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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Long-range dysconnectivity in frontal and midline structures is associated to psychosis in 22q11.2 deletion syndrome

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Abstract Patients affected by 22q11.2 deletion syndrome (22q11DS) present a characteristic cognitive and psychiatric profile and have a genetic predisposition to develop schizophrenia. Although brain morphological alterations have been shown in the syndrome, they do not entirely account for the complex clinical picture of the patients with 22q11DS and for their high risk of psychotic symptoms. Since Friston proposed the "disconnection hypothesis" in 1998, schizophrenia is commonly considered as a disorder of brain connectivity. In this study, we review existing evidence pointing to altered brain structural and functional connectivity in 22q11DS, with a specific focus on the role of dysconnectivity in the emergence of psychotic symptoms. We show that widespread alterations of structural and functional connectivity have been described in association with 22q11DS. Moreover, alterations involving long-range association tracts as well as midline structures, such as the corpus callosum and the cingulate gyrus, have been associated with psychotic symptoms in this population. These results suggest common mechanisms for schizophrenia in syndromic and non-syndromic populations. Future directions for investigations are also discussed.

Keywords Velo-cardio-facial syndrome · Connectivity · DTI · Resting-state fMRI · Schizophrenia

Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a neurogenetic disease with a prevalence of 1/4000–1/6000 live births (Oskarsdottir 2004), caused by a microdeletion on the chromosome 22. Key clinical features of the 22q11DS phenotype include congenital heart defects, cleft palate, recurrent infections and hypocalcemia (Oskarsdottir et al. 2005). The syndrome has been of particular interest due to its association with specific cognitive difficulties and psychiatric disorders, notably an increased risk to develop schizophrenia. The cognitive picture associated with 22q11DS includes mild mental delay with specific visuo-spatial difficulties (Niklasson and Gillberg 2010; Swillen et al. 1997), as well as impaired executive functions (Antshel et al. 2008) and social skills (Campbell et al. 2015; Jansen et al. 2007; Kiley-Brabeck and Sobin 2006; Woodin et al. 2001). At the clinical level, the phenotype associated with the microdeletion is marked by a strong risk of schizophrenia, which is diagnosed in about one-third of the adults with 22q11DS (Murphy et al. 1999; Schneider et al. 2014a). With such a high genetic predisposition to develop schizophrenia, 22q11DS represents a unique neurodevelopmental model to study behavioural

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and neural biomarkers associated with the development of psychotic symptoms (Bassett and Chow 1999; Murphy et al. 1999).

Initial neuroimaging studies in 22q11DS contributed to the delineation of brain alterations associated with the microdeletion. During childhood, decreased white and grey matter volumes have been identified in posterior parts of the brain, particularly in the occipital and parietal lobes (Gothelf et al. 2008; Tan et al. 2009). In adults, volumetric reduction is mostly located in the frontal and temporal lobes, suggesting the presence of abnormal brain development in these regions (Gothelf et al. 2008; Tan et al. 2009). Furthermore, 22q11DS and non-syndromic schizophrenia show common anatomical impairments. Notably, in 22q11DS, associations between grey matter alterations and psychotic symptoms have been found in the anterior cingulate cortex (ACC) (Dufour et al. 2008), in the adjacent ventromedial and orbital prefrontal cortices (Jalbrzikowski et al. 2013), in the left dorsolateral prefrontal cortex (Gothelf et al. 2011), in the medial temporal lobe and in the cerebellum (Kates et al. 2011). These same structures have also been involved in non-syndromic schizophrenia [reviewed in (Keshavan et al. 2008)], suggesting common mechanisms for the emergence of psychotic symptoms in 22q11DS and in the general population. However, these studies reporting localized neuroanatomical alterations do not give any information about the way these affected regions interact together and with the rest of the brain. In fact, the idea that schizophrenia might be a dysconnectivity syndrome is an old hypothesis that dates back to Wernike in (1906) and Bleuler in (1911), and that re-emerged following new developments in magnetic resonance imaging (MRI). Indeed, modern MRI methodologies provide a way to empirically test in vivo the integrity of structural and functional large-scale brain networks.

Several methods have been employed to identify abnormal brain network organization in schizophrenia and in 22q11DS. At the structural level, metrics extracted from diffusion tensor imaging (DTI) provide valuable insights about white matter integrity, by measuring the characteristics of water diffusion. Tractography algorithms can also be used on DTI images to reconstruct white matter tracts anatomy, providing a "virtual dissection" of the brain (Hagmann et al. 2003). Functional connectivity, by contrast, is defined as the synchronized brain activity of distant brain regions and is often investigated using resting-state fMRI. This technique refers to the recording of brain activity when the subject is quietly lying in the scanner without performing any particular task. Resting-state fMRI is commonly used on young and cognitively impaired populations because it requires limited contribution from the participants. Furthermore, resting-state fMRI has

shown to reflect endogenous characteristics of brain connectivity leading to the identification of large-scale functional networks that are highly reproducible across populations (Rosazza and Minati 2011). The description of the methods for investigating brain connectivity is beyond the scope of this review; however, we reported essential definitions of technical terms employed in this manuscript (Box 1, Glossary).

By using DTI and resting-state fMRI, widespread impairment of structural and functional connectivity has been described in schizophrenia. A recent meta-analysis showed that the majority of the studies using DTI in schizophrenia found altered white matter integrity in the left frontal and temporal lobes (Ellison-Wright and Bullmore 2010). This fronto-temporal dysconnectivity has been implicated in self-monitoring impairments and in the inability to distinguish between internal thoughts and external stimuli (Hubl et al. 2004). Tractography studies also reported alterations in several long association fibres, such as the superior (SLF) and inferior longitudinal fasciculi (ILF), the inferior fronto-occipital fasciculus (IFOF) and the cingulum bundle (Canu et al. 2015). Functional studies investigating brain connectivity at rest reported impairments in several regions including the default mode network (DMN), a network particularly active during rest that is responsible for self-oriented thoughts and mind wandering (Raichle 2001). Dysconnectivity in auditory/language networks, cortical-subcortical networks and in the prefrontal cortex have also been described in patients with schizophrenia (Karbasforoushan and Woodward 2012). In agreement with the alterations of the long-range white matter tracts, graph theory analysis revealed reduced measures of integration in important hubs such as prefrontal, limbic, temporal and parietal regions (Fornito et al. 2012; Griffa et al. 2015). Thus, far in 22q11DS, depending on the methods employed and the demographic characteristics of the patients' sample, the application of the same techniques gave heterogeneous results. Findings published in 22q11DS, however, provide a better delineation of the anatomical and functional brain phenotype associated to the microdeletion, leading to a better comprehension of the pathophysiological mechanisms underlying the cognitive and clinical manifestations of 22q11DS. Furthermore, patterns of connectivity in 22q11DS could represent risk factors for the development of schizophrenia and related psychotic disorders, and may provide a framework for better understanding the mechanisms that underlie the emergence of this disorder in the general population.

In this review, we aim to summarize research on structural and functional brain connectivity in 22q11DS. We start by reviewing the brain connectivity alterations described in structural and functional large-scale brain networks in children, adolescents and adults with
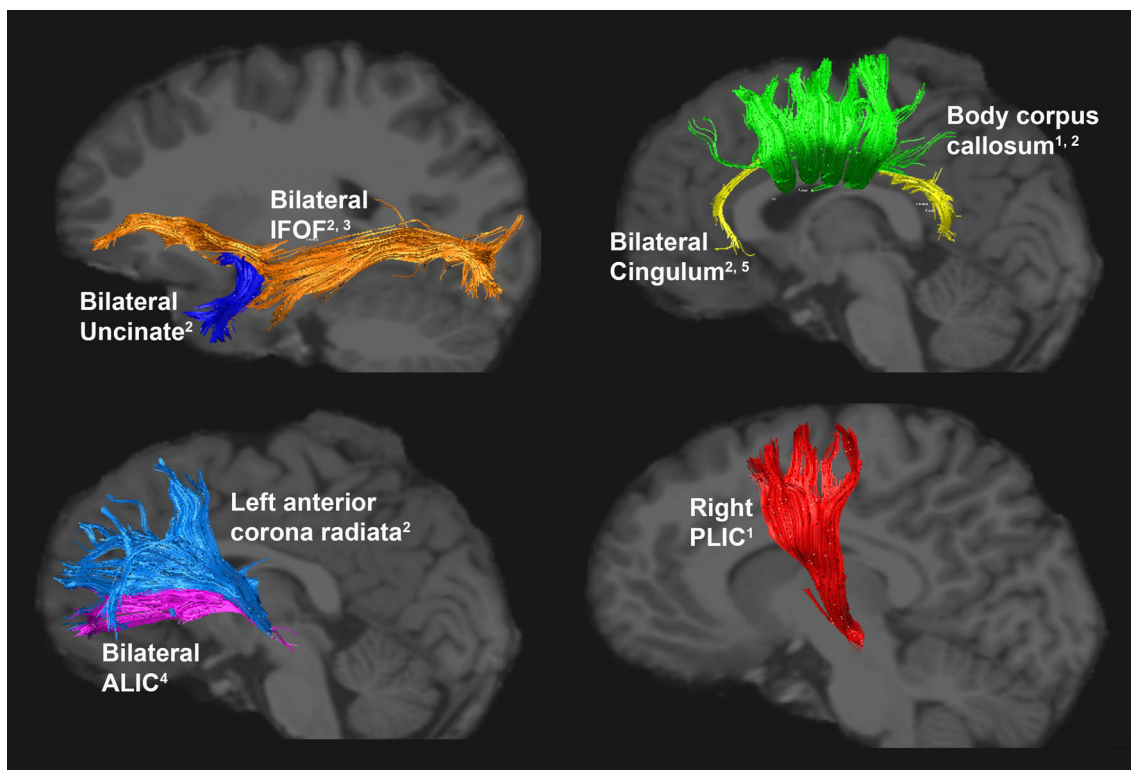
Fig. 1 White matter tracts showing relationships with psychosis in studies including patients with 22q11DS

22q11DS, thereby looking for a common pattern of alterations that may constitute a core connectivity phenotype associated to the microdeletion. Then, we review evidence for relationships between dysconnectivity and cognitive or clinical symptoms expression, with particular emphasis on psychotic symptoms and schizophrenia.

Method

Published studies that investigated structural or resting-state connectivity in 22q11DS were selected in August 2015 using the PubMed database with the following keywords: "22q11.2 connectivity", "22q11.2 DTI", "22q11.2 fractional anisotropy", "22q11.2 tractography", "22q11.2 resting-state". We excluded all the studies investigating brain morphology in 22q11DS, as they have already been reviewed elsewhere (Gothelf et al. 2008; Tan et al. 2009) and provide less direct information about cerebral connectivity. Moreover, we included only the studies using MRI acquisitions, namely DTI and resting-state fMRI, and excluded the EEG studies.

The PubMed search retrieved 17 published studies investigating structural connectivity in 22q11DS, using either using voxel-based DTI methodologies (Barnea-Goraly et al. 2003, 2005; da Silva et al. 2011; Deng et al. 2015; Jalbrzikowski et al. 2014; Kates et al. 2015; Kikinis et al. 2012; Perlstein et al. 2014; Radoeva et al. 2012; Simon et al. 2005, 2008; Sundram et al. 2010; Villalon-Reina et al. 2013) or tractography, with measures of fibres' count (Kikinis et al. 2013; Ottet et al. 2013a; Padula et al. 2015) or graph theory (Ottet et al. 2013b). In addition, 4 published studies to date examined resting-state functional connectivity in 22q11DS (Debbane et al. 2012; Padula et al. 2015; Scariati et al. 2014; Schreiner et al. 2014).

The results extracted from some of these studies cannot be considered fully independent, because they used overlapping samples of participants recruited by the same lead investigator in the same University centre. By examining the authors' list and description of participants, we identified seven different cohorts of patients: Stanford University (Barnea-Goraly et al. 2003, 2005), Brigham and Massachusetts Hospitals in Boston (Kikinis et al. 2012, 2013), Children's Hospital of Philadelphia (Simon et al. 2005, 2008), University of California Los Angeles (Jalbrzikowski et al. 2014; Schreiner et al. 2014), State University of New York (SUNY) Upstate Medical University (Kates et al. 2015; Perlstein et al. 2014; Radoeva et al. 2012), the University of California Davis Medical Centre (Deng et al. 2015; Villalon-Reina et al. 2013) and our cohort of subjects recruited at the Geneva University (Debbane et al. 2012; Ottet et al. 2013a, b; Padula et al. 2015; Scariati et al. 2014).

Results

Structural connectivity in 22q11DS: DTI studies

The main results of the 17 studies that used structural connectivity in individuals with 22q11DS are reviewed in Table 1. The majority of the studies ($n = 13$) reviewed in this manuscript used voxel-based DTI measures, namely fractional anisotropy (FA) (Barnea-Goraly et al. 2003, 2005; da Silva et al. 2011; Deng et al. 2015; Jalbrzikowski et al. 2014; Kates et al. 2015; Kikinis et al. 2012; Perlstein et al. 2014; Radoeva et al. 2012; Simon et al. 2005, 2008; Sundram et al. 2010; Villalon-Reina et al. 2013), or axial (AD) and radial (RD) diffusivity (Jalbrzikowski et al. 2014; Radoeva et al. 2012; Simon et al. 2008; Villalon-Reina et al. 2013). More recent investigations used tractography techniques (Kikinis et al. 2013; Ottet et al. 2013a, b; Padula et al. 2015), with measures of fibre tracts count (Kikinis et al. 2013; Ottet et al. 2013a; Padula et al. 2015) or graph theoretical metrics (Ottet et al. 2013b).

Most of the voxel-based studies were conducted using whole-brain approaches (Barnea-Goraly et al. 2003; da Silva et al. 2011; Jalbrzikowski et al. 2014; Kikinis et al. 2012; Radoeva et al. 2012; Simon et al. 2005, 2008; Sundram et al. 2010; Villalon-Reina et al. 2013), while a few of them investigated the integrity of specific tracts of interest (Deng et al. 2015; Kates et al. 2015; Perlstein et al. 2014).

Whole-brain studies reported discordant results in 22q11DS, pointing to both reduced (Barnea-Goraly et al. 2003; da Silva et al. 2011; Kikinis et al. 2012; Radoeva et al. 2012; Simon et al. 2005; Sundram et al. 2010; Villalon-Reina et al. 2013) and increased (da Silva et al. 2011; Jalbrzikowski et al. 2014; Simon et al. 2005; Sundram et al. 2010) FA in several brain regions spanning mainly the frontal, parietal and temporal lobes (see Table 1 for detailed findings of the voxel-based studies).

In terms of fibre bundles, alterations have been shown in several long association tracts including the superior (SLF) and inferior (ILF) longitudinal fasciculus, the inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus, the arcuate fasciculus and the cingulum bundle. Some of the results are consistent and show reduced FA in the ILF (Barnea-Goraly et al. 2003; Sundram et al. 2010; Villalon-Reina et al. 2013), the uncinate fasciculus (Radoeva et al. 2012; Sundram et al. 2010) and the fronto-parietal course of the arcuate fasciculus (Sundram et al. 2010). More discordant results have been found in the SLF with Barnea-Goraly et al. (2003) and Villalon-Reina et al. (2013) indicating reduced FA and Jalbrzikowski et al. (2014) and Simon et al. (2008) reporting increased FA. These studies present, however, some methodological differences.

Although both Barnea-Goraly et al. (2003) and Jalbrzikowski et al. (2014) used a sample comprising children, adolescents and young adults, in Jalbrzikowski et al. (2014), the analysis was corrected for the age and the gender of the participants, while in Barnea-Goraly et al. (2003) these confounding effects have not been taken into account. Similarly, Sundram et al. (2010) and Villalon-Reina et al. (2013) conducted their analyses in a sample of children and adolescents, but (Villalon-Reina et al. 2013) included only female subjects and corrected the analysis for age and total brain volume. Simon et al. (2008) also found increased FA in the IFOF, while the opposite result was reported by Sundram et al. (2010), when correcting for the IQ. Inconsistent results about reduced (Jalbrzikowski et al. 2014; Sundram et al. 2010) and increased (da Silva et al. 2011; Simon et al. 2005) FA in the cingulum bundle have also been reported. However, a recent study that included a large sample of adolescents and adults and that specifically investigated the integrity of this white matter tract (Kates et al. 2015) reported decreased FA and AD in the anterior portion of the cingulum bundle and a concomitant increase in FA and decrease in RD in its more posterior aspect. Impairments in the fornix, another white matter tract involved in the limbic system, have been reported in 22q11DS by two other studies that specifically investigated the integrity of this tract (Deng et al. 2015; Perlstein et al. 2014). Finally, alterations in the corpus callosum (Jalbrzikowski et al. 2014; Simon et al. 2005; Sundram et al. 2010) and in the internal capsule including the corona radiata (Jalbrzikowski et al. 2014; Perlstein et al. 2014; Sundram et al. 2010; Villalon-Reina et al. 2013) have been observed in patients with 22q11DS.

By contrast to FA results, studies reporting AD and RD show a more consistent decrease of these measures in patients with 22q11DS. In particular, reduced AD indicating axonal damage (Budde et al. 2009; Song et al. 2003) has been reported in the SLF, ILF, IFOF and the cingulum bundle (Jalbrzikowski et al. 2014; Kates et al. 2015; Radoeva et al. 2012; Simon et al. 2008).

Although some of the studies using voxel-based measures reported inconsistent findings, robust evidence points to a prefential alteration of long-range fibres connecting the frontal lobe to the temporal, parietal and occipital lobes, as well as limbic tracts, such as the cingulum bundle and the fornix.

Consistent with voxel-based findings, three studies using tractography published by our group, confirmed the altered connectivity in fronto-temporal (Ottet et al. 2013a, b), parietal (Ottet et al. 2013b) and limbic regions (Ottet et al. 2013a; Padula et al. 2015). Using a whole-brain analysis, we showed a 10 % reduction in the number of total reconstructed streamlines in 22q11DS (Ottet et al. 2013a).

Table 1 Summary of DTI studies

Reference (cohort)	Sample size 22q11 (males/females)	Sample size controls (males/females)	Method	Results
Barnea-Goraly et al. 2003 (Stanford University)	19 (13/6), age range = 7.2–21.8 years (mean age = 12.2, SD = 3.9)	19 (13/6), age range = 7.2–21.8 years (mean age = 14.4, SD = 4.2)	Voxel-based analysis with SPM No covariates	↓FA Bilateral middle frontal gyrus, left external capsule, right superior postcentral sulcus, right temporal stem, bilateral postcentral gyrus, left superior parietal gyrus, left precentral gyrus, left deep parietal lobe white matter, left cruz cerebri. ↑FA Bilateral tracts from splenium of the corpus callosum into occipital lobe
Barnea-Goraly et al. (2005) (Stanford University)	Same sample as Barnea-Goraly et al. (2003)	Same sample as Barnea-Goraly et al. (2003)	Voxel-based analysis with SPM No covariates	↓FA parietal lobe
Radoeva et al. (2012) (State University of New York)	33 (12/21) (mean age = 17.7, SD = 1.8)	16 (8/8) (mean age = 18, SD = 1.7)	Voxel-based analysis with DTI studio No covariates	↓FA Bilateral uncinate fasciculus ↑RD left posterior corona radiata ↓AD posterior thalamic radiation, anterior, superior and posterior corona radiata, cingulate gyrus, SLF, IFOF, sagittal stratum, external capsule, retrolenticular part of internal capsule, superior cerebellar peduncle
Jalbrzikowski et al. (2014) (University of California Los Angeles)	36 (11/25), age range = 10–26 years (mean age = 16.3, SD = 4.3)	29 (15/14), age range = 10–26 years (mean age = 15.5, SD = 3.8)	Voxel-based analysis with TBSS With covariates (age, gender, scan site)	↑FA Right posterior limb of internal capsule, right superior and posterior corona radiata, body of corpus callosum, left SLF ↓FA left cingulum bundle. ↓AD and RD body and splenium of corpus callosum, bilateral anterior thalamic radiation, bilateral SLF and ILF. ↓AD bilateral IFOF, anterior cingulum bundle, uncinate fasciculus. ↓RD left superior corona radiata, corticospinal tract.
Villalon-Reina et al. (2013) (California Davis Medical Centre)	19 (−/19), age range = 7 to 14 years (mean age = 10.75, SD = 1.87)	20 (−/20), age range = 7 to 14 years (mean age = 10.17, SD = 2.28)	Voxel-based analysis with FSL With covariates (age and total brain volume)	↓FA Bilateral superior temporal gyrus and superior corona radiata, SLF, ILF ↓AD bilateral superior temporal gyrus and superior corona radiata, middle temporal gyrus, right posterior internal capsule. ↓RD superior corona radiata, superior and inferior temporal lobes. ↑AD and RD corpus callosum (genu and splenium), anterior limb of internal capsule, external capsule, inferior and posterior thalamus
Simon et al. (2005) (Philadelphia)	18 (7/11), age range = 7.3–14 years (mean age = 9.9, SD = 1.42)	18 (11/7), age range = 7.5–14.2 years (mean age = 10.4, SD = 1.99)	Voxel-based analysis with SPM No covariates	↓FA corpus callosum ↑FA cingulate gyrus, right inferior parietal lobule

Table 1 continued

Reference (cohort)	Sample size 22q11 (males/females)	Sample size controls (males/females)	Method	Results
Simon et al. (2008) (Philadelphia)	Same sample as Simon et al. (2005)	Same sample as Simon et al. (2005)	Voxel-based analysis with FSL and diffeomorphic groupwise normalization to standard MNI space No covariates	↑FA nucleus caudatus, superior temporal gyrus, SLF, IFOF ↓RD sulcus callosomarginalis, Forceps major, Tapetum, SLF, ILF, IFOF, optic radiation, inferior parietal lobule, cingulate gyrus
Sundram et al. (2010)	11 (5/6), age range = 9–17 years (mean age = 12, SD = 2.2)	12 (8/4), age range = 9 to 17 years (mean age = 13, SD = 2.5)	Voxel-based analysis with SPM and VBM toolbox With and without covariates (IQ)	Model without covariates: ↓FA left posterior limb of internal capsule, superior region of corona radiata, tapetum, posterior thalamic radiation, fronto-parietal course of the arcuate fasciculus ↑FA genu and anterior limb of internal capsule, anterior and superior corona radiata Model with covariates (IQ): ↓FA left corticopontine and corticospinal tracts and middle cerebellar peduncle, body and splenium corpus callosum, retrolenticular and posterior limbs internal capsule, superior corona radiata, right cingulate gyrus, right ILF and IFOF
Da Silva Alves et al. (2011)	27 (13/14) (Mean age = 30, SD = 7.67)	31 (17/14) (Mean age = 32.35, SD = 9.74)	Voxel-based analysis with SPM and VBM toolbox With and without covariates (IQ)	Model without covariates: ↓FA right frontal (precentral, postcentral and sub-gyral) ↑FA bilateral anterior cingulate, left frontal subgyral Model with covariates (IQ): ↓FA right frontal (superior and sub-gyral), left parietal postcentral, bilateral precentral and parahippocampal
Kikinis et al. (2012) (Boston)	9 (2/7), age range = 18 to 39 years (mean age = 27.3, SD = 7.1)	9 (2/7), age range = 18 to 37 years (mean age = 27.2, SD = 6.9)	Voxel-based analysis with TBSS. No covariates	↓FA Left parietal lobe at intersection between I FOF, ILF, SLF, cingulate gyrus, anterior thalamic radiation. ↓AD left parietal lobe at intersection between IFOF, ILF, SLF, cingulate gyrus, anterior thalamic radiation
Perlstein et al. (2014) (State University of New York)	52 (22/30) (mean age = 18, SD = 2.2)	47 (24/23) (mean age = 18.1, SD = 1.6)	Voxel-based analysis with DTI studio in specific tracts of interest (ALIC, fornix, uncinate fasciculus)	↑FA ALIC ↓FA left fornix ↓AD right fornix and bilateral uncinate ↓RD left ALIC, uncinate fasciculus
Kates et al. (2015) (State University of New York)	51 (22/29), age range = 14–24 years (mean age = 18, SD = 2.3)	46 (23/23), age range = 15–21 years (mean age = 18, SD = 1.6)	Voxel-based analysis with DTIStudio in specific tracts of interest (Cingulum bundle)	↓FA left anterior cingulate gyrus ↑FA bilateral posterior cingulum bundle. ↓AD bilateral anterior and superior cingulum bundle ↓RD bilateral posterior and right superior cingulum bundle

Table 1 continued

Reference (cohort)	Sample size 22q11 (males/females)	Sample size controls (males/females)	Method	Results
Deng et al. (2015) (California Davis Medical Centre)	45 (22/23), age range = 7–14 years (mean age = 10.8, SD = 1.9)	38 (19/19), age range = 7–14 years (mean age = 10.1, SD = 2.3)	Voxel-based analysis with VISTASOFT package in specific tracts of interest (Fornix)	↓FA bilateral fornix ↑RD in bilateral fornix
Ottet et al. (2013a) (Geneva)	30 (17/13), age range = 7–25 years (mean age = 14.8, SD = 4)	30 (16/14), age range = 7–25 years (mean age = 14.9, SD = 3.7)	Whole-brain tractography with connectome mapper. Fibres' count With covariates (age, gender)	↓Number of streamlines in left fronto-temporal and parieto-limbic connections, left occipital lobe, bilateral limbic structures ↑Number of streamlines in right frontal and parietal lobes and right parieto-occipital connections
Ottet et al., 2013b (Geneva)	56 (23/22), age range = 6–26 years (mean age = 15.2, SD = 4.53)	48 (25/24), age range = 7–24 years (mean age = 15.28, SD = 4.35)	Whole-brain tractography with connectome mapper Graph theory	↓Global efficiency ↑Characteristic path length ↓Degree in bilateral pars opercularis, precentral, superior and inferior parietal cortices, lingual and parahippocampal gyri; right medial-orbito-frontal, middle and superior frontal, anterior cingulate, lateral occipital and inferior temporal cortices, precuneus; left pericalcarine and middle temporal cortices, fusiform gyrus, thalamus, caudate nucleus
Kikinis et al. (2013) (Boston)	Same sample as Kikinis et al. (2012)	Same sample as Kikinis et al. (2012)	Tractography with 3D slicer software in specific tract of interest (IFOF, ILF)	↓FA left IFOF and ILF ↓AD bilateral IFOF and ILF
Padula et al. (2015) (Geneva)	41 (17/24), age range = 8–28 years (mean age = 17.1, SD = 5.3)	43 (15/28), age range = 6–25 years (mean age = 16.1, SD = 4.5)	Tractography with FSL in specific tracts of interest (DMN connections) With covariates (age, gender, white matter volume)	↓Number of streamlines and mean connectivity index in anterior—posterior DMN and anterior DMN—left parietal lobule connections

For the studies conducted on the same cohort of participants, the cohort name has been indicated

SD standard deviation, *FA* fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *IFOF* inferior fronto-occipital fasciculus, *ALIC* anterior limb of internal capsule

More specifically, reduced number of virtual fibres was still observed when this decrease was accounted for in left fronto-temporal (−34 %) and parieto-limbic (−10 %) connections as well as in the left occipital lobe (−18 %) and in bilateral limbic structures (−6 %) (Ottet et al. 2013a). By contrast, the right frontal and parietal lobes as well as the right parieto-occipital connections showed a relative increase in the number of fibres in the patients group. In line with these findings of reduced limbic connectivity, in a following study (Padula et al. 2015), we reported a reduction of the fibre tracts connecting the anterior and posterior regions of the DMN, which are part of the cingulum bundle. An additional tractography study conducted on an adult sample by Kikinis and colleagues found a reduced FA and AD by investigating the integrity of the fibre tracts belonging to the ventral visual stream (IFOF and ILF) in 22q11DS (Kikinis et al. 2013).

Only one study investigated the impact of these alterations on the organization of the structural network (Ottet et al. 2013b). Using a graph theoretical analysis of the structural connectome, this study showed reduced global efficiency and increased characteristic path length in patients with 22q11DS compared to healthy controls. These results reflect a deficit of network integration in 22q11DS that is related to a reduced connectivity (decreased degree) of important brain hubs including the bilateral hippocampus, superior parietal and precentral regions, right rostral middle frontal and superior frontal

cortices, the precuneus and the left thalamus. Segregation, as measured with the mean clustering coefficient, was preserved in patients with 22q11DS.

Association between altered white matter integrity and age in 22q11DS

Given the altered trajectories of clinical and cognitive development in patients with 22q11DS, it is of particular interest to examine age-related effects in altered connectivity. Indeed, patients affected by 22q11DS undergo cognitive decline (Schneider et al. 2014b; Vorstman et al. 2015) and have an increased risk to develop psychiatric symptoms (Schneider et al. 2014b) when they transition from adolescence to adulthood. Furthermore, given that neurodevelopmental processes have been strongly involved in schizophrenia development (Rapoport et al. 2005), understanding the temporal course of connectivity alterations in 22q11DS is crucial to identify potential risk markers for psychosis. Neuroimaging studies reported evidence for altered cortical volume and thickness development (Gothelf et al. 2007, 2011; Schaer et al. 2009), which may account for the behavioural alterations. However, no longitudinal studies on brain connectivity have been conduced to date in patients with 22q11DS. Nevertheless, four cross-sectional studies suggested an abnormal development of white matter with age in 22q11DS (Deng et al. 2015; Jalbrzikowski et al. 2014; Ottet et al. 2013a; Padula et al. 2015). A first analysis conducted by our group showed that while the total white matter volume increases with age in both healthy controls and patients with 22q11DS, whole-brain mean FA was positively correlated with age only in controls (Ottet et al. 2013a). By contrast, no association between age and the total number of streamlines was observed in any of the groups. Subsequently, several analyses focusing on tracts of interest revealed similar findings. In a partially overlapping sample of patients, we reported a lack of normal increase in the number of streamlines between the anterior and posterior nodes of the DMN with age in patients with 22q11DS (Padula et al. 2015). In this study, we also showed that the number of tracts connecting the anterior and posterior DMN was preserved in children and adolescents with 22q11DS, while impairments started to appear in young adults (Padula et al. 2015). In Jalbrzikowski et al. (2014), the authors found an increase in ILF FA and a reduction in ILF RD with age in control participants, but not in patients with 22q11DS. Similarly, Deng et al. (2015) reported a lack of the age-associated increase in AD and RD in the fornix in patients compared with healthy individuals (Deng et al. 2015). These findings give preliminary evidence of altered white matter maturation in 22q11DS and suggest that structural dysconnectivity, together with cortical

abnormalities, may precede the development of psychosis. Indeed, a recent study showed that in non-syndromic patients at risk for schizophrenia who have prodromal psychotic symptoms, white matter abnormalities are already present before the onset of full psychosis (Chung and Cannon 2015).

Functional connectivity in 22q11DS: resting-state fMRI studies

To date, four studies investigated functional brain connectivity using resting-state fMRI in 22q11DS (Debbane et al. 2012; Padula et al. 2015; Scariati et al. 2014; Schreiner et al. 2014). The first three were performed on our cohort of patients, while the last (Schreiner et al. 2014) used an independent sample. We performed two whole-brain connectivity investigations (Debbane et al. 2012; Scariati et al. 2014). In Scariati et al. (2014), we investigated the distribution of the functional connectome alterations associated with 22q11DS. We found widespread alterations of the functional network with a predominant frontal dysconnectivity and an impairment of visuo-spatial networks including occipital, parietal and right inferior temporal connectivity. In Debbané et al. (2012), we investigated the functional networks communities using an ICA in a partially overlapping sample of adolescents with the microdeletion compared to healthy controls. This study also showed the presence of altered connectivity in visuo-spatial networks as well as in sensory-motor and default mode networks.

Two seed-based studies (Padula et al. 2015; Schreiner et al. 2014) further investigated DMN connectivity in patients with 22q11DS and confirmed a specific impairment of this network. In Padula et al. (2015), we used a seed-based multimodal approach focusing on DMN connectivity in a sample of patients with the microdeletion ranging from children to adults (Padula et al. 2015). More specifically, we found decreased functional connectivity between anterior and posterior DMN nodes, mirroring the above-mentioned structural connectivity impairment, and an isolated decrease in functional connectivity between left and right inferior parietal DMN nodes. The study from Schreiner and colleagues (2014) used a seed-to-voxel and a seed-to-seed analysis centred on the posterior cingulate cortex (PCC) to identify the DMN. They also found a global decrease in functional connectivity within the DMN in 22q11DS, specifically involving the connections between the anterior ventro-medial prefrontal cortex and the PCC. Moreover, they found that the DMN was more diffuse in 22q11DS with an increased connectivity between the PCC and the right inferior frontal cortex (Schreiner et al. 2014). Only this last study tested the effect of age on functional connectivity in 22q11DS and suggested the

presence of abnormal DMN development with age. In particular, patients showed an increase with age of long-range connections between the PCC and regions located outside the DMN.

Association between impaired connectivity, cognitive abilities and manifestation of psychotic symptoms in 22q11DS

Several of the studies discussed above reported an association between altered structural and functional connectivity and cognitive (Barnea-Goraly et al. 2005; Debbane et al. 2012; Jalbrzikowski et al. 2014; Kates et al. 2015; Radoeva et al. 2012; Schreiner et al. 2014; Simon et al. 2008) or psychiatric (da Silva et al. 2011; Debbane et al. 2012; Jalbrzikowski et al. 2014; Kates et al. 2015; Ottet et al. 2013a, b; Perlstein et al. 2014; Scariati et al. 2014; Sundram et al. 2010) impairments in 22q11DS.

Two studies showed that structural dysconnectivity in the parietal lobe is associated with poorer arithmetic abilities (Barnea-Goraly et al. 2005) and visuo-spatial attention (Simon et al. 2008) in patients with the syndrome. However, the direction of the FA difference was different in the 2 studies, with one reporting reduced (Barnea-Goraly et al. 2005) and the other reporting increased (Simon et al. 2008) FA in 22q11DS. Furthermore, Radoeva et al. (2012) showed an association between white matter microstructural impairment in parietal/occipital cortices, SLF, IFO and poorer executive functions (Radoeva et al. 2012). Also, resting-state functional dysconnectivity of the DMN (Schreiner et al. 2014) and reduced axonal coherence in IFO and uncinate fasciculus (Jalbrzikowski et al. 2014) were associated with dysfunctional social behaviour in patients with 22q11DS. An additional study showed that patients with 22q11DS with a low IQ have reduced connectivity in striatal structures (cortico-striatonigral-thalamocortical circuit) with respect to 22q11DS individuals with higher IQ (Meskaldji et al. 2011).

Relationships between structural and functional connectivity and psychosis have also been reported. White matter tracts alterations that have shown associations with psychotic symptoms in patients with 22q11DS are shown in Fig. 1. By comparing a group of patients with the microdeletion suffering from schizophrenia to a group of patients that does not, Da Silva Alves et al. (2011) have shown that schizophrenia is associated to increased FA in the left cingulum bundle, the anterior corona radiata and in the corpus callosum. These authors further refined their results by performing correlations between FA and the different dimensions of schizophrenia using the PANSS [positive and negative syndrome scale (Kay et al. 1987)].

They showed the presence of a negative relationship between the intensity of positive symptoms and FA in bilateral uncinate fasciculus and ILF as well as in the left IFOF, corpus callosum and superior corona radiata. Associations between positive symptoms and the microstructure of the bilateral IFOF (Jalbrzikowski et al. 2014), the uncinate (Perlstein et al. 2014) and the superior cingulum bundle (Kates et al. 2015) were confirmed on an independent sample of patients. Furthermore, positive symptoms also showed a positive correlation with FA in the anterior limb of the internal capsule, and a negative correlation at the same place in patients with 22q11DS (Perlstein et al. 2014). Finally, the graph theory study (Ottet et al. 2013b), even though performed at the cortical level, also reported congruent results by showing a correlation between the local efficiency of left middle and inferior frontal cortices and transverse temporal gyri.

The majority of the studies reported that the integrity of long-range white matter tracts connecting the frontal lobe is associated with psychotic symptoms. Results of all the studies that reported correlations between DTI measures (FA, AD, RD or number of streamlines) and positive or negative psychotic symptoms in 22q11DS are included in the figure. Precise details about the measures employed in the different studies can be found in Table 2. The tracts were reconstructed in a control subject of our cohort using the Connectome mapper (http://www.cmtk.org/mapper/) and diffusion toolkit (www.trackvis.org/dtk) and were displayed using trackvis (http://trackvis.org).

Two out of the four studies measuring resting-state connectivity in 22q11DS examined the relationship between psychosis and functional connectivity. Both were conducted on our cohort. In Debbané et al. (2012), reduced activation in the left superior frontal gyrus, considered as part of the DMN, was related to the importance of positive and negative prodromal psychotic symptoms. The second study (Scariati et al. 2014) further showed that patients with prodromal positive symptoms could be accurately distinguished from the rest of the patients using resting-state connectivity patterns. The discriminative graph contains connections originating from frontal and limbic regions (left ACC, right inferior frontal and rectus gyri) as well as superior parietal and precentral regions. Contrarily, our multimodal study (Padula et al. 2015), even if performed on a partially overlapping sample, failed to identify any relationship between psychosis and dysconnectivity in the DMN. However, this study tested only a limited sample of DMN connections, namely between anterior (medial prefrontal cortex and ACC) and posterior (PCC and precuneus) nodes that did not completely overlap with the regions identified in the previous studies.

Table 2 Summary of studies reporting a correlation between white matter alterations and psychotic symptoms

Study	Clinical measure	Statistical method	Connectivity measure	Results
Sundram et al. (2010)	Schizotypal traits (scale adapted to populations with 22q11DS)	Pearson's correlation in significant clusters between 22q11DS and healthy controls. No covariates	FA	Negative correlation in right posterior limb of internal capsule, body of corpus callosum, left splenium of corpus callosum
Da Silva Alves et al. (2011)	PANSS positive, negative and general symptoms scale	Voxel-wise correlation. No covariates	FA	Negative correlations: with positive symptoms: bilateral uncinate fasciculus and ILF, left IFOF, corpus callosum and superior corona radiata.
				With negative symptoms: left superior corona radiata, ILF and superior cerebellar peduncle.
				With general symptoms: bilateral uncinate fasciculus, IFOF, left cingulum bundle, ILF and superior corona radiata.
Ottet et al. (2013a) (Geneva)	BPRS hallucinations subscale	Pearson's correlation coefficient. With covariates (age and gender)	Local efficiency	Positive correlation: left rostral middle frontal gyrus.
				Negative correlation: left transverse temporal region and left pars triangularis.
Jalbrzikowski et al. (2014) (University of California Los Angeles)	SIPS positive symptoms scores	Pearson's correlation in regions showing significant difference between patients with 22q11DS and controls. With covariates (age, gender and scanner location)	AD	Negative correlation in bilateral IFOF
Perlstein et al (2014) (State University of New York)	SIPS positive symptoms scores	Zero-inflated poisson regressionNo covariates	FA	Positive correlation in right ALIC
			RD	Negative correlation in left ALIC and bilateral uncinate fasciculus
Kates et al. (2015) (State University of New York)	SIPS positive symptoms scores	Zero-inflated poisson regression. No covariates	FA	Positive correlation in bilateral superior cingulum bundle
			RD	Negative correlation in bilateral superior cingulum bundle

For the studies conducted on the same cohort of participants, the cohort name has been indicated

FA fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *IFOF* inferior fronto-occipital fasciculus, *ALIC* anterior limb of internal capsule

Discussion

General considerations about brain connectivity in 22q11DS

The findings reviewed in this manuscript indicate that alterations in structural connectivity are widespread in patients with 22q11DS and involve most of the white matter tracts. However, studies using FA as measure of white matter integrity reported inconsistent results, with some of them pointing to reduced FA (Barnea-Goraly et al. 2003; da Silva et al. 2011; Kikinis et al. 2012; Radoeva et al. 2012; Simon et al. 2005; Sundram et al. 2010; Villalon-Reina et al. 2013) and some to increased FA (da Silva et al. 2011; Jalbrzikowski et al. 2014; Simon et al. 2005;

Sundram et al. 2010) in convergent brain regions. The reason for this heterogeneity may be attributed to the small size of the samples and the variable age ranges, related to the low prevalence of the disease. Also, methodological differences in the DTI analysis, in terms of registration algorithms and choice of templates, can be identified through the studies (Table 1). In particular, as discussed in (Barnea-Goraly et al. 2003; Ottet 2013; Radoeva et al. 2012), registration is an important issue in patients with 22q11DS. Indeed, morphological brain alterations, such as enlarged ventricles, could impact the accuracy of registration to standard templates and affect the results. While several studies published on 22q11DS used standard templates [usually the MNI template (Mazziotta et al. 1995)], several other papers used alternative strategies. For

instance, Jalbrzikowski et al. 2014 and Kikinis et al. 2012 used tract-based spatial statistics (TBSS) to create a group-based white matter "skeleton" to which individual images were non-linearly registered. A few others also performed measurements in subject space (Deng et al. 2015; Kates et al. 2015; Ottet et al. 2013a, b; Padula et al. 2015; Perlstein et al. 2014; Radoeva et al. 2012). Therefore, the different registration approaches that were adopted in the different studies may have influenced the accuracy of the results. However, it is not possible to identify a specific pattern that could explain the different directionalities in the findings. Furthermore, it should be noticed that FA summarizes the diffusion in all the three diffusion directions (x, y, z), thus being not specific for the diffusion in one single axis (Armitage and Bastin 2000). Also, the sensitivity of FA depends on the mean diffusion of the environment (Ottet 2013). Given these limitations of FA and the difficulties in the interpretation of this measure, it is important to consider complementary measures of diffusivity, such as RD and AD, which provide more specific information about the axonal damage (Budde et al. 2009; Song et al. 2003, 2005).

In line with the structural connectivity findings, resting-state studies reported altered functional connections in several networks, with most of the results pointing to impaired DMN connectivity (Debbane et al. 2012; Padula et al. 2015; Schreiner et al. 2014). Taken together, the structural and functional connectivity findings show a predominant involvement of frontal, parietal and limbic connectivity and their association with the presence of cognitive impairments (Barnea-Goraly et al. 2005; Jalbrzikowski et al. 2014; Kates et al. 2015; Radoeva et al. 2012; Schreiner et al. 2014) and psychotic symptoms (da Silva et al. 2011; Debbane et al. 2012; Jalbrzikowski et al. 2014; Kates et al. 2015; Ottet et al. 2013a, b; Perlstein et al. 2014; Scariati et al. 2014).

The studies reporting associations between altered white matter connectivity and psychosis are also heterogeneous, with different directions of FA changes being reported. On the one hand, three studies reported a negative correlation, with decreased FA or AD measures related to increased positive symptoms scores (da Silva et al. 2011; Jalbrzikowski et al. 2014; Sundram et al. 2010). On the other hand, two studies reported a positive correlation between increased FA values in the ALIC (Perlstein et al. 2014) and in the cingulum bundle (Kates et al. 2015) and positive symptoms scores in an overlapping cohort of participants. As noted by (Kates et al. 2015), similar positive correlations between FA values and positive symptoms have been reported in patients with schizophrenia. These authors also argue that this positive correlation may rely on reduced axonal pruning, which would cause a concomitant increase

in the FA values and reduced efficiency of neural transmission. This hypothesis remains, however, speculative.

The majority of the studies included in the present review investigated the relationship between altered connectivity and positive psychotic symptoms, while only one study (da Silva et al. 2011) used also negative and general symptoms scores. As negative symptoms are predominant in the 22q11DS population (Schneider et al. 2014c), their association with white matter dysconnectivity should be better investigated in future studies.

Despite the inconsistency in the results, most of the findings have shown alterations in long-range and midline white matter tracts in patients with 22q11DS. In the following paragraph, we discuss how these alterations may be implicated in the cognitive and clinical symptomatology.

Abnormalities of brain connectivity related to cognitive alterations and psychotic symptoms in 22q11DS

All the studies reporting an association between white matter dysconnectivity and psychotic symptoms (listed in Table 2) have shown an involvement of one or more long-range white matter bundle (cingulum bundle, IFOF, ILF, corona radiata, internal capsule), many of which connecting the frontal lobe. Furthermore, altered connectivity in midline structures (cingulum bundle and corpus callosum) has also been related to psychotic symptoms (da Silva et al. 2011; Kates et al. 2015; Sundram et al. 2010).

Long-range connections sustain the interaction between distant brain regions and ensure brain functional integration (van den Heuvel and Sporns 2013). Functional brain integration is essential for the execution of cognitive functions, and disruption in brain hubs has been reported in several psychiatric disorders (Crossley et al. 2014). In 22q11DS, long-range dysconnectivity may reflect impaired functional integration and communication between distant brain areas. In a previous study (Ottet et al. 2013b), we indeed found reduced efficiency of the brain network in affected patients, related to decreased connectivity of several important brain hubs. As such, reduced long-range connections and impaired efficiency may account for the difficulties observed in patients with 22q11DS, such as deficits in social skills (Campbell et al. 2015; Jansen et al. 2007; Kiley-Brabeck and Sobin 2006; Woodin et al. 2001) and altered executive functions [reviewed in (Antshel et al. 2008)]. Specifically, decreased working memory as well as altered flexibility, planning and inhibition capacities have been reported in 22q11DS (Campbell et al. 2010). A few studies reviewed in the present work confirm the link between long-range and frontal dysconnectivity and cognitive difficulties. Specifically, it has been shown that

alterations in long-range white matter tracts connecting the frontal lobe (i.e. the IFO and SLF) are concomitant with impairments in working memory, executive functions (Radoeva et al. 2012) and social competences (Jalbrzikowski et al. 2014; Radoeva et al. 2012; Schreiner et al. 2014) in patients with 22q11DS. Other studies report a relationship between long-range dysconnectivity and the expression of psychotic symptoms in this population, either positive (da Silva et al. 2011; Debbane et al. 2012; Jalbrzikowski et al. 2014; Ottet et al. 2013a, b; Perlstein et al. 2014) or negative (da Silva et al. 2011; Debbane et al. 2012). Moreover, three studies, in particular, reported altered fronto-temporal connectivity in 22q11DS (da Silva et al. 2011; Ottet et al. 2013a, b). Fronto-temporal dysconnectivity has largely been implicated in the pathogenesis of schizophrenia in the general population (Samartzis et al. 2014) and has been related to the presence of and hallucinations (Ottet et al. 2013a, b) in 22q11DS, further suggesting common mechanisms in syndromic and non-syndromic schizophrenia.

Alterations in midline brain regions have been shown in previous studies investigating brain morphology in 22q11DS. For instance, increased area (Antshel et al. 2005; Machado et al. 2007; Shashi et al. 2004) and volume (Machado et al. 2007; Shashi et al. 2012) of the corpus callosum have been reported and have been related with higher cognitive scores (Shashi et al. 2012), thus suggesting that increased corpus callosum volume may be a compensatory mechanism. Shashi et al. (2012) proposed that increased corpus callosum volume could be driven by either an increased number of axons, an increase in their myelination or an enlargement of the axons' diameter. However, the first two mechanisms are not compatible with the observation of reduced FA in the corpus callosum (da Silva et al. 2011; Sundram et al. 2010), thus suggesting that the more valid hypothesis is the axons enlargement. Future investigations in animal models are needed to confirm whether common mechanisms are present that explain both the increased corpus callosum volume and the reduction of FA.

Midline structures dysconnectivity has been related with psychotic symptoms in 22q11DS (Debbane et al. 2012; Kates et al. 2015; Ottet et al. 2013a; Scariati et al. 2014). For instance, we showed that functional ACC dysconnectivity strongly contributes in identifying patients with 22q11DS that present prodromal positive psychotic symptoms (Scariati et al. 2014). In the general population, ACC dysconnectivity has been involved in several network theories about schizophrenia. This is probably due to the fact that this region is involved in several functions [reviewed in (Bush et al. 2000)] and is part of several networks, including the saliency network and the DMN, where

it plays a role in self-related processing (Murray et al. 2012); (Menon and Uddin 2010; Rosazza and Minati 2011). Recently, it has been proposed that a dysconnectivity between the DMN, the central executive (that includes the dorsolateral prefrontal and dorsal parietal cortices) and the salience networks may be involved in several psychopathologies (Menon 2011; Menon and Uddin 2010), including schizophrenia (Nekovarova et al. 2014). According to this theory, the salience network is dysfunctional and improperly manages the switch between resting and active mental activity, leading to incorrect DMN deactivation when the subject is engaged in a cognitive task. A deficient DMN deactivation has indeed been described in schizophrenic populations, as well as their unaffected relatives [reviewed in (Nekovarova et al. 2014)]. Other complementary models propose that self-monitoring deficits play a role in the development of psychosis (Frith 1992). These deficits correspond to a difficulty in recognizing self-generated from externally generated thoughts or actions and are thought to underlie key symptoms such as alien control or hallucinations. Interestingly, self-monitoring deficits have been related to abnormal functions of medial limbic structures, including the ACC (Allen et al. 2008). Although none of the reviewed studies directly investigated triple network structural and resting-state connectivity in 22q11DS, several studies reported impaired DMN connections (Debbane et al. 2012; Padula et al. 2015; Schreiner et al. 2014). Furthermore, two EEG studies reported impairment in class C and D microstates (Tomescu et al. 2014; Tomescu et al. 2015). These maps have been shown to correspond to salience and executive networks, respectively, in a normative sample of subjects (Britz et al. 2010). More specifically, the time coverage and the occurrence of class D microstate were decreased in youths with the microdeletion, while the opposite was observed for class C microstate. This result has been replicated in a sample of adults with chronic schizophrenia, strongly suggesting common mechanisms in syndromic and non-syndromic psychosis (Tomescu et al. 2015). Finally, it has been shown that patients with the microdeletion also present self-monitoring difficulties (Debbane et al. 2008; 2010) and that ACC dysfunction during a self-referential processing task was correlated with the intensity of positive symptoms in a sample of adolescents with 22q11DS (Schneider et al. 2012).

Limitations

Taken together, existing studies in 22q11DS report a complex pattern of connectivity alterations, among which altered midline and long-range connections are mostly

associated with psychotic symptoms. However, this review comes with some limitations. First of all, several studies have been published by the same groups, so they do not present independent results and likely show congruent findings since they share part of the sample. Therefore, we tried to highlight results reported by independent samples throughout this review whenever possible. Furthermore, given the low prevalence of the 22q11DS, published studies usually include a limited sample of patients with wide or variable age ranges. Studies based on DTI also share some limitations. First of all, exclusion of DTI scans because of excessive motion often relied, except for three studies (Kates et al. 2015; Perlstein et al. 2014; Radoeva et al. 2012), on visual inspection. For this reason, we cannot completely exclude the possibility that residual motion may have affected the results. Second, DTI acquisitions do not allow an accurate reconstruction of fibres that cross, kiss or fan (Bammer et al. 2003). In addition, the number of resting-state fMRI studies is limited in this population, and two studies presented a focus on DMN connectivity, which can provide a bias towards alterations found in this network. Studies targeting other networks of interest will be necessary to confirm whether the DMN is particularly affected in 22q11DS. Furthermore, studies investigating functional connectivity during cognitive tasks may reveal more precise alterations in specific domains.

Conclusion and perspectives

In conclusion, current literature in 22q11DS shows a predominant impairment of long-range connectivity, involving frontal and midline structures. Relationships between these alterations and cognitive deficits or psychotic symptoms have been described. However, future studies on independent samples are needed to confirm these results. Furthermore, new methodologies may be used to overcome the limitations of current literature and to obtain refined brain connectivity measurements. For instance, new DSI sequences that acquire more diffusion directions in a shorter amount of time are today available. This kind of acquisition would provide finer white matter tracts reconstruction while keeping a scanning duration suited to paediatric populations (Cahoon 2011). Further methodological developments will also permit the study of resting-state connectivity dynamics as well as the relationships between structural and functional connectivity alterations. Similarly, functional connectivity studies using task-related fMRI should be used to test current hypotheses about the mechanisms that underlie schizophrenia.

Finally, given the low prevalence of the 22q11DS, collaborations between different groups will be necessary to obtain large samples of patients with smaller age ranges. International collaborative work has been started by the International 22q11.2 Brain Behaviour Consortium (22q-IBBC) that already lead to the publication of results on genetic (Guo et al. 2011; Herman et al. 2012; Mlynarski et al. 2015), cognitive and clinical (Bassett et al. 2011; Schneider et al. 2014a; Vorstman et al. 2015) data including up to 1400 participants with 22q11DS. However, such collaborations will pose particular challenges for neuroimaging studies since the inclusion of different scanning sites and sequences into the same study may increase noise and introduce a systematic bias in the analyses (Focke et al. 2011; Takao et al. 2012). Several research groups are also continuing to acquire longitudinal data with the aim of describing the trajectories of brain structural and functional connectivity development. This on-going work will allow testing whether part of the described connectivity alterations precede psychosis onset and have a predictive value for the development of schizophrenia.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to report.

Appendix

BOX 1: Summary of methods used to measure connectivity in 22q11DS:

Methods for structural connectivity analysis using diffusion tensor imaging (DTI):

- *Voxel-based measures* Measures that describe the properties of water diffusion. In white matter, water molecules are constrained by the cell's structures to diffuse preferentially along the axon axis. Such an environment is called anisotropic, as the probability of water diffusion is not equal in all directions (Basser et al. 1994).

    - *Fractional anisotropy (FA)* FA is a scalar value between 0 and 1 and reflects the degree of

anisotropy in an environment (Armitage and Bastin 2000). It gives information about the microarchitecture of the white matter (Mukherjee and McKinstry 2006).

- *Axial diffusivity (AD)* AD measures the amplitude of water diffusion along the main diffusion direction. Animal studies suggest that AD is a measure of axonal integrity (Budde et al. 2009; Song et al. 2003; Song et al. 2005).
- *Radial diffusivity (RD)* RD measures the amplitude of water diffusion perpendicular to the main diffusion direction. Studies in mouse models suggest that increased RD reflects reduced myelination (Song et al. 2003; Song et al. 2005).

- *Tractography* Tractography algorithms are used to reconstruct the anatomy of the white matter bundles. With this method, virtual fibres (also called streamlines) are initiated in each point of the image and are grown in both directions, point by point, following the main diffusion direction. Thus, the pathway of the major white matter tracts can be reconstructed and the presence of a white matter bundle between two brain regions can be measured by the number of streamlines that connect them (Bammer et al. 2003; Hagmann et al. 2003).

Methods for functional connectivity analysis using resting-state fMRI:

Resting-state fMRI records spontaneous brain activity that takes place during rest, providing information about the intrinsic structure of the functional brain network through the measure of synchrony among brain regions (Biswal et al. 1995; Greicius 2008). Two methods have principally been used in studies about 22q11DS:

- *Independent Component Analysis (ICA)* ICA is a data-driven approach retrieving a set of networks (components) that include regions with a coherent temporal activity (Calhoun et al. 2009; Raichle 2009). These networks are highly consistent across populations and sustain different brain functions, example of such resting state networks include the saliency, auditory, central executive or default mode networks (Rosazza and Minati 2011).
- *Correlation analysis* Correlation analyses are based on the computation of the Pearson's correlation coefficient between time series of predefined regions of interest (ROIs). It can be computed from one ROI to all the points on the brain surface resulting in a complete brain map representing the connectivity of a particular region. Alternatively, the correlation can be computed for a set of ROIs that can eventually cover the whole brain.

Glossary

Connectome	Complete map of brain connections where the brain network is represented as a set of nodes that correspond to brain regions (Hagmann 2005; Sporns et al. 2005). These nodes are connected by edges that can be either structural connectivity (for example tractography measures between a pair of nodes) or functional connectivity measurements (for example correlation analysis between the nodes' time series)
Degree	of a node is the number of edges connecting that node
Hubs	Highly connected nodes providing necessary shortcuts between distant network nodes (Sporns et al. 2007)
Local clustering coefficient	Number of connections between the neighbours of a node (Watts and Strogatz 1998)
Path length	Shortest path connecting pair of regions in the network (Sporns 2006)
Global efficiency	Inverse of the path length (Latora and Marchiori 2001)

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