A SYSTEMATIC REVIEW AND META-ANALYSIS OF STRUCTURAL AND FUNCTIONAL BRAIN ALTERATIONS IN INDIVIDUALS WITH GENETIC AND CLINICAL HIGH-RISK FOR PSYCHOSIS AND BIPOLAR DISORDER

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Abstract

Neuroimaging findings in people at either genetic risk or at clinical high-risk for psychosis (CHR-P) or bipolar disorder (CHR-B) remain unclear. A meta-analytic review of whole-brain voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) studies in individuals with genetic risk or CHR-P or CHR-B and controls identified 94 datasets (N=7942). Notwithstanding no significant findings were observed following adjustment for multiple comparisons, several findings were noted at a more liberal threshold. Subjects at genetic risk for schizophrenia or bipolar disorder or at CHR-P exhibited lower grey matter (GM) volumes in the gyrus rectus (Hedges' g = -0.19). Genetic risk for psychosis was associated with GM reductions in the right cerebellum and left amygdala. CHR-P was associated with decreased GM volumes in the frontal superior gyrus and hypoactivation in the right precuneus, the superior frontal gyrus and the right inferior frontal gyrus. Genetic and CHR-P were associated with small structural and functional alterations involving regions implicated in psychosis. Further neuroimaging studies in individuals with genetic or CHR-B are warranted.

Keywords: bipolar disorder; psychosis; schizophrenia; neuroimaging; meta-analysis; psychiatry

1. Introduction

Although schizophrenia spectrum disorders and bipolar disorders were once thought to represent distinct psychopathological entities (Kendler and Engstrom, 2018), a large body of evidence indicates that these heterogeneous disorders present strong genetic correlation (2018; 2019; Lichtenstein et al., 2009). This genetic overlap is partially reflected in similar alterations in brain structure and function (Arnone et al., 2009; Goodkind et al., 2015; Hulshoff Pol et al., 2012; Magioncalda et al., 2020; McTeague et al., 2020; Potvin et al., 2019). However, disease-specific alterations in brain structure and function have also been reported. For example, in a twin study genetic liability to schizophrenia was associated with thicker prefrontal cortex, whilst genetic liability for bipolar disorder was associated with larger intracranial volume (Hulshoff Pol et al., 2012). Furthermore, a brain network subserving time/cognitive control was found to be specifically altered in schizophrenia but not in bipolar disorder (Alustiza et al., 2017).

The study of functional and structural neuroimaging abnormalities in unaffected first-degree relatives of probands with schizophrenia or bipolar disorder may provide unique insights into potential shared and distinct neurobiological substrates underpinning both disorders without the interference of known confounders, such as medication use and illness duration. Likewise the identification of functional and structural neuroimaging alterations in individuals at clinical high-risk (CHR-P) for psychosis (Fusar-Poli et al., 2020) or bipolar disorder (CHR-B) (Faedda et al., 2019) may further unravel shared as well as specific mechanisms for these disorders. For example, gray matter reductions in the anterior cingulate have been reported as markers of genetic liability to psychosis, while reductions in the superior temporal gyrus and cerebellum may be interpreted as markers of a first onset of the illness (Fusar-Poli et al., 2014b).

Previous studies have compared structural as well as functional neuroimaging alterations between first-degree relatives of probands with bipolar disorder or schizophrenia (Arat et al., 2015; de Zwarte et al., 2019; Khadka et al., 2013). In addition, a previous meta-analysis found evidence that individuals with ultra high-risk for psychosis had increased gray matter volumes in bilateral median cingulate, the right fusiform gyrus, the left superior temporal gyrus, and the right thalamus as well as decreases in the right gyrus rectus, the right superior frontal gyrus, and the left superior frontal gyrus relative to healthy controls (Ding et al., 2019a). However, to our knowledge no previous study has attempted to synthesize evidence from structural and functional neuroimaging studies in first-degree relatives or individuals at CHR for either psychosis or bipolar disorder. Thus, we provide a systematic review and meta-analysis of voxel-based morphometry (VBM) and functional magnetic resonance (fMRI) studies of individuals with either genetic risk or CHR for psychosis or bipolar disorder.

2. Methods

2.1.Search Strategy, Eligibility Criteria, and Data Extraction

Systematic searches in the Pubmed/MEDLINE and PsycINFO databases from inception up until April 27th, 2020 were conducted. Search strings are provided in **Table S1** (Supplementary online material). This study followed a previously established protocol which is available upon reasonable request to the corresponding author. This search strategy was augmented through hand searching the reference lists of included articles. When studies reported on overlapping samples of participants, we included the larger sample if this provided data.

We included voxel-based morphometry (VBM) or functional magnetic resonance imaging (fMRI) studies that provided gray matter volumes or differences in activation patterns between individuals at either familial risk (i.e., first-degree relatives) or CHR of psychosis or

bipolar disorder and matched control participants. We excluded studies that used a region-of-interest approach (rather than a voxel-based analysis), studies that did not cover the whole brain, and studies that used spatially heterogeneous statistical thresholds such as small volume corrections. The reason to exclude these studies is that in them, a finding with the same t-value may be considered statistically significant and thus reported if it lays in brain regions that the authors of the study thought that were of interest, while it may be considered non-statistically significant and thus unreported if it lays in other brain regions. Including these studies would therefore bias the meta-analysis towards the regions that the authors of previous studies thought that were of interest. All age groups were included in the current systematic review and meta-analysis. We also excluded studies from which we could not extract the required information (**Table S2**, supplementary online material).

The studies could report findings at any level of statistical significance, and in case that a study reported findings with more than one level of statistical significance, we preferred the more liberal level because it provides more information. It is worthy to note that seed-based d mapping (SDM) only considers information of the peaks to recreate a map of effect sizes, but it does not make any assumption about the statistical significance of the peaks.

The screening, selection of eligible studies and data extraction were independently performed by two investigators of the team. Disagreements were resolved through consensus or through discussion with a third investigator. This systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) (checklist in the **Supplementary online material**).

2.2.Statistical Analysis

Data were pooled using Seed-based d Mapping (formerly Signed Differential Mapping) (Radua and Mataix-Cols, 2009; Radua et al., 2012) with Permutation of Subject Images (SDM-PSI)

(Albajes-Eizagirre et al., 2019b) using the default parameters. The software, first converts all coordinates to a common MNI space using the Lancaster matrix (taking into account the small changes in MNI space between SPM and FSL, and undoing the MNI conversions conducted with the old Brett method) (Lancaster et al., 2007). Second, it creates the maps of the lower and upper bounds of possible effect sizes for each study based on the level of statistical significance, the coordinates and effect sizes of the reported peaks, and the anisotropic covariance between adjacent voxels (Radua et al., 2014). Third, it finds the maximum likely effect size map based on the lower and upper bounds of possible effect sizes of all studies, and it imputes effect size maps (and the corresponding variance maps) for each study, adding normal spatially correlated noise to the map of maximum likely effect size within the bounds of possible effect sizes (Albajes-Eizagirre et al., 2018). Fourth, it combines the effect size maps of each imputation dataset using random-effects meta-analysis. Fifth, it combines the meta-analytic maps resulting from the different imputation datasets using Rubin's rules. Finally, it imputes subject images for each imputation of each study and permutes using the Freedman Lane algorithm (Winkler et al., 2014) to derive the family-wise error rate (FWER). We considered statistically significant after correction for multiple testing those voxels with FWER < 0.05, and statistically significant without formal correction for multiple testing those voxels with uncorrected $P < 0.001$, in clusters of at least 10 voxels.

To provide a more comprehensive summary of the findings, we also report the heterogeneity statistic I^2 (values > 50% are usually considered to indicate high heterogeneity) and conducted tests to evaluate potential reporting bias in the main findings. Specifically, we conducted a test to detect small-studies effects (SSE, i.e., small studies show larger effect sizes, potentially because small negative studies are not published) by means of a meta-regression by the standard errors (Albajes-Eizagirre et al., 2018) as implemented in SDM-PSI.

We conducted an overall analysis of all VBM studies, an overall analysis of all fMRI studies, and sub-analyses for samples with either familial or CHR for either psychosis or bipolar disorder. Finally, a multimodal meta-analysis was also conducted.

3. Results

A PRISMA flow diagram (Moher et al., 2009) of study selection is shown in Supplementary **Figure S1**. After removal of duplicates, 2006 unique references were screened. Two thousand, one hundred and fifty-two references were excluded after title/abstract screening. Of the 645 full-text articles assessed, 551 were excluded with reasons (see **Table S3**, supplementary online material).

We could include 41 independent VBM datasets, with a total of 2810 individuals at risk of psychosis (49.1% males, mean age 26.3 years) and 2036 controls (48.9% males, mean age 27.0 years) and 55 independent fMRI datasets, including a total of 1441 individuals at high risk of psychosis (52.1% males, mean age 29.3 years) and 1655 controls (52.5% males, mean age 28.1 years). See **Supplementary Tables S4 and S5** for details of the included studies.

Most studies included individuals at risk for schizophrenia (30/41 VBM, 43/55 fMRI), whereas the risk of bipolar disorder was little studied (9/41 VBM, 11/55 fMRI). Approximately, half studies investigated genetic risk (21/41 VBM, 32/55 fMRI) and half CHR (18/41 VBM, 21/55 fMRI). One fMRI study (Yaakub et al., 2013) mixed individuals with genetic and with CHR; we did not include this study in the sub-analyses for genetic risk or for CHR. Most of studies about CHR referred to clinical risk of psychosis (18/39 VBM, 22/44 fMRI), and all studies about the risk of bipolar disorder referred to genetic risk of bipolar disorder (9/9 VBM, 11/11 fMRI). Therefore, the sub-analyses for CHR may be interpreted as

clinical risk for psychosis, and the sub-analyses for risk of bipolar disorder may be interpreted as genetic risk for bipolar disorder.

3.1.Voxel-based morphometry

The analysis of all studies revealed a decrease of gray matter volume in right gyrus rectus and medial frontal gyrus (**Table 1** and **Supplementary Figure S2**). The effect size of the abnormality was small (Hedges' *g* = -0.19 and -0.17, respectively) and it did not reach statistical significance after FWER-correction for multiple comparison (uncorrected p = 0.0002, FWER > 0.05). We did not detect evidence of high heterogeneity or of small-study effects.

The sub-analysis of participants with genetic risk for schizophrenia revealed an abnormality in the right cerebellum (**Figure 1**) (Hedges' *g* = -0.24, uncorrected p = 0.0002, FWER > 0.05), and in which again we did not detect high heterogeneity or small-studies effects. This sub-analysis also revealed a decrease of gray matter in the left amygdala, with same effect size (Hedges' *g* = -0.24) that did not reach statistical significance after FWER-correction for multiple comparison (uncorrected p = 0.0001, FWER > 0.05), and in which we did not detect high heterogeneity or small-studies effects.

The sub-analysis of participants with CHR for psychosis revealed a decrease of gray matter in medial frontal gyrus (**Figure 2**), this time showing a larger effect size (Hedges' *g* = -0.28) but still not reaching statistical significance after FWER-correction for multiple comparisons (uncorrected p = 0.0003, FWER > 0.05). We did not observe evidence of high heterogeneity or small-study effects.

The sub-analyses of participants with either genetic risk or CHR for bipolar disorder did not reveal any result considering P < 0.001 and a cluster extent of 10 voxels.

3.2.Functional magnetic resonance imaging

The analysis of all studies revealed hypoactivation in the superior left superior frontal gyrus (Hedges' *g* = -0.19, uncorrected p = 0.0001, FWER > 0.05) (**Table 1** and **Supplementary Figure S3**).

The sub-analysis of participants at CHR for psychosis revealed hypoactivation in the right precuneus, superior frontal gyrus and right inferior frontal gyrus (**Figure 3**). The effect sizes were larger (Hedges' *g* = -0.40, -0.33 and -0.34) but it still did not reach statistical significance after FWER-correction for multiple comparisons (uncorrected p = 0.000007, p = 0.00002 and p = 0.0002, FWER > 0.05). We did not detect high heterogeneity or small-study effects.

The sub-analyses of patients with genetic risk of bipolar disorder or for psychosis did not reveal any result considering P < 0.001 and cluster extent of 10 voxels.

3.3.Multimodal meta-analyses

The multimodal meta-analyses for VBM and fMRI with all subjects and those with CHR of psychosis or genetic risk for psychosis or bipolar disorder did not reveal any result considering P < 0.001 and cluster extent of 10 voxels. However, using a more liberal statistical threshold (i.e., P < 0.05), we observed a decreased volume along with a hyperactivation in the left amygdala (MNI [-28,-2,-18]).

4. Discussion

This is the largest systematic review and meta-analysis conducted to date that included all VBM and fMRI studies performed in individuals at either genetic for schizophrenia or bipolar disorder or CHR for psychosis or bipolar disorder. It should be noted however from the outset

that fewer eligible studies including participants with bipolar disorder were available, and therefore most of the evidence provided by this study relates to schizophrenia spectrum disorders. Several previous meta-analyses have studied putative neuroimaging predictors of the transition to psychosis. However, several of those previous meta-analyses included region of interest (ROI) studies, which are prone to selection bias (Pearlson and Calhoun, 2007). In addition, a recent meta-analysis examined only VBM studies from participants at ultra-high risk for psychosis (which captures a specific construct but not the overall CHR for psychosis phenotypes), whereas fMRI studies were not included in that previous meta-analyses (Ding et al., 2019a). However, the previous meta-analysis has also included studies that have examined cortical thickness although the authors found no evidence that participants at ultra-high risk for psychosis had alterations in cortical thickness relative to controls. In addition, it should be noted that the current up-dated effort included substantially more studies than the previous meta-analysis.

We observed a decrease in a large gray matter (GM) cluster predominantly comprising the right gyrus rectus in the analysis comprising all individuals at-risk for either schizophrenia/psychosis or bipolar disorder. However, the effect size was small. This abnormality however was not observed in sub-analysis that excluded participants at either genetic or CHR for bipolar disorder. Frontal lobe dysfunction is related to affective symptoms and cognitive deficits in patients with schizophrenia (Kim et al., 2015). The gyrus rectus, which is an extension of the anterior cingulate onto the frontal cortex has been implicated in the psychopathology of schizophrenia (Kim et al., 2017). Interestingly, a small decrease in the medial frontal gyrus was observed in the sub-analysis that included individuals at CHR for psychosis.

Among participants at genetic risk for schizophrenia we observed a small decrease in grey matter volumes in the right cerebellum and the left amygdala. Of note, we predominantly

observed a volumetric decrease in the superior/anterior cerebellum (i.e., lobules IV, V and VI) which is more closely related to motor function. A recent meta-analysis of VBM studies found similar abnormalities in drug-naive patients with schizophrenia or first-episode psychosis (Ding et al., 2019b). In addition, several studies have indicated that a bilateral volumetric decrease in the amygdalae is observed in schizophrenia predominantly during early stages of illness, as suggested by a recent review on this topic (Ho et al., 2019). Therefore, the volumetric abnormalities herein detected in participants at familial risk for schizophrenia reflect abnormalities consistently reported in schizophrenia spectrum disorders.

Two additional findings deserve further discussion. First, hypoactivation in right precuneus was observed among participants at CHR for schizophrenia. A recent meta-analysis found a decrease in intrinsic brain activity in the precuneus bilaterally among people with schizophrenia during resting-state (Gong et al., 2020). Furthermore, hypoactivation in large clusters comprising the superior frontal gyrus and the right inferior frontal gyrus were observed in individuals at CHR for psychosis. Those regions are implicated in functional networks underpinning the expression of multiple symptomatic domains in psychotic disorders including the relative lack of empathy and deficiencies in theory of mind (Vucurovic et al., 2020) as well as self-related processing (Potvin et al., 2019) and even aggressive behaviors (Schoretsanitis et al., 2019).

4.1.Clinical and Research Implications

Accepting the uncorrected results at face, genetic and clinical liability, primarily for psychosis, appeared associated with small and circumscribed changes in grey matter volume and functional activation. These findings contradict prior primary studies and meta-analyses in high-risk individuals (vide supra). There are several possible explanations for this that involve both methodological and conceptual issues. With regards to methodology we note that we analyzed only studies that reported results from whole-brain analyses. Many prior studies

included region of interest (ROI) studies, which may distort the findings because of their spatial bias (Pearlson and Calhoun, 2007). In prior work, we have shown that at least in task-fMRI studies the likelihood of any brain region being consistently implicated in any disorder is low and significantly distorted by ROI analyses (Sprooten et al., 2017). The findings here are aligned with these observations and extend them to structural datasets. The underlying mechanism is undoubtedly linked to methodological variation. A recent paper by Botvinick-Nezer and colleagues provides resounding evidence for the influence of methodological variation on the results of task-fMRI datasets (Botvinik-Nezer et al., 2019). Future biological models of disease would have to account for these methodological issues. The regions identified here as functionally hypoactive in high-risk individuals are unlikely to hold special significance for the pathogenesis of psychosis and more likely to represent regions commonly reported in primary studies because they are frequently engaged by a variety of tasks or internal conditions. For example, the precuneus is one of the most metabolically active and functionally connected brain regions (Cavanna and Trimble, 2006; Margulies et al., 2009) and is one of the most reliably identified rich club hubs (van den Heuvel and Sporns, 2011).

Structural datasets are considered more robust to methodological variation in the primary studies. Yet there is considerable variability in the definitions of the brain "regions" and their correspondence to cytoarchitectural fields. This has been amply demonstrated by Uylings and colleagues (Uylings et al., 2010), specifically in connection to the orbitofrontal regions, which is of direct relevance to this study. With regards to the gyrus rectus, there is little evidence for a specific contribution to cognition in health or disease. This brain region is functionally connected to the rest of the orbitofrontal cortex while its posterior segment is functionally connected to the ventral anterior cingulate. Inspection of data available through Neurosynth provides support for the notion that activation within the rectus gyrus occurs within the wider context of orbitofrontal engagement. As regions within this part of the brain are

involved in multiple tasks relating to affect integration and inhibitory control they are likely to be involved in the expression of multiple types of psychopathology. Therefore, this may provide a rationale to recent attempts to develop transdiagnostic risk calculators to predict the onset of psychosis among individuals at CHR albeit with limited success (Fusar-Poli et al., 2019a; Fusar-Poli et al., 2019b).

4.2.Limitations

Our findings should be interpreted within the context of some limitations. First, individuals at CHR for psychosis are known to have psychiatric comorbidities (e.g. mood and anxiety disorders) (Fusar-Poli et al., 2014a), which might have influenced some of our findings. Second, we only considered peak values in the SDM meta-analysis which may omit subtle changes from single studies that may reach statistical significance with the inclusion of larger samples. Third, neuroimaging abnormalities had a small effect size. In general, effect sizes should not depend on sample size. We cannot discard that within SDM-PSI, effect sizes are slightly biased towards zero when few studies are included, although previous simulation work with the maximum likelihood / multiple imputation algorithms used in MetaNSUE/ SDM-PSI has shown that this bias is nearly negligible (Albajes-Eizagirre et al., 2019a). Fourth, although our findings were significant considering a conservative threshold for statistical significance (i.e., $P < 10^{-3}$), they were no longer statistically significant after correction for multiple comparisons. Fifth, included studies had methodological differences. However, we found no evidence of high heterogeneity in our analysis. Sixth, most eligible studies included samples at CHR-P, whilst very few studies on either genetic or clinical high risk for bipolar disorder were available for this meta-analysis. Seventh, due to the relatively small number of studies available we decided a priori to pool different fMRI studies regardless of the underlying task. This methodological shortcoming of the current meta-analysis could have influenced our neuro-functional findings despite the fact that heterogeneity was low. Seventh, none of the findings

pertained to VBM studies in the current study has survived statistical adjustment for multiple comparisons, and hence findings should be cautiously interpreted and viewed as tentative. Finally, all studies included in the current meta-analysis have adjusted their findings to whole-brain volume, and hence the current meta-analysis could not rule out the possibility that a global brain volume reduction could be evidenced in individuals at genetic or CHR for psychosis.

4.3.Conclusion

The current systematic review and meta-analysis observed that individuals with either genetic high-risk or CHR for psychosis display subtle structural neuroimaging findings. Those findings suggest that both affective as well as non-affective psychosis may share common neurobiological mechanisms although further studies investigating individuals at either genetic high risk or CHR for bipolar disorder are clearly warranted. However, none of the findings herein reported survived statistical adjustment for multiple comparisons and therefore should be considered tentative. Furthermore, the design of prospective studies are an unmet need in this field and are necessary to confirm/refute the finding of our study. Lastly, other methods for studying structural brain findings (e.g., gyrification and cortical thickness) could provide additional insights for this emerging field.

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Table 1

Decreases of gray matter volume and functional activation detected in the meta-analyses of voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) studies in individuals at risk of psychosis.

	Peak							Cluster
Brain region	MNI	*g*	Z	*P*	I^2	SSE *P*	Voxels	Breakdown
VBM - All individuals at risk of schizophrenia/psychosis or bipolar disorder								
Gyrus rectus	6, 52, -18	-0.19	-3.6	0.0002	19%	n.s.	17	R gyrus rectus (9), BA 11
Medial frontal gyrus	-10, 34, -12	-0.17	-3.6	0.0002	18%	n.s.	13	Medial orbital frontal gyrus (8), BA 11
VBM - Only individuals at genetic risk of schizophrenia								
R cerebellum	14, -58, -22	-0.24	-3.6	0.0002	11%	n.s.	86	R cerebellum, lobule IV / V (48), mostly BA 37 R cerebellum, lobule VI (19), BA 18 and 19
L amygdala	-20, -2, -16	-0.24	-3.7	0.0001	12%	n.s.	59	L amygdala (42), BA 34 and 28 L superior temporal gyrus (8), BA 34
VBM - Only individuals with clinical high-risk of psychosis								
Medial frontal gyrus	-10, 34, -12	-0.28	-3.4	0.0003	11%	n.s.	11	Medial orbital frontal gyrus (9), BA 11
fMRI - All individuals at risk of schizophrenia/psychosis or bipolar disorder								
Frontal superior gyrus	-4,28,54	-0.19	-3.7	0.0001	8%	n.s.	32	L frontal superior gyrus (26), BA 8 L supplementary motor area (6), BA 8
fMRI - Only individuals with clinical high-risk of psychosis								
R precuneus	14, -80, 30	-0.4	-4.3	0.000007	10%	n.s.	114	R cuneus (32), mostly BA 7 R precuneus (17), BA 7
Superior frontal gyrus	0, 32, 26	-0.33	-3.9	0.00005	2%	n.s.	102	B anterior cingulate córtex (82), BA 24 and 32 L superior frontal gyrus (20), BA 9 and 32
	0, 32, 46	-0.33	-3.3	0.0004	27%	n.s.	16	L superior frontal gyrus (14), BA 8
R inferior frontal gyrus	50, 26, 30	-0.34	-4.1	0.00002	1%	n.s.	34	R inferior frontal gyrus (95), BA 44 and 45 R middle frontal gyrus (15), mostly BA 44 and 45
fMRI – Genetic risk for schizophrenia								
No significant difference relative to controls								
VBM, fMRI – Genetic risk for bipolar disorder								
No significant difference relative controls								

Threshold: uncorrected p-value < 0.001 with 10 voxel cluster extent. BA: Brodmann area, ESB: excess significance bias, L: left, R: right, MNI: Montreal Neurological Institute, n.s.: non-statistically significant, SSE: small-studies effects.

FIGURE LEGENDS

Figure 1. Sub-analysis of patients with risk of schizophrenia vs healthy controls showing decrease in gray matter volume in right cerebellum (Hedges' g = -0.24, uncorrected p = 0.0002, FWER > 0.05) and left amygdala (Hedges' g = -0.24, uncorrected p = 0.0001, FWER > 0.05).

Figure 2. Sub-analysis of patients with clinical risk vs healthy controls showing decrease in gray matter volume in medial frontal gyrus (Hedges' g = -0.28, p = 0.0003, FWER > 0.05).

Figure 3. Sub-analysis of patients with clinical risk of psychosis vs healthy controls showing hypoactivation in right precuneus, superior frontal gyrus and right inferior frontal gyrus (Hedges' *g* = -0.40, -0.33 and -0.34, uncorrected p = 0.000007, p = 0.00002 and p = 0.0002, FWER > 0.05).