Systematic Review and Multi-Modal Meta-Analysis of Magnetic Resonance Imaging Findings in 22q11.2 Deletion Syndrome: is more evidence needed?

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Abstract:

22q11.2 deletion syndrome (DS) is considered to be the most robust genetic model of psychosis. In the last decade, there has been increased interest in the brain abnormalities associated with these genetic changes. Most imaging findings in this population come from small samples. This increases the risk of reporting spurious effects that reflect the **idiosyncrasies** of each study. Thus, the current work is aimed at identifying whether there are spatially consistent structural and functional brain abnormalities in individuals with 22q11.2 DS through (i) a comprehensive label-based systematic review and (ii) a coordinate-based meta-analysis of magnetic resonance imaging studies. The systematic review identified the frontal middle gyri, posterior cingulum, right cuneus and bilateral precuneus as the most affected regions. The meta-analysis revealed consistent abnormalities in the bilateral inferior parietal lobe, right precuneus, right superior temporal gyrus and posterior cingulate cortex. This study provides an important starting point for future research as it sheds light on possible genetically determined psychosis susceptibility regions.

Keywords: 22q11.2 deletion syndrome, fMRI, structural MRI, DTI, genetic model, meta-analysis, systematic review

1. Introduction

In an effort to elucidate underlying vulnerability mechanisms, research in the last 15 years has increasingly focused on identifying genetic models of susceptibility to psychosis. Several genetic models have been proposed (DeLisi et al. 2005; Van et al. 2017), however, the 22q11.2 Deletion Syndrome (22q11.2 DS) is considered, by far, the most robust (Van et al. 2017).

The 22q11.2 is the most common microdeletion in humans, affecting 1 in 3000 to 1 in 6000 live births (Kobrynski and Sullivan 2007). About 90-95% of individuals with this deletion have a hemizygous deletion of 3 million base pairs of DNA in the long arm (q) of chromosome 22. This is inherited in an autosomal dominant manner and causes haploinsufficiency in around 40 genes in the 22q11.2 subregion (McDonald-McGinn et al. 2015; Karayiorgou, Simon, and Gogos 2010). **Crucially, a recent genome-wide association study conducted on 41321 participants identified the deletion of the 22q11.2 gene as one of the main psychosis susceptibility candidates (Marshall et al. 2017). To further support the importance of 22q11.2 as a genetic model for psychosis, micro-duplications of 22q11.2 appear to confer protection from the illness (Marshall et al. 2017; Rees et al. 2014).**

The term 22q11.2 DS refers to more than one syndrome. The different syndromes are phenotypically heterogeneous but share the presence of the chromosomic deletion (Kobrynski and Sullivan 2007). The term 22q11.2 DS is then used when referring to individuals who have the deletion, while any other syndrome nomenclature (e.g. DiGeorge Syndrome, velocardiofacial syndrome or, in some cases, the CHARGE syndrome) is used when the diagnosis relies solely on clinical features (Kobrynski and Sullivan 2007). Despite some differences in the clinical presentation, the most commonly observed features are cardiac abnormalities, mild to moderate immune-deficiency, facial dysmorphia and palatal dysfunction (Kobrynski and Sullivan 2007).

Individuals with 22q11.2 DS usually present with mild to severe developmental delay, which mainly affects linguistic abilities such as reading and writing (Gur et al. 2014). They often present with learning disabilities and cognitive deficits, affecting both verbal and non-verbal skills (Shapiro

et al. 2014). Individuals with 22q11.2 DS are also likely to develop psychosis and other psychiatric conditions such as autistic spectrum disorders (Richards et al. 2015), attention deficit with hyperactivity disorder (Tang et al. 2015), anxiety (Swillen and McDonald-Mcginn 2015) and mood disorders (Schneider et al. 2014). The prevalence of psychotic disorders in the general population is around 1%; however up to 40% of 22q11.2 DS individuals develop psychosis (Schneider et al. 2014; Van et al. 2017). This makes them the largest clinical population at genetic high-risk for psychosis.

An increased interest in the neuroanatomical and functional abnormalities associated with 22q11.2 DS genetics has risen in the last decade. By investigating the neuroanatomical basis of 22q11.2 DS, researchers hope to deepen the knowledge of the neural basis of psychosis that might be genetically determined and to ultimately identify possible predictive biomarkers of psychosis onset. Magnetic resonance imaging (MRI) has been providing useful data on structural and functional alterations associated with the syndrome (Bohm et al. 2017). For example, a meta-analysis of structural MRI (sMRI) studies showed that 22q11.2 DS was associated with a reduction in hippocampal, cerebellar and global brain volume and an increase in the volume of the corpus callosum (Tan et al. 2009). However, this work included a mixture of whole brain and region of interest (ROI) studies. This limits the conclusions that can be drawn from the analyses as the results are driven in part by an a-priori selection of brain regions.

Since the publication of this meta-analysis (Tan et al., 2009), more studies have been published that employed a whole-brain as opposed to an ROI approach (Schmitt et al. 2015; O'Hanlon et al. 2016; Gothelf et al. 2011; Sundram et al. 2010; Shashi et al. 2010), however results are still inconclusive partially because most studies analysed relatively small samples due to the low prevalence of the deletion. The main limitation of small studies is that the interpretation of their results is limited, there is a higher risk of producing false-positive results and they can over-estimate the magnitude of an association (Button et al. 2013). The exception is a recent large-scale multi-site study published as part of the ENIGMA-Schizophrenia Working Group (Sun et al. 2018).

Sun and colleagues (2018) identified the presence of thicker cortical gray matter volume overall, with focal reductions in the temporal and cingulate cortex in patients with 22q11.2 DS compared to healthy controls (Sun et al. 2018). Importantly, this study also compared 22q11.2 DS individuals with and without psychosis and reported significantly thinner cortex in several regions including the frontal, temporal and occipital cortices in patients with psychosis compared to those without. While these studies provided key information on the brain structure differences in 22q11.2 DS individuals, it is also crucial to examine differences in brain function in order to reach a more comprehensive understanding of neural abnormalities associated with the syndrome.

Several studies have investigated brain function in 22q11.2 DS individuals and reported abnormalities in several brain regions (Eliez et al. 2001; Gothelf, Hoeft, et al. 2007; Debbané et al. 2012; Mattiaccio et al. 2016; Schneider et al. 2012; Montojo, Congdon, et al. 2015). The inconsistencies observed across these studies may be due to the use of different tasks used to elicit brain activation or the use of resting state functional MRI (fMRI). To date, it is therefore unclear whether, regardless of the task or the imaging modality used, there are consistent and robust functional brain abnormalities associated with the 22q11.2 DS and how these relate to increased vulnerability to psychosis.

The aim of this work was therefore twofold. The first aim was to provide a comprehensive label-based review of the available literature. This will enhance our understanding of brain structural and functional abnormalities in 22q11.2 DS compared to healthy controls and clarify whether any of the abnormalities are consistently reported. The second aim was to perform a coordinate-based meta-analysis to investigate if there are statistically consistent structural and functional brain abnormalities in 22q11.2 DS.

2. Materials and methods

2.1. Studies selection

The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO - Registration Number: CRD42017075630). An in-depth search was conducted on 7 databases (PubMed, ETHOS, Kings Open Portal, EMBASE, MEDLINE, PsycINFO and CINHAL) up to December 2018. The following terms were used: “velocardiofacial syndrome” OR “22q11.2 deletion” OR “diGeorge” AND “MRI” OR “functional” OR “structural” OR “DTI” AND “psych*” NOT “Otorhi*” AND/OR “cardi*”. All imaging studies on 22q11.2 deletion were included, regardless of the clinical syndrome. We also searched for studies in review articles and performed a reference tracing.

Studies meeting the following inclusion criteria were included in the systematic review: i) studies using structural (sMRI), functional (fMRI) or diffusion tensor imaging (DTI); ii) studies reporting results from a whole brain analysis (i.e. studies performing region of interest (ROI) analyses only were excluded); iii) original peer-reviewed studies and those reporting novel data; iv) studies including a healthy control (HC) group or investigating neural differences between 22q11.2 DS individuals with and without psychotic symptoms and v) studies with a sample size >= 5 (per group). Additional inclusion criteria for the meta-analysis were the following: i) studies reporting results from a contrast representing locations of greater activation/deactivation, increase/decrease functional connectivity, increased/decreased grey matter (GMV) or white matter (WMV) volume between 22q11.2 DS individuals and HC; ii) studies reporting results in a standardised coordinate space (e.g. Talairach (Talairach and Tournoux 1988), or Montreal Neurologic Institute (MNI)).

The literature screening and final selection was performed according with the PRISMA guidelines (Moher et al. 2009). The PRISMA checklist is available in Supplementary Materials A.

2.2. Label-Based Systematic review

Two authors (GML and CS) extracted and screened the data independently. The opinion of a third author (ST) was sought in case of discordance. Characteristics such as the sample size, gender, age, IQ, details of the psychological/psychiatric tests participants underwent and their average

scores and details of every MRI comparison performed (i.e. coordinates, coordinate system, statistics values, regions and results) were recorded.

To facilitate comparisons between studies that used different brain atlases and labels, every region was transformed into AAL atlas classification areas. This was performed by using the coordinates provided by the studies and, if these were not available, by extracting the information from the figures or supplementary material. The AAL atlas divides the cerebellum into 26 regions. In order to simplify the interpretation of the data, these regions were condensed into the left and right cerebellar hemispheres. In addition, the corpus callosum was added to the list although it is not included in the AAL atlas, as several studies examined this structure.

Finally, we used the Newcastle-Ottawa Scale (Wells et al. 2013) to assess the quality and comparability of each included study.

2.3. Coordinate-Based Multi-modal meta-analysis

For a quantitative assessment of inter-study concordance, the Activation Likelihood Estimation (ALE) methods (Eickhoff et al. 2009; Laird et al. 2005; Turkeltaub et al. 2002) were applied to both sMRI and fMRI data, as in previous works (Tahmasian et al. 2016; Tahmasian et al. 2018). This approach aims to: i) increase the power to detect even small effects; ii) increase the robustness of the findings; and iii) provide superior evidence for the generalization of the findings across different MRI modalities and experimental conditions. This approach reveals converging findings and identifies important network nodes via different neuroimaging modalities.

The coordinate-based meta-analysis guidelines (Müller et al. 2018) were followed (the checklist for neuroimaging meta-analysis is available in Supplementary Materials B). The peaks of activation/deactivation, increased/decreased connectivity or of increased/decreased grey matter volume (GMV) were used to generate an ALE map, using the revised ALE algorithm (Turkeltaub et al. 2012) running under Ginger ALE software (http://brainmap.org/ale/) version 2.3.6. This approach aims to identify areas with a convergence of reported coordinates across experiments that

is higher than that expected from a random distribution of foci. Briefly, this algorithm treats activated foci of brain regions as three-dimensional Gaussian probability distributions centered at the given coordinates (Eickhoff et al. 2009; Laird et al. 2005). The algorithm calculates the size of the probability distributions by considering the sample size of each study and uses random-effect inference. It does so by testing the above chance clustering between contrasts rather than the above-chance clustering between foci. If a study reports both activation and deactivations (or increased and decreased GMV) in 22q11.2 DS compared with HC, the increases and decreases are pooled together (i.e. they are considered as a single study) (Turkeltaub et al. 2012). This procedure was applied in order to adjust for multiple contrasts from the same sample (Müller et al. 2018). Tailarach coordinates were first transformed to MNI space using a linear transformation (Laird et al. 2010; Lancaster et al. 2007). Then, statistical tests were performed to identify the regions where the likelihood of activation in a particular set of experiments is higher than that expected by chance, i.e., where there is a non-random convergence. The resulting statistical parametric maps were thresholded using cluster level family-wise error (FWE) correction at $p<0.05$ (cluster-forming threshold at voxel-level $p<0.001$, (Eickhoff et al. 2016). The corresponding brain regions were identified using the SPM Anatomy toolbox (version 1.5, (Eickhoff et al. 2006; Eickhoff et al. 2007; Eickhoff et al. 2005). For further details on the ALE method please refer to previous publications (Eickhoff et al. 2012; Eickhoff et al. 2009; Turkeltaub et al. 2012).

3. Results

3.1. Search results and screening process

Five hundred and five studies were identified. After removing 195 duplicates, 310 abstracts were screened. 121 articles were excluded after the first screening because: articles were on other conditions; they were not original studies; the full text was not retrievable; they had a clinical sample <5 or they were investigating animal models. A further 111 were excluded following a comprehensive assessment of the remaining 189 articles as they did not meet our inclusion criteria.

This left a total of 78 original articles eligible to be included in the systematic review. Of these, 24 studies were also eligible for the meta-analysis. This procedure is summarised in Figure 1. The full databases are available as supplementary materials (C1 and C2).

**********Please add Figure 1 here**********

3.2. Systematic Review

3.2.1. Characteristics of included studies

Seventy-eight original articles were included in the systematic review (see supplementary material C and D). Together, these studies reported 487 statistically significant foci (with "study/studies" referring to original article/s, "focus/foci" referring to any peak/s of statistical significance reported within the article/s). The risk of bias assessment found an overall low risk of bias (see supplementary material E).

The number of 22q11.2 DS individuals per study ranged from 8 to 474, for a total of 3238 22q11.2 DS individuals included. The mean age was 16.5 years (range = 5.4–52 years) and 1606 individuals (49.6%) were female (two studies, (Barnea-Goraly et al. 2003; Kates, Antshel, et al. 2011) did not provide details on gender). It is important to note that the included studies did not always analyse independent samples, thus the data included in the systematic review might in part suffer from non-independency.

**********Please add Figure 2 here**********

3.2.2. Summary of Label-Based Systematic Review Findings

In order to provide a qualitative summary of the results of the label-based systematic review, sMRI and fMRI data were pooled together and graphically represented in Figure 2 (DTI studies were not included in Figure 2 as results are not reported using coordinates or AAL areas). Figure 2 summarises the frequency of the significant results in each AAL region.

According to the included studies, the brain regions most frequently reported as statistically different between 22q11.2 DS individuals and controls are the bilateral middle frontal gyrus (38 foci), the bilateral precuneus (31 foci), the posterior cingulate cortex (30 foci) and the right cuneus (17 foci). Results are briefly described in the following paragraphs while a comprehensive description and an additional graphical representation are available in supplementary material F.

3.2.2.1. Structural MRI

Forty-seven studies, with a total of 2108 subjects, reported structural abnormalities in 22q11.2 DS individuals compared with HC. Among the included studies, 38 performed a cross-sectional comparison, 3 performed a longitudinal comparison and 6 performed both. The follow-up time in the longitudinal studies ranged between 40-144 months. Fifteen studies (31.9%) reported a measure of psychotic symptoms in a total of 1005 participants, of which 206 (20.49%) experienced psychotic symptoms.

According to the included literature, the most frequently affected region is the frontal lobe (82 foci), in particular the bilateral middle frontal gyrus (23 foci). Other brain lobes are affected in a similar number of foci: 48, 46 and 39 foci are reported in the occipital, parietal and temporal lobes, respectively. Within these lobes, the regions that are most frequently reported are the bilateral cuneus (18 foci), the bilateral posterior cingulated cortex (18 foci) and the right superior temporal gyrus (11 foci). Furthermore, 44 foci are reported in subcortical structures and 17 in the cerebellum.

3.2.2.2. Functional MRI

Twenty-five studies, with a total of 706 subjects, reported functional abnormalities in 22q11.2 DS individuals compared with HC. All of the 25 studies performed cross-sectional comparisons. Fifteen studies (60%) provided a measure of psychiatric symptoms in a total of 517 22q11.2 DS individuals, of which 68 (13.15%) experienced psychotic symptoms.

According to the included literature, the parietal and frontal lobes are similarly affected (69 and 67 foci, respectively). Alterations are quite homogeneously distributed within the frontal lobe, with a peak of 8 foci in the left middle frontal gyrus. Conversely, alterations in the parietal lobe are more localised to the left parietal inferior lobe (11 foci) and in the precuneus, bilaterally (21 foci). The occipital (33 foci) and temporal (20 foci) lobes are less affected. Furthermore, 10 foci are reported in subcortical structures and 5 in the cerebellum.

3.2.2.3. DTI

Twelve studies, with a total of 418 subjects, reported white matter abnormalities in 22q11.2 DS individuals compared with HC. These studies reported differences in fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), structural connectivity (SC), closeness centrality (CC), mean tract length, short- and long-range connectivity and total number of fibres. Overall, 188 22q11.2 DS individuals were clinically assessed in 5 studies; 29 of them (15.42%) experienced psychotic symptoms. All studies performed cross-sectional comparisons.

Six studies found decreased FA, 3 studies a decreased RD, 3 studies a decreased AD and one study a decreased SC in 22q11.2 DS individuals compared to HC. One study found a decreased SC between the anterior and the posterior medial regions of the DMN and between the anterior node of the DMN and the left inferior parietal lobule (Padula et al. 2015). Mean tract length and short- and long-range connectivity were found to be both increased and decreased in several areas by one study (Padula et al. 2017b). Ottet and colleagues (2013) investigated the total number of fibres in 22q11.2 DS individuals compared to HC using the human connectome technique, and found decreases in limbic areas as well as increases in the fronto-parietal and parieto-occipital structural connectivity (Ottet et al. 2013).

3.3. Coordinate-based Multi Modal Meta-analysis

3.3.1. Characteristics of included studies

Twenty-four sMRI (n=7) and fMRI (n=17) studies met the inclusion criteria for the coordinate-based meta-analysis. A study by Schreiner and colleagues (2017) reported data on two independent samples: a sample from UCLA and one from Syracuse. A second study also reported data from two independent samples: a sample of 22q11.2 DS individuals with psychosis and one without (van Amelsvoort et al., 2004). These samples were entered in the meta-analysis as independent groups. Thus, the meta-analysis comprises a total of 26 comparisons, and 283 foci of activation. If two studies investigated the same sample and used the same imaging technique to investigate the same cognitive process, only one of them was included (Montojo, Congdon, et al. 2015; Montojo, Jalbrzikowski, et al. 2015).

The demographic and clinical features of the samples investigated in the included studies are reported in Table 1. In brief, the coordinate-based meta-analysis comprises 533 individuals with 22q11.2 DS and 564 healthy controls. Age ranged between 9.8±1.4 and 34±11 years for participants with 22q11.2 DS and between 10.4±1.9 and 37±11 for healthy controls. Mental health status was assessed in most studies. Among the included studies, the highest reported prevalence of psychosis was 37.5%, with the exception of one study which reported 78% prevalence of subclinical symptoms of psychosis.

**********Please add Table 1 here **********

3.3.2. Convergence of findings

The ALE meta-analysis revealed consistent abnormalities in 22q11.2 DS individuals compared with HC in three clusters located in the posterior part of the brain. In particular, two significant clusters were found in the inferior parietal lobe (IPL). In the right hemisphere, the convergent findings (a cluster of 1624 voxels) are mainly located in the IPL (MNI coordinates: 46, -56, 46) and extend to the right superior temporal gyrus (50 -58 34). In the left hemisphere, the convergent

findings (a cluster of 904 voxels) are located in the IPL (-44, -52, 48, and -42, -50, 38, and -50 -50 50). An additional cluster of significant results (1480 voxels) is located in the right posterior cingulate cortex (PCC) (6, -50, 16) and right precuneus (18, -52, 20). Results are displayed in Figure 3.

**********Please add Figure 3 here**********

Critically, all but two foci contributing to the cluster in the right IPL, PCC and precuneus come from independent samples. A focus from Schreiner et al. (2017) and one from Mattiaccio et al. (2016) included partially overlapping samples. All foci contributing to the cluster in the left IPL come from independent samples.

In order to test whether the partially overlapping samples (Mattiaccio et al. 2016; Schreiner et al. 2017) could have significantly influenced the results, the meta-analysis was repeated removing one of the two studies (Mattiaccio et al. 2016). A new meta-analysis involving 23 (25 comparisons) studies and 251 foci was conducted. This second meta-analysis was not planned *a priori* but was performed post-hoc based on the results of the first one. After removing one study, the results of the meta-analysis did not substantially change: the first cluster (i.e. right IPL) included 1256 voxels, while the second cluster (i.e. encompassing PCC and precuneus) included 1450 voxels.

Furthermore, in order to evaluate the impact of combining structural and functional modalities on the results, we ran an additional meta-analysis limited to fMRI studies (this was not planned a priori). This second meta-analysis included 18 studies and 225 foci of activation. The results of the second meta-analysis were comparable with the main analysis. Specifically, the analysis identified the following foci: one located in the IPL (46, -56, 46 and -44, -52, 48), one located in the superior temporal gyrus (50 -58 34), one located in the posterior cingulated cortex (6, -50, 16) and one in the precuneus (18, -52, 20). Only 7 sMRI studies (8 comparisons) were available, therefore we did not run a separate meta-analysis on sMRI data only, as the minimum number of studies needed in an ALE meta-analysis (i.e. 17) was not reached (Eickhoff et al. 2016).

4. Discussion

Through a label-based systematic review and a coordinate-based meta-analysis, this study aimed to identify the brain abnormalities most commonly associated with 22q11.2 DS. To the best of our knowledge, this is the first systematic review and multi-modal meta-analysis of whole-brain sMRI, fMRI and DTI findings in 22q11.2 DS individuals.

A number of regional differences were identified between 22q11.2 DS individuals and HC. Specifically, the results of the label-based systematic review highlighted that, compared to HC, 22q11.2 DS individuals present with structural and functional abnormalities which are mainly located within the middle frontal gyri, the posterior cingulum (PCC), the right cuneus and the bilateral precuneus. These results were also partially confirmed by the coordinate-based meta-analysis, which identified the bilateral inferior parietal lobe (IPL), the right STG, the precuneus and the PCC as areas consistently altered in 22q11.2 DS individuals.

The results of the current meta-analysis are in line with some of the findings of a recent large-scale study of cortical alterations in 22q11.2 DS (Sun et al. 2018). Consistent with Sun and colleagues, the present meta-analysis revealed that brain abnormalities were mostly located in posterior brain regions. This finding is also in line with imaging findings in 22q11.2 DS mouse model (Ellegood et al. 2014a, 2014b; Sun et al. 2018). Sun and colleagues (2018) also reported that the size of the deletion was associated with more prominent abnormalities in the parietal cortex, where the present meta-analysis identified the largest cluster.

22q11.2 DS is known to confer increased vulnerability to psychosis. Thus, it is particularly important to understand whether the profile of brain abnormalities detected by the current coordinate-based meta-analysis is similar to the one characterizing psychosis according to previous literature. This would allow the identification of neural bases of psychosis that may be genetically determined. Since the current paper did not meta-analyze literature on

psychosis and did not directly compare brain alterations between 22q11.2 and psychosis, the following paragraph is purely descriptive.

Interestingly, the brain regions identified in this meta-analysis have also been found to be altered in people with established psychosis and in those at clinical high risk of developing psychosis (Bartholomeusz et al. 2017). In particular, recent studies investigating samples at clinical high risk for psychosis indicate that compared to HC, they present abnormalities in several brain regions including the inferior parietal lobe (Broome et al. 2010a, 2010b; Niendam et al. 2014; Dutt et al. 2015), the precuneus (Fusar-Poli et al. 2011; Wang et al. 2016; Clark et al. 2017; Broome et al. 2010a), the PCC (Benetti et al. 2013; Wang et al. 2016; Clark et al. 2017); the right superior temporal gyrus (Pantelis et al. 2003; Witthaus et al. 2009; Benetti et al. 2013; Fusar-Poli et al. 2011; Fusar-Poli et al. 2014; Dutt et al. 2015; Chang et al. 2016); the middle frontal gyrus (Fusar-Poli et al. 2011; Chang et al. 2016) and the cuneus (Seiferth et al. 2008). Moreover, clinical high risk individuals show a progressive alteration of brain structure and/or function when they go on to develop a first episode of psychosis. This progressive alteration seems to affect several brain regions including the PCC (Pantelis et al. 2003; Witthaus et al. 2009; Smieskova et al. 2010); the right superior temporal gyrus (Borgwardt et al. 2007; Chang et al. 2016); the precuneus (Cropley et al. 2016) and the middle frontal gyrus (Chang et al. 2016; Cropley et al. 2016). The abnormalities in the PCC, the IPL, the STG and the precuneus identified by both our systematic review and meta-analysis and reported as abnormal in clinical high risk individuals, including those later developing psychosis (Bartholomeusz et al. 2017), may be indicative of an increased genetic vulnerability to psychosis. On the other hand, previous meta-analyses of imaging findings in individuals at clinical high risk for psychosis have consistently reported the STG and precuneus but not the IPL or PCC (Fusar-Poli et al. 2011; Fusar-Poli et al. 2014; Fusar-Poli et al. 2012). This indicates that these two populations (clinical high risk and 22q11.2 DS) may share some but not all of the underlying alterations involved in increased vulnerability to psychosis. This only partial overlap between the neural basis of 22q11.2 DS individuals and clinical high risk individuals is likely to be due to the

inclusion, **in both samples, of individuals who will not develop psychosis.** However, these results are important as they highlight the brain regions that have a higher spatial convergence than expected from a random spatial association in 22q11.2 DS individuals. This might provide a falsifiable hypothesis, **that should be tested in future studies**, on the brain regions that are more likely to be associated with an increased genetic vulnerability to psychosis.

Importantly, all of the brain regions identified by the coordinate-based meta-analysis as consistently affected in 22q11.2 DS (i.e. PCC, precuneus, bilateral IPL) are located in the posterior part of the DMN. Critically, although the DMN has repeatedly been found to be altered in psychosis (Clark et al. 2017; Peeters et al. 2015; Wotruba et al. 2014), the posterior DMN has been identified as a possible genetically determined endophenotype of psychosis, an alteration that is present both in affective and non-affective psychosis (Khadka et al. 2013). The current results thus provide independent support for the genetic underpinning of the posterior DMN alteration. Previous research highlighted that alterations within the posterior DMN could predict psychosis risk as it has been observed in individuals with 22q11.2 DS (Schreiner et al. 2017), individuals at clinical high risk for psychosis (Heinze et al. 2015), and in siblings of patients with schizophrenia (van Buuren, Vink, and Kahn 2012; Jukuri et al. 2013). Taken together with our findings, this suggests that posterior DMN alterations are likely to be associated with an increased risk for psychosis. This is also in line with research investigating the functional meaning of the DMN, which found that intact DMN functioning facilitates cognitive performance, whereas decreased DMN functioning hinders cognitive performance. For instance, decreased connectivity within the DMN has been shown to underlie deficits in attention control and externally directed cognitive processes (i.e. working memory) (Sheline et al. 2009). These neuro-cognitive deficits are known to be highly prevalent in both 22q11.2 DS individuals (Larsen et al. 2018) and in idiopathic psychosis (Hochberger et al. 2018).

As we could not compare 22q11.2 DS individuals with and without psychosis, we are still unable to clarify which of these brain regions represent a marker of psychosis onset as opposed to a sign of

an increased vulnerability to psychosis. This topic has been carefully examined in Sun et al. (Sun et al. 2018) where the authors observed that 22q11.2 DS individuals with psychosis had significantly lower IQ than those without. Critically, the current work highlighted that besides the work of Sun et al. (Sun et al. 2018), only 2 imaging studies so far have directly investigated the differences in brain structure and function in 22q11.2 DS individuals with and without psychosis (van Amelsvoort et al. 2004; Dufour et al. 2008). Furthermore, only 9 studies adopted a longitudinal design to investigate whether and how brain structural and functional abnormalities change over time in 22q11.2 adults with and without psychosis (Gothelf et al. 2011; Schaer et al. 2009; Kates, Antshel, et al. 2011; Kates, Bansal, et al. 2011; Flahault et al. 2012; Kunwar et al. 2012; Sandini et al. 2018; Gothelf, Penniman, et al. 2007; Berhanu et al. 2017). This is surprising, since 22q11.2 DS is considered the most robust genetic model of vulnerability to psychosis. This might be due to the fact that this is a rare genetic syndrome and stratifying the sample according to the presence of psychotic symptoms would require a high number of subjects, which may be difficult to achieve for any single-centre research study. Another possible explanation is that the mean age of the sample may have been too low for psychotic symptoms to have already manifested (i.e. the mean age of the sample included is 16.53 years SD =5.63), making the comparison between individuals with and without psychosis unfeasible. Indeed, the diagnosis of 22q11.2 DS is usually possible around the age of 10 (Van et al., 2017) whereas neuropsychiatric disorders can only be diagnosed later in life. Thus, further studies are needed to provide independent support for the main results from the ENIGMA-Schizophrenia Working Group (Sun et al. 2018). In particular, it would be important to study longitudinal brain changes in individuals with and without psychosis. This would allow a better understanding of the possible mechanisms underlying the increased genetic vulnerability to psychosis observed in this population.

It is important to note that, despite the fact that results from the label-based review and the coordinate-based meta-analysis are partially overlapping, (as both reported significant alterations in

the PCC, and precuneus) the meta-analysis revealed consistent alterations in the bilateral IPL, while the review highlighted that a high number of studies reported alterations in the middle frontal areas. Although these two methodologies seem to provide *prima facie* inconsistent results, the meta-analysis only included a sub-group of the identified articles. Similarly, the current results are inconsistent with those of a previous meta-analysis on 22q11.2 DS (Tan et al. 2009), which identified alteration in 22q11.2 DS compared to controls in the prefrontal cortex, hippocampi and corpus callosum. The differences between the results obtained in the previous (Tan et al. 2009) and the current meta-analysis might be easily explained by significant methodological differences. Unlike the previous meta-analysis, which only included structural studies, our ALE analysis included both structural and functional (e.g. task-fMRI and rs-fMRI) neuroimaging studies in order to comprehensively assess both types of abnormalities in 22q11.2 DS. In addition, we excluded all the ROI-based studies, which were included in the previous meta-analysis, to prevent the results from being biased by previous a priori hypotheses.

Psychosis is a very complex disorder, where biological, psychological and environmental factors interact (van Os, Rutten, and Poulton 2008). To date, no reliable and robust biomarkers of psychosis have been identified (Prata, Mechelli, and Kapur 2014), hampering the clinical translation of research findings. The study of 22q11.2 DS offers a unique model to study both the causes and the early neuroanatomical signature of psychosis proneness. The current work significantly enhances the existing literature by providing a clear, exhaustive and meaningful synthesis of the imaging research findings so far. Indeed, multicentre (Sun et al. 2018) and meta-analytical studies in this population are of pivotal importance to shed light on the neural basis of psychosis that may be genetically determined. This is of outmost importance for research aiming to identify possible predictive biomarkers of psychosis onset.

4.1. Limitations

This study has some limitations. Firstly, a proportion of studies included in the systematic review included partially overlapping samples. This is due to the relatively low prevalence of 22q11.2 DS (Kobrynski and Sullivan 2007) which makes participant enrolment extremely challenging. Although the systematic review included partially overlapping samples, these were excluded from the meta-analysis.

A second limitation is that not all included studies reported data on 22q11.2 DS individuals' psychopathological assessment, therefore non-comprehensive information on the prevalence of psychosis in this population was available. In addition, many of the original studies did not control for IQ and cases and controls were not matched. For this reason, it is possible that the observed differences were mainly driven by a low IQ or/and developmental delay in 22q11.2 DS individuals compared to normally developed healthy individuals. Despite this not being a limitation of the current study, it clearly has a strong influence on the possible interpretation of the current findings. However, somewhat reassuring are the results reported by Sun and colleagues (2018), which indicate that, even when controlling for IQ, the observed abnormalities in their large sample remained unchanged.

Thirdly, the relatively young age of the included individuals and scarcity of longitudinal studies available do not allow us to draw definitive conclusions about brain structural and functional abnormalities in adults with 22q11.2 DS. Therefore, the neuroanatomical and functional evolution of the disorder remains unknown.

4.2. Conclusions

In conclusion, brain abnormalities in 22q11.2 DS are consistently located in the bilateral IPL, right STG, precuneus and posterior cingulate cortex. These abnormalities, which are mainly located within the posterior DMN, are, at least in part, in line with those of the largest study available so far (Sun et al. 2018). Despite the efforts of the present study to provide a comprehensive picture, it was not possible to disentangle whether these brain abnormalities are the result of neurocognitive as

opposed to psychopathological features of the syndrome. Indeed, the current results are based on the available literature and thus do not allow the clarification of whether the reported abnormal brain areas might be involved in increased vulnerability to psychosis in these individuals, or if they are the result of the developmental delay observed in this population. Clarifying this would lead to a better understanding of the possible mechanisms underlining the increased genetic vulnerability to psychosis observed in this population and might aid the identification of predictive biomarkers of psychosis onset.

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Figures Legend:

Figure 1. PRISMA flow chart.

Figure 2. Summary of label-based systematic review findings, including sMRI and fMRI studies. Results are displayed by pooling structural and functional data together. Each colour represents the number of reported foci per area.

Figure 3. Convergent results from the coordinate-based meta-analysis. A) Results are displayed in the axial view; b) results are displayed in the sagittal view; c) results are displayed in the coronal view.