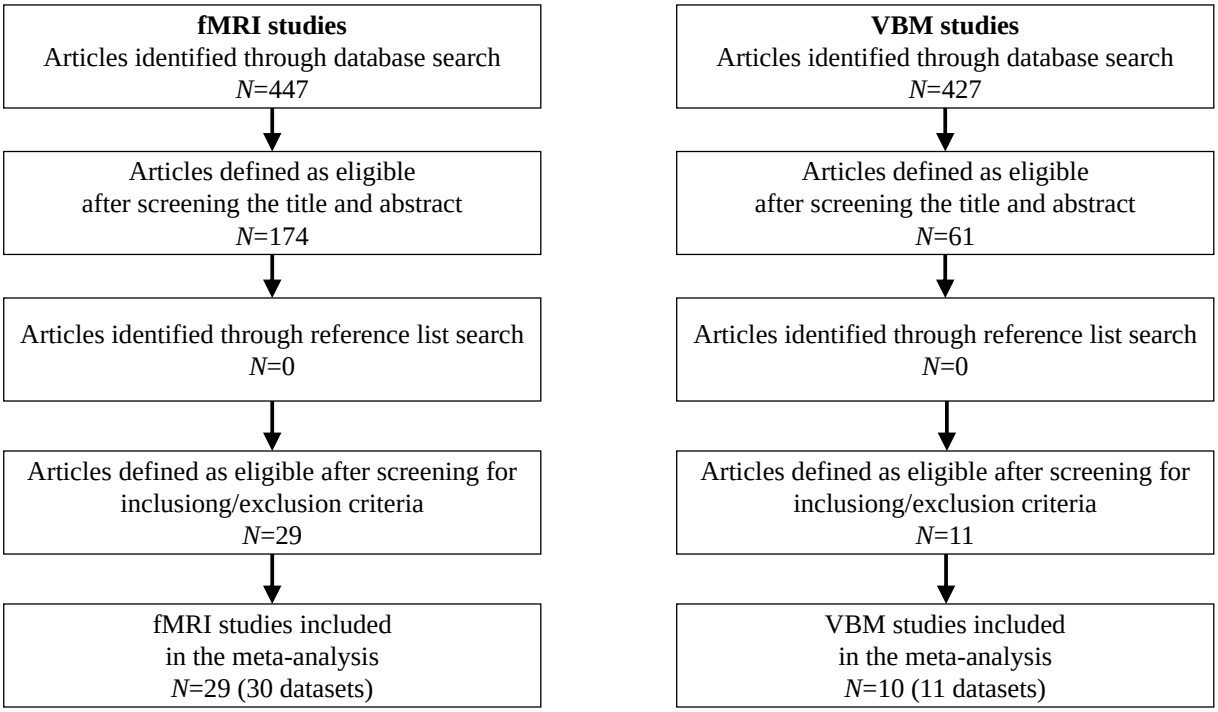

Figure 1. The selection process of the fMRI and VBM studies that were included in the meta-analysis.

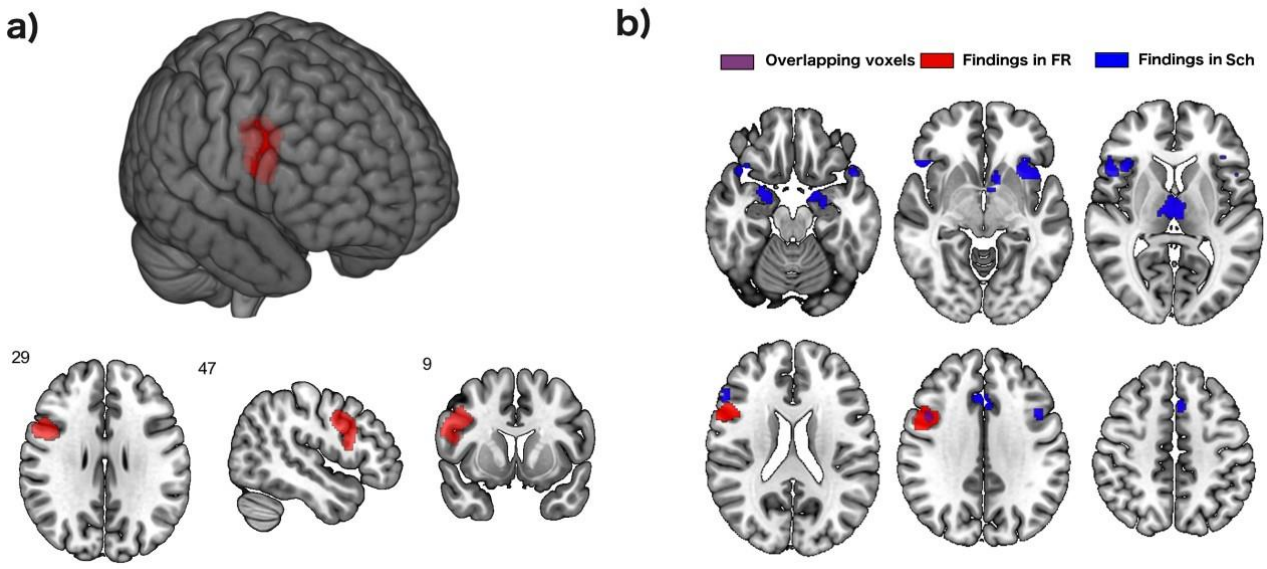

Figure 2. (a) Brain regions with increased (red) or decreased (blue) activity (fMRI) or volume (VBM) (in blue color) in FRs during different types of cognitive tasks, when compared to healthy controls. (b) Brain regions with overlap between meta-analyses in FRs and schizophrenia patients (Sch).

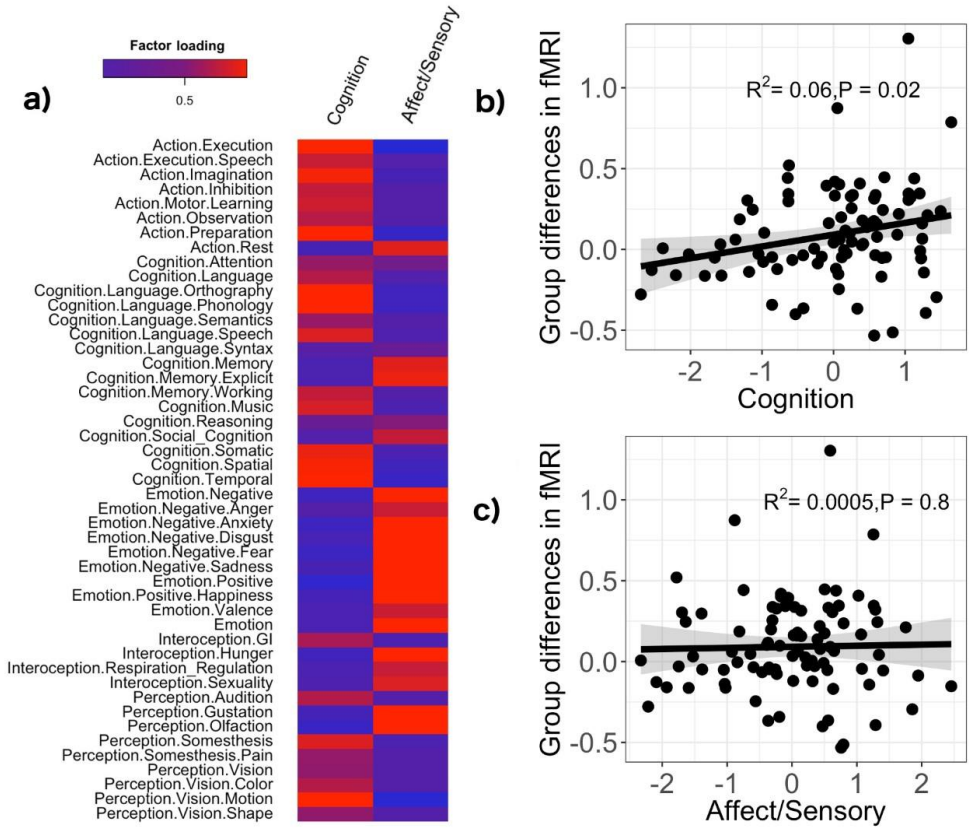

Figure 3. (a) The results of the principal component analysis: the loadings of the brain activity patterns of different behavioral domains to the cognition- and affect/sensory-related components in healthy individuals. (b) The correlations of the brain activation patterns during cognition- and affect/sensory-related 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.