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Neuroimaging Phenotypes Associated with Risk and Resilience for Psychosis and Autism-spectrum Disorders in 22q11.2 Microdeletion Syndrome

Maria Jalbrzikowski[1]

[1]Department of Psychiatry, University of Pittsburgh School of Medicine

Abstract

Identification of biological risk factors that contribute to the development of complex neuropsychiatric disorders such as psychosis and autism spectrum disorders (ASD) is key for early intervention and detection. Furthermore, parsing apart the biological heterogeneity associated with these neuropsychiatric syndromes will help us understand the neural mechanisms underlying psychiatric symptom development. 22q11.2 Microdeletion syndrome (22q11DS) is caused by a recurrent genetic mutation that carries significantly increased risk for developing psychosis and/or ASD. In this review, I provide an brief introduction to 22q11DS and discuss common phenotyping strategies that are used to assess psychosis and ASD in this population. I then summarize neuroimaging phenotypes associated with psychosis and ASD in 22q11.DS. Next, I discuss challenges within the field and provide practical suggestions to overcome these obstacles. Finally, I end the review with a discussion of future directions for moving 22q11DS risk and resilience research forward.

Psychosis and autism spectrum disorders (ASD) are neuropsychiatric syndromes that share many features, including deficits in cognition, altered language processing and production, and social impairments (1,2). ASD and psychosis also share underlying genetic contributions (3–7). Despite similarities, ASD and psychosis have different developmental onsets. ASD typically presents in early childhood while psychosis onset usually occurs in late adolescence and early adulthood. Gaining a better understanding of biological risk factors contributing these differential trajectories will help identify causes of the illness and treatment targets, facilitating early detection and intervention.

An approach providing valuable insights into the causes of psychosis and ASD is the detailed examination of a more homogeneous subtype, with a known genetic cause. The 22q11.2 Microdeletion Syndrome (Velocardiofacial/ DiGeorge syndrome; 22q11DS) is a compelling model, as 14–50% of 22q11DS youth meet criteria for ASD (22q11DS-ASD+; 8–11) and 23–41% of 22q11DS adolescents and adults meet criteria for a psychotic disorder (22q11DS-psychosis+; 12–18). 22q11-ASD+ individuals ***do not*** have increased risk of later developing psychosis (19,20), suggesting that separate neurobiological mechanisms contribute to the manifestation these syndromes in 22q11DS. The purpose of this review is

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to examine structural and functional neuroimaging factors that contribute to psychosis and ASD in 22q11DS. First, I provide a brief introduction to 22q11DS and discuss phenotyping strategies used to assess psychosis and ASD in 22q11DS. Next, I summarize how brain alterations in gray matter, diffusion-weighted imaging, and resting-state functional magnetic resonance imaging (rsfMRI) in 22q11DS are related to psychotic and ASD symptoms and social impairments. Third, I discuss current challenges faced in field and provide suggestions to overcome these obstacles. I conclude with future directions for 22q11DS risk and resilience research.

An Introduction to 22q11.2 Microdeletion Syndrome

22q11DS is caused by a hemizygous deletion at chromosome 22q11.2, an area that encompasses ~90 genes (~46 protein-coding genes), including those that play a role in neuronal migration, myelination, and brain development (21,22). 22q11DS is the second most common neurogenetic disorder, affecting approximately 1 in 4000 live births (23). 22q11.2 microdeletions range from 1–3 megabases (Mb) in size (24,25), with the most common deletion size being 3 Mb. 22q11DS is most frequently caused by a de novo mutation, although approximately 10% of the cases are inherited from parents (26). While the phenotype of 22q11DS is highly variable, there are common physical characteristics, including craniofacial anomalies, cardiovascular abnormalities, and immune deficiency (27–29). 22q11DS is also distinguished by a characteristic neurocognitive profile: 22q11DS individuals show visuospatial deficits relative to their verbal performance, and often have lower than average full-scale IQ (30,31). While 22q11DS is considered an ideal “human-knock out” model for understanding psychiatric disorders, unique aspects of 22q11DS may also reflect distinct risk and resilience factors within this population.

Psychosis and ASD phenotyping strategies commonly used in 22q11DS

It is important to understand how psychosis and ASD phenotypes are typically characterized in 22q11DS. The Structured Interview for Prodromal Syndromes (SIPS; 32,33), is commonly used to assess psychosis risk in 22q11DS (Figure 1A). Positive symptoms are assessed dimensionally, ranging from no symptoms to psychotic-level symptom severity (Figure 1B). A 22q11DS participant is usually considered to be at “ultra-high risk” for developing psychosis (22q11DS-UHR+) when symptom severity falls within a sub-threshold range. Researchers also compare 22q11DS individuals with a diagnosed psychotic disorder (22q11DS-psychosis+) to 22q11DS individuals who do not meet criteria for psychosis (22q11DS-psychosis-). Psychotic disorder diagnosis is determined from level-6 severity scores on individual positive symptoms and/or through a semi-structured clinical interview. Others combine individuals with sub-threshold and psychotic level severity symptoms (score ≥ 3 on any positive symptom measure), creating a “psychosis-spectrum” group (22q11DS-pychosis-spectrum+) and compare them to 22q11DS individuals without clinically significant positive psychotic symptoms (22q11DS-psychosis-spectrum-). All positive symptom severity scores on the SIPS can be summed to obtain a dimensional measure of psychotic symptoms.

There are important differences in how 22q11DS-UHR+ are assessed in comparison to UHR youth without a known 22q11.2 deletion (idiopathic). Most idiopathic UHR participants meet criteria for "Attenuated Positive Symptom Syndrome", which means they endorse subthreshold positive symptoms that have started or gotten worse in the past year and symptoms are present at least once per week in the past month. In contrast, frequency and onset criteria are not typically used when assessing positive symptoms in 22q11DS. Despite these differences, multiple studies find that positive symptom presentation is similar in 22q11DS in comparison to idiopathic forms of psychotic symptom presentation (14,34,35).

There are also detailed phenotyping measures used to characterize ASD in 22q11DS. ASDs in 22q11DS are commonly determined through: 1) the Autism Diagnostic Observation Schedule (ADOS; 36), and/or 2) the Autism Diagnostic Interview-Revised (ADI-R; 37). The ADOS is a semi-structured interview administered to the youth and elicits behaviors associated with social interactions and communication (Figure 1C). ADOS scores can be used to create a categorical diagnosis (22q11DS-ASD+ vs. 22q11DS-ASD-) or as a dimensional measure of symptom severity (Figure 1C). The ADI-R is a semi-structured interview administered to the youth's primary caretaker; dimensional and categorical approaches in the three domains of social interactions, communication, and repetitive behaviors are also used (Figure 1D). Typically, in idiopathic ASD research settings, an individual must meet the identified cut-offs in all three domains of the ADOS and ADI-R to receive an ASD diagnosis, though there is variability in cut-off criteria for an ASD diagnosis, as the Collaborative Programs for Excellence in Autism (CPEA)-defined ASD diagnostic criteria required social communication deficits on the ADI-R and ADOS, but does not require repetitive behavioral impairments (38). Like the CPEA guidelines, in many 22q11DS-ASD studies, if 22q11DS individuals score below the diagnostic threshold on the repetitive domain, but meet the cut-offs for the other two domains, they are still given an ASD diagnosis (e.g., 39,40).

Two studies have directly compared the 22q11DS-ASD+ phenotype to the idiopathic ASD phenotype (41,42). Both studies found that the severity of repetitive behaviors was similar in the two groups, but 22q11DS-ASD+ had less severe communication impairments in comparison to individuals with idiopathic ASD (41,42). Impairments in joint attention, gestural communication, initiating conversation, as well circumscribed interests are characteristic phenotypes associated with 22q11DS individuals, independent of ASD diagnosis (41,42). Taken together, these findings suggest that a "broader autism phenotype" may be more applicable to the 22q11DS population.

Neuroimaging Factors associated with psychosis and ASD in 22q11DS

A brief description of the neuroimaging metrics covered in this review, as well as possible biological interpretations of these measures, is reported in Table 1.

Grey matter alterations that contribute to psychosis vulnerability and ASD in 22q11DS

Cross-sectional neuroimaging work in 22q11DS provided proof of concept that cortical regions implicated in idiopathic psychosis (43–49) were also altered in 22q11DS-psychosis+ vs. 22q11DS-psychosis- (50,51). Subsequent longitudinal investigations found

that progressive structural changes, particularly in temporal and frontal regions, predicted severity of positive symptoms at follow-up, in those who have or develop sub-threshold psychosis symptoms (52,53) and in 22q11DS-psychosis+ (54,55). Simialrly, a large-scale study compared cortical measures in 22q11DS-psychosis+ vs. 22q11DS-psychosis- and found largest group differences in lower frontal and temporal cortical thickness (56). Effect sizes for these group differences were similar to the cortical thickness differences observed in idiopathic schizophrenia (49). These findings suggest that there are convergent biological mechanisms contributing to progressive cortical gray matter changes in those who develop psychosis, both with and without 22q11DS.

There are also deficits in subcortical regions associated with 22q11DS-psychosis-specturm+. A longitudinal investigation found that, in comparison to 22q11DS-psychosis-spectrum-, 22q11DS-psychosis-spectrum+ exhibited reduced overall hippocampal volumes, an effect driven by CA2/3, CA4, and dentate gyrus subregions (57). In 22q11DS-psychosis-spectrum+, these regions exhibited had a steeper age-related slope, suggesting aberrant hippocampal development contributes to the psychosis onset. Another study found that 22q11DS individuals who endorsed clinically significant auditory hallucinations compared to those who did not had lower baseline volume and steeper age-related slopes in the medial geniculate nuclei of the thalamus (58). Both studies only assessed the sub-regions of one subcortical region, and neither study assessed how change of these metrics (e.g., Visit 2-Visit 1) was associated with psychotic symptoms at follow-up. The ENIGMA 22q11DS Working Group also found subcortical alterations in 22q11Ds-psychosis+, with 22q11DS-psychosis+ exhibiting lower hippocampal, thalamic, and amygdala volumes in comparison to those with 22q11DS-psychosis- (59). In this study, the effect sizes associated with 22q11DS-psychosis+ were similar to multiple psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and obsessive-compulsive disorder (59). Thus, subcortical aberrations in 22q11DS may reflect a general vulnerability for psychiatric disorders and/or illness severity.

Table 1 summarizes published longitudinal investigations relating gray matter changes to 22q11DS psychosis vulnerability. STable 1 summarizes single site cross-sectional grey matter neuroimaging studies of 22q11DS-psychosis-spectrum+. Importantly, the 22q11DS general neuroanatomic phenotype is unlike idiopathic psychosis. Compared to healthy controls, 22q11DS individuals have overall greater cortical thickness and pervasive surface area reductions (56). It is the 22q11DS-psychosis+ vs. 22q11DS-psychosis- comparisons that are similar to idiopathic psychosis vs. controls.

Cross-sectional studies have examined structural grey matter differences in 22q11DS-ASD+ vs. 22q11DS-ASD-. Compared to 22q11DS-ASD-, 22q11DS-ASD+ exhibited increased cortical volume and surface area in the dorsolateral prefrontal regions, posterior cingulate cortices, and temporal areas (39). 22q11DS-ASD+ also had reduced entorhinal volume and surface area (39). An earlier study (which included a subset of participants examined in (39)) found that 22q11DS-ASD+ had thinner parahippocampal cortices and smaller right amygdala volumes than 22q11DS-ASD- (60). However, there is also evidence of increased amygdala volumes in children with 22q11DS-ASD+ vs. 22q11DS-ASD- (8). In contrast, the largest-scale study of idiopathic ASD found increased frontal and decreased temporal

cortical thickness in ASD vs. healthy controls, suggesting that different neurobiological mechanisms may underlie symptom presentation in idiopathic ASD (61).

One study compared cortical measures in 22q11DS-ASD+, 22q11DS-ASD-, idiopathic ASD, and healthy controls. An ASD diagnosis (regardless of deletion status) was associated with increased cortical surface area in insula, superior temporal, fusiform, parahippocampal, lingual, and supramarginal regions, and increased cortical thickness in the isthmus cingulate and the superior temporal gyrus (62). This study conducted a dimensional analysis of ASD phenotypes and found that distinct patterns of neuroanatomic variability were associated with clinical profiles in 22q11DS-ASD+ and idiopathic autism (62). Consistent with these dimensional findings, an investigation of local gyrification indices that differing patterns of abnormalities in 22q11DS-ASD+ vs. individuals with idiopathic autism (63). These findings highlight the importance of comparing 22q11DS-psychosis-spectrum+ and 22q11DS-ASD+ to idiopathic forms of the respective illness.

Diffusion-weighted imaging metrics are related to psychosis and social impairments in 22q11DS

Single site cross-sectional findings of diffusion-weighted abnormalities in 22q11DS-psychosis-spectrum are inconsistent (50,51,56,59,64–77,78, reviewed in STable 2). However, a recent multisite study examined diffusion-weighted imaging measures in 22q11DS-psychosis+ vs. 22q11DS-psychosis- (75), providing a ‘ground truth’ for future investigations of 22q11DS psychosis risk. In comparison to 22q11DS-psychosis-, 22q11DS-psychosis+ had reduced axial diffusivity in multiple white matter tracts, namely those consisting of subcortical-cortical connections (75; reviewed in Table 2). Multiple neurobiological mechanisms could contribute to reduced axial diffusivity in 22q11DS-psychosis+, including axonal damage (79), reduced axonal diameter (80), and/or greater tortuosity in axons (81). A histological examination of postmortem brain tissue of an 22q11DS infant found an increased number of interstitial neurons in comparison to a control group (82). Interstitial neurons are believed to be fetal subplate remnants, and the fetal subplate is involved in guidance and morphogenesis of early development of subcortical-cortical connections (83); disruption of this instruction may contribute to reduced axial diffusivity in 22q11DS-psychosis+.

Unlike the grey matter findings, these 22q11DS-psychosis+ white alterations diverged from ENIGMA Schizophrenia-DTI Working group, which found widespread reduced fractional anisotropy in idiopathic schizophrenia (74). The reduced fractional anisotropy in idiopathic schizophrenia is most often driven by increased radial diffusivity (75, presented in Table 2), possibility reflecting reduced myelination (84). These divergent findings suggest that different white matter neurobiological alterations may lead to similar, downstream phenotypes in 22q11DS and idiopathic forms of the illness.

Though there are no published studies comparing diffusion-weighted imaging measures in 22q11DS-ASD+ vs. 22q11DS-ASD-, impaired social cognition is a core feature of idiopathic ASD and psychosis. Relationships between diffusion-weighted imaging metrics and social cognition have been observed in 22q11DS. Increased axial diffusivity, which may reflect greater axonal coherence, in two association tracts (uncinate fasciculus and inferior

fronto-occipital fasciculus) was associated with better emotion recognition and theory of mind performance (85), features impaired in idiopathic ASD and psychosis (86–89). Future studies should examine to what extent the neural mechanisms underlying social cognition in 22q11DS converge or diverge with risk factors for psychosis and ASD phenotypes.

Altered functional connectivity is related to psychotic symptoms and social impairments in 22q11DS

Multiple cross-sectional studies have investigated effects of psychotic symptoms on rsfMRI in 22q11DS (76,77,90–92) and one study examined the relationship between functional connectivity and a dimensional measure of ASD in 22q11DS (93). The first rsfMRI study of 22q11DS and psychosis found that reduced activation in superior frontal regions was associated with increased total positive symptoms (90). Later, others found that increased positive symptoms in young adults with 22q11DS were associated with increased connectivity between the precuneus and superior frontal cortex (77), brain regions typically believed to be part of the default mode network (DMN). Still, others found no relationship between rsfMRI DMN connectivity and positive symptoms in 22q11DS (91). Support vector machine (SVM) approaches have been used to distinguish between 22q11DS participants with and without psychotic symptoms; variability in within-network connectivity of DMN regions differentiated 22q11DS-psychosis-spectrum+ from 22q11DS-psychosis-spectrum- with a high-degree of accuracy, in both the training sample and an independent validation data set (92). Finally, increased connectivity between DMN regions (e.g., posterior cingulate cortex, medial prefrontal regions and the anterior cingulate cortex) was associated with fewer autism-spectrum behaviors in 22q11DS (93). Taken together, these findings suggest that altered DMN connectivity contributes to psychosis and autism-spectrum symptoms in 22q11DS.

To date, seed-based approaches have not achieved the same level of success as network-based rsfMRI analyses. Consistent with previous studies of idiopathic schizophrenia and individuals at clinical high risk for developing psychosis (94,95), a recent study found over-connectivity between the thalamus and somatosensory regions and under-connectivity between the thalamus and cerebellum in 22q11DS vs. controls. However, machine-learning techniques did not differentiate 22q11DS-UHR+ vs. 22q11DS-UHR with sufficient accuracy, nor were there significant relationships between thalamic connectivity patterns and psychotic symptoms (78).

Novel approaches to rsfMRI connectivity analyses highlight their potential for understanding 22q11DS psychosis and ASD risk. An examination of dynamic “brain states” across a rsfMRI session found that longer anti-coupling (i.e., one region exhibits increased activation while another shows decreased activation) between the dorsolateral prefrontal cortex and anterior cingulate was associated with higher positive symptoms in 22q11DS (96). Studies have also identified relationships between altered graph theory metrics, which measure network connectivity, and increased psychotic symptoms in 22q11DS (96,97). Future studies should examine these metrics in multisite, longitudinal samples and determine to what extent group differences are observed in 22q11DS-ASD+ vs. 22q11DS-ASD-.

Challenges faced in 22q11DS risk research

This review highlights some of the challenges we face in understanding psychosis and ASD in 22q11DS, including: 1) phenotyping issues and 2) the need to incorporate the role of development into future studies.

Phenotyping challenges in psychosis and ASD in 22q11DS

First, there is no consistent method for determining 22q11DS psychosis-spectrum status. Some studies restrict comparisons to 22q11DS-psychosis+ vs. 22q11DS-psychosis- (56), some include individuals experiencing subthreshold symptoms and those with full-blown psychotic symptoms (57), and some focus specifically on individuals experiencing sub-threshold psychotic symptoms (53). Whilst all approaches have value, I propose that, in future, researchers specify their main approach to psychosis-classification in the primary analyses, and report alternative approaches in supplemental, exploratory analyses. Also, because 22q11DS-ASD neuroimaging research has found that categorical and dimensional approaches provide complementary information (40), it will be important to assess psychosis dimensionally.

Regardless of classification strategy, psychotic symptoms are not always stable in 22q11DS (98,99). In 22q11DS participants who presented with psychotic symptoms at the baseline assessment, 55–61% continued to endorse psychotic symptoms at follow-up, while the remainder experienced symptom remission (98,99). In 22q11DS youth who did not endorse psychotic symptoms at baseline, 13–39% adolescents endorsed emergent symptoms at follow-up (98,99). Researchers must fully characterize psychotic symptoms at baseline and follow-up assessments in 22q11DS. It is important to include variation in symptom severity at the baseline assessments as a predictor when assessing symptom severity at follow-up. This approach is not typically employed in longitudinal studies 22q11DS-psychosis-spectrum+; many studies only include symptom measures at follow-up. Omitting this measure from statistical models is likely leaving out an important source of variation. Finally, other assessment methods may better capture psychotic symptom fluctuations in 22q11DS, like ecological momentary assessment.

We also face phenotyping challenges in understanding neurobiological risk factors for 22q11DS-ASD+. The reported prevalence 22q11DS-ASD+ is highly variable across studies, which may be due to: 1) wide-ranging methodological differences in clinical assessment, 2) ASD diagnosis in 22q11DS possibly reflecting a generalized social impairment, distinct from idiopathic autism (103), and/or 3) core autism behaviors often being recognized as characteristic phenotypes in individuals with 22q11DS regardless of ASD diagnosis (42). One way to mitigate this challenge is with a detailed phenotyping study that includes social cognition, social functioning, and comprehensive ASD assessments, examining how these metrics are related to and/or distinct from each other. Additionally, the temporal stability of ASD symptoms in 22q11DS is not known; it will be essential to examine 22q11DS-ASD symptom fluctuations over time.

Finally, studies rarely report both ASD and psychotic symptoms. Previous 22q11DS-ASD+ neuroimaging results remained significant when 22q11DS-psychosis+ were removed from

analyses and when psychotic symptoms were included as a covariate; furthermore, ASD and psychotic symptoms were not correlated (40). Similar approaches are necessary for future investigations. It will also be important to determine what extent of the variance is shared in categorical and dimensional measures of ASD and psychotic symptoms in 22q11DS.

It is essential to incorporate development into 22q11DS risk and resilience research

Another methodological challenge facing 22q11DS research is understanding how development affects onset of symptoms. Most studies report on participants that fall within a large age range, and well-established work shows significant age-associated brain changes across development (104–106). Though most published research covaried for age in analyses, neurobiological factors may exert differential influences on symptomatology at distinct points in development (60,107), resulting in developmentally-specific risk markers. One solution is to use a time-varying analytic approach to characterize how connectivity measures relate to individual differences at different stages of development (60,108). Furthermore, it is important to obtain an accurate estimate of normative age-effects and to identify how 22q11DS neuroimaging profiles deviate from them. Using growth charting methods, deviations from normative age-associated trajectories were linked to psychopathology, suggesting that age-deviation phenotypes provide meaningful information (109,110). Tracking within-subject deviations from normative development in 22q11DS, in reference to an accurately quantified neurodevelopmental growth chart (111), will be informative for understanding risk and resilience to ASD and psychosis in 22q11DS.

Future Directions

I conclude with a discussion of key areas of future focus for 22q11DS risk and resilience research. I discuss the necessity of investigating links between neuroimaging metrics and transdiagnostic psychiatric conditions, the need to conduct resilience research, the importance of large-scale, longitudinal investigations, and the need to link genes to risk and resilience factors.

Importance of transdiagnostic research in 22q11.2 Microdeletion Syndrome

Most 22q11DS individuals meet criteria for at least one psychiatric disorder (47–85%; 53,57,58,112,113). Despite this finding, the transdiagnostic neuroimaging alterations common across psychiatric disorders in 22q11DS are unknown. This is important for earlier identification of 22q11DS high-risk youth and can be probed with existing longitudinal neuroimaging data sets. In addition, future studies of risk factors in 22q11DS could use a data-driven transdiagnostic approach derived from empirical investigations of psychological symptom co-occurrence (114,115). Indeed, elevated levels of mood and anxiety predispose 22q11DS youth for later developing psychosis (as reviewed in 116). Others have highlighted the importance of studying constructs that cut across psychiatric diagnostic boundaries, such as emotion regulation, in 22q11DS (117).

A need to focus on resilience in 22q11DS research

Given that many 22q11DS participants have a psychiatric disorder diagnosis, this deleted suite of genes clearly confers increased risk for psychiatric disorders. However, how

do we assess resilience within 22q11DS? Resilience processes are increasingly framed as ‘the dynamic outcome of a dynamic process of successful adaptation to adversity” (118). Is the absence of a psychiatric disorder sufficient to determine that a 22q11DS individual is “resilient”? Researchers must assess perspectives of individuals with lived experience of 22q11DS to understand how they view resilience. Additionally, resilience is a complex construct with temporal aspects that can be measured on multiple levels (119,120). Furthermore, evidence suggests that that one-time measurements of responses to resilience questionnaires are poor predictors of mental health outcome (121). To accurately characterize resilience in 22q11DS, large, longitudinal studies must be implemented to assess the dynamic and multidimensional nature of resilience. Furthermore, consistent with the need for a transdiagnostic approach, neurobiological mechanisms underlying resilience must be “dysfunction specific”, not “disorder-specific’ (121).

To date, there are no published studies linking resilience to neuroimaging phenotypes \in 22q11DS. There is evidence that the reciprocal condition, duplication at the 22q11.2 locus, protects against schizophrenia (122,123). One neuroimaging study found, compared to controls, individuals with 22q11.2 deletions and 22q11.2 duplications had opposing structural brain alterations (124). Protection against psychosis may have neurobiological underpinnings in brain regions with a 22q11.2 gene dosage effect and should be related to measures of resilience.

It is also necessary to characterize how modifiable factors protect against psychopathology in 22q11DS. Higher socioeconomic status is associated with improved psychological functioning in 22q11DS (127). High quality peer relationships, greater parental warmth, and lower levels of neuroticism all contribute to resilience to psychopathology in other high-risk cohorts (128–130), and are potential targets for future investigation to better understand resilience in 22q11DS. Finally, the presence or absence of unique features associated with 22q11DS (e.g., craniofacial or cardiovascular anomalies) may contribute resilience (and/or risk) within this population.

Longitudinal approaches must become the norm in 22q11DS risk and resilience research

22q11DS neuroimaging studies must continue to shift to prospective, risk- and resilience-based studies. Longitudinal investigations of 22q11DS-ASD risk factors have not been conducted. Prospective fetal and infant studies found that distinct neurobiological abnormalities reflect an increased likelihood of later developing idiopathic ASD (131; see 132 this issue). It will be important to conduct prospective neuroimaging studies of 22q11DS infants to see if a similar pattern emerges. Retrospective analyses of fetal MRI may prove useful, as existing evidence shows that 22q11DS-psychosis-spectrum+ are more likely to have incidental radiological findings than 22q11DS-psychosis-spectrum- (133). It may be possible to use fetal and infant clinical MRIs paired with later ASD evaluations to conduct similar investigations in 22q11DS.

As longitudinal designs become more prevalent in 22q11DS research, it is important to focus on statistical rigor. To identify a true risk factor, a study must assess if a baseline predictor contributes to a *later* outcome. Neurobiological change over time is an important question; however, this question addresses how brain changes shift in concordance with

clinical symptomatology, or how neural changes drive later behavioral change. Second, when assessing many neuroimaging variables, correcting for multiple comparisons is essential. If many variables are assessed, it may be more fruitful to focus on feature selection techniques or dimension reduction techniques. Finally, to ensure sufficient power in analyses, we must conduct multisite, prospective investigations of 22q11DS neurobiological risk and resilience factors, similar to the work conducted in UHR psychosis(135,136).

Linking genes within the 22q11.2 locus to neuroimaging phenotypes associated with risk and resilience

If separate neurobiological risk factors underlie psychosis and ASD phenotypes in 22q11DS, then, presumably differing genes within the 22q11.2 locus contribute to these phenotypes. Preliminary evidence suggests that 22q11 deletion size influences clinical and neurobiological phenotypes (56),(137), while another investigation of the 22q11.2 transcriptome found that separate gene co-expression networks were associated with ASD and psychosis (138). However, these networks consisted of genes outside the 22q11.2 locus, suggesting that downstream genomic interactions may drive these phenotypic differences (138). Future research is necessary to understand how genes inside and outside the 22q11.2 locus are related to risk and resilience in 22q11DS.

Conclusions

To date, studies find reduced fronto-temporal cortical thickness in 22q11DS-psychosis+ and idiopathic psychosis, suggesting convergence of grey matter neural mechanisms underlying psychosis onset. Preliminary work suggests that 22q11DS-ASD+ have increased surface area in specific brain regions compared to 22q11DS-ASD-. Together, these findings provide support for differential neurobiological mechanisms underlying risk for psychosis and ASD in 22q11DS. However, white matter alterations in 22q11DS-psychosis+ are markedly different from the idiopathic psychosis, suggesting that distinct white matter neural mechanisms contribute to psychosis onset in these groups. Finally, rsfMRI work suggests that DMN alterations are important for both psychosis and social impairments in 22q11DS. In the future, research must focus on development, longitudinal investigations, statistical rigor, and transdiagnostic risk factors, as well as resilience, in 22q11DS psychiatric research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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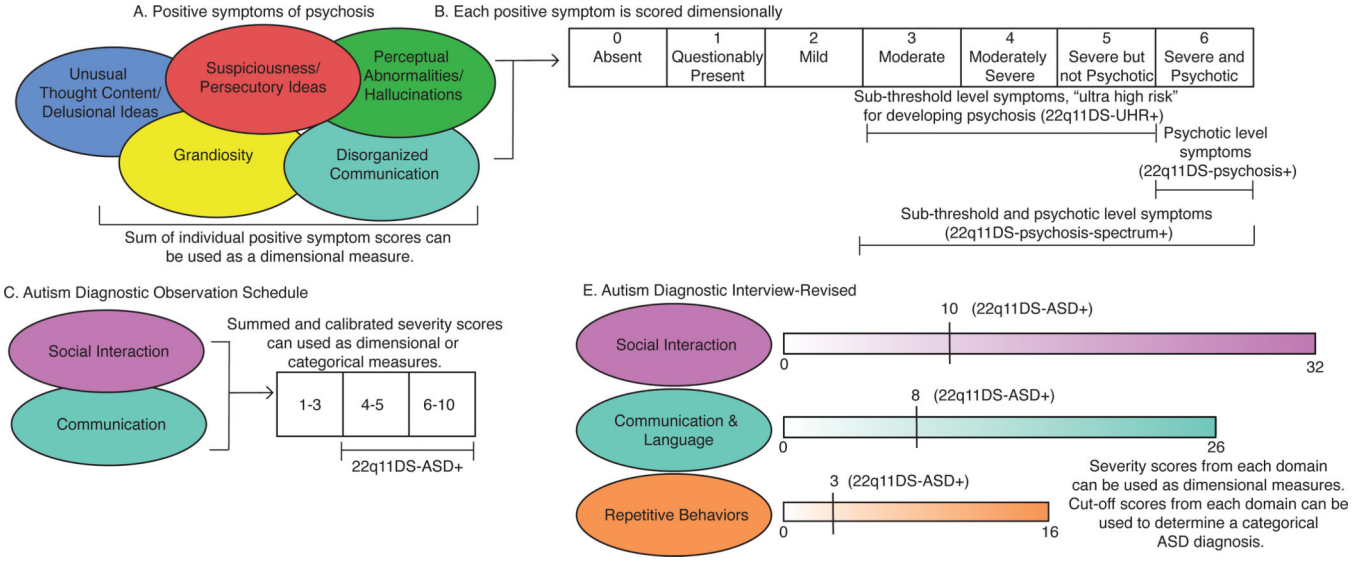

Table 1.

Definitions and possible biological interpretations of the neuroimaging metrics covered in this review.

T1-weighted (Gray matter) neuroimaging: morphometry of brain structure is measured.		
Measure	**Definition**	**Possible Biological Interpretation**
Cortical Thickness	The thickness of the cerebral cortex, measured from the pial surface to the white/gray matter boundary in the cortex.	Number of neurons in ontogenetic columns (139).
Surface Area	Total area of a particular brain region	Measure of proliferation of radial unit progenitors (139).
Local Gyrification Index	Amount of cortex buried within the sulcal folds as compared with the amount of cortex on the outer visible cortex.	Believed to reflect early brain development, as cortical folding is determined in the first months of life.
Diffusion-weighted neuroimaging: measures how fast water diffuses across a space; greater diffusion indicates that there is more restriction in the opposing directions.		
Measure	**Definition**	**Possible Biological Interpretation**
Fractional anisotropy	a general metric of overall white matter integrity	Greater fractional anisotropy is typically associated with higher white matter integrity.
Axial diffusivity	diffusion of water parallel to white matter fibers	Decreased axial diffusivity is associated with axonal damage (140).
Radial diffusivity	diffusion of water perpendicular to white matter tracts	Increased radial diffusivity is associated with demyelination (84,141,142).
Mean diffusivity	measure of the magnitude of diffusion	Greater mean diffusivity is typically associated with greater white matter pathology.
Resting-state functional magnetic resonance imaging: measures spontaneous fluctuations in neural activity. A functional MRI is acquired in the absence of a task (i.e., participant lies in the scanner while awake but does not engage in a task).		
Measure	**Definition**	**Possible Biological Interpretation**
Network-Based Connectivity	Multiple individual brain regions that are more likely to correlate with each other are in the same network.	Varies based on network connectivity measure being assessed.
Seed-Based Connectivity	One region of the brain is chosen as the “seed” region (e.g., thalamus). Correlations between the time series extracted from this region and other regions of the brain are assessed. “Other regions” may consist of specific regions of interest or the entire rest of the brain.	Higher levels of correlation between two brain areas suggests that there is greater coupling between the two regions.

Table 2.

Summary of studies to date that use a longitudinal framework to examine relationships between neuroimaging metrics and psychotic symptoms in 22q11DS. The majority of studies also studied a control sample; however, this table presents comparisons within the 22q11.2 Microdeletion Syndrome (22q11DS) sample because this review focuses on psychosis risk within this group. N=Number; T1=time point 1; T2=time point 2; T3=time point 3; T4=time point 4; 22q11DS-psychosis+=22q11DS individuals with a psychotic disorder diagnosis; 22q11DS-psychosis-=22q11DS individuals who do not have a psychotic disorder diagnosis; 22q11DS-psychosis-spectrum+=22q11DS individuals that had subthreshold and/or psychotic level positive symptoms; 22q11DS-psychosis-spectrum-=22q11DS individuals who did not have clinically significant positive symptoms; CSF=cerebrospinal fluid; ROI=region of interest; SIPS=Structured Interview for Prodromal Syndromes; *Berhanu et. al. 2016 was a study of 22q11DS participants who had four time points but T1 and T4 were the focus of the study.

Author and year	**Total N 22q11DS**		**Neuroimaging predictors examined**	**Analysis conducted**	**Results**
	N 22q11DS-psychosis+ at T1	**N 22q11DS-psychosis+ at final follow-up**			
	Age Information (e.g., range, mean ± SD)				
	Number of time points Approximate length of time between each time point				
Gothelf et al. 2007 (16)	Total N 22q11DS=19		Semi-automated segmentation: cortical lobes (frontal, parietal, temporal, occipital), cerebellum, ventricular CSF (143) Manually delineated ROIs: caudate, amygdala, hippocampus, superior temporal gyrus (144–146)	Analysis: Repeated measures analysis of variance Between-subjects factor: Group; Within-subjects factor: brain volumes at T1 and T2	No significant differences in developmental trajectories between 22q11DS-psychosis+ vs. 22q11DS-psychosis-
	N 22q11DS-psychosis+ at T1=0	N 22q11DS-psychosis+ at T2=7			
	Age range: 5–20 years Mean age (±SD) 12.3±4.0 years				
	2 time points Mean 4.9 (± 0.7) years between time points				
Kates et al., 2011 (52)	Total N 22q11DS=72		Semi-automated segmentation (147–150) Manually delineated ROIs: frontal lobe subregions, amygdala, hippocampus, superior temporal gyrus, cerebellum, ventricles (145,146,151–155)	Analysis: Poisson zero-inflated regression Predictors: ((T2 volume-T1 volume) * 100) / (T1 volume * interval between scans in years) for each segmentation or ROI Outcome: Total SIPS positive symptom score at T2	Greater decreases in superior temporal gyrus volume (T1-T2) predicted higher positive symptom scores at T2
	N 22q11DS-psychosis+ at T1=0	N 22q11DS-psychosis+ at T2=0			
	Age range: 9–15; Mean age (±SD): 11.9 (±2.1) years				
	2 time points ~3 years between time points				
Kunwar et al., 2012 (156)	Total N 22q11DS=58		Gyrification index of frontal, temporal, parietal, and occipital lobar ROIs	Analysis: Poisson zero-inflated regression Predictors: T2 gyrification index-T1 gyrification index for each ROI Outcome: Total SIPS positive symptom score at T2	Greater decreases in occipital gyrification index (T2-T1) predicted higher positive symptom scores at T2
	N 22q11DS-psychosis+ at T1=0	N 22q11DS-psychosis+ at T2=0			
	Age range: 9–15 years Mean age: 14.9±2.5 years				
	2 time points ~3 years between time points				

Author and year	Total N 22q11DS N 22q11DS-psychosis+ at T1 / N 22q11DS-psychosis+ at final follow-up Age Information (e.g., range, mean ± SD) Number of time points Approximate length of time between each time point	Neuroimaging predictors examined	Analysis conducted	Results
Berhanu et al., 2016 (157)	Total N 22q11DS=73 N 22q11DS-psychosis+ at T1=0 / N 22q11DS-psychosis+ at T4=Not reported. Age range: 9–15 years Mean age (±SD) 12.1 ± 2.2 years 2 time points* ~12 years between time points examined	Cortical volume-to-amygdala ratios for 68 ROIs from Desikan atlas (158)	Analysis: Poisson zero-inflated regression Predictors: Cortical volume-amygdala ratios at T1; Outcome: Total SIPS positive symptom score at T4	Lower anterior cingulate to amygdala volume ratios at T1 predicted higher levels of positive symptoms at T4 Higher occipital to amygdala volume ratios and parietal to amygdala volume ratios at T1 baseline predicted higher positive symptom scores at T4
Ramanathan et al., 2017 (54)	Total N 22q11DS=72 N 22q11DS-psychosis+ at T1=0 / N 22q11DS-psychosis+ at T3=6 Age range: 9–18 years Mean age: 11.8 years 2–3 time points ~3 years between each time point	Cortical thickness and surface area for 5 lobes: frontal, parietal, temporal, occipital and cingulate. Followed up with examination of individual brain regions in any lobe that showed a differential trajectory in 22q11DS vs. controls.	Analysis: Mixed model regressions Model 1: Age*Group (22q11DS-psychosis-spectrum+ vs. 22q11DS-psychosis-spectrum-) Model 2: Age*Group (22q11Ds-psychosis+ vs. 22q11DS-UHR+ vs. 22q11DS-psychosis-spectrum) Model 3: Age*Total SIPS positive symptom score at T3 Outcomes: neuroimaging ROIs	Model 1: Accelerated decreases in superior frontal cortical thickness in 22q11DS-psychosis-spectrum+ vs. 22q11DS-psychosis-spectrum- Model 2: Accelerated decreases in frontal cortical thickness in 22q11DS-psychosis+ vs. others Model 3: steeper linear trajectories in occipital and parietal cortical thickness are associated with higher positive symptoms at T3
Mancini et al., 2019 (57)	Total N 22q11DS=107 N 22q11DS-psychosis+ at T1=not reported. / N 22q11DS-psychosis+ any time point=20 Age range: 6–35 years Mean age (±SD): 13.5 ± 6.4 years 1–5 time points Mean 3.8 (± 1.07) years between each time point	whole hippocampal volume; hippocampal subfields	Analysis: Mixed model regression Predictors: Age*Group (22q11DS-psychosis-spectrum+ vs. 22q11DS-psychosis-spectrum-) Outcomes: hippocampal ROIs	Group effect: reduced bilateral whole hippocampal volume, reduced bilateral subregions: CA2/CA3, CA4, dentate gyrus, Group x age effect: Steeper decrease in left whole hippocampus in 22q11DS-psychosis-spectrum+ Effect driven by sub-regions: CA2/CA3, CA4, and dentate gyrus
Mancini et al., 2020 (58)	Total N 22q11DS=120 N 22q11DS-psychosis+ at T1=not reported. / N 22q11DS-psychosis+ any time point=20 Age range: 8–35 years Mean age (±SD): 17.7 ± 6.0 years 1–4 time points ~3 years between each time point	whole thalamus volume, thalamic sub-regions	Analysis: Mixed model regression Predictors: Age*Group (22q11DS-hallucinations+ vs. 22q11DS-hallucinations-) Outcome: thalamic ROIs	Group effect: reduced bilateral medial geniculate nuclei in 22q11DS-hallucinations+ vs. 22q11DS-hallucinations- Group x age effect: Steeper decrease in medial geniculate nuclei 22q11DS- hallucinations+

Table 3.

A). Names of white matter tracts that were disrupted in the largest diffusion-weighted imaging study to date of 22q11DS-psychosis+ vs. 22q11DS-psychosis- (75) B). The known anatomical region connected by each white matter tract. C). Direction of the effects in 22q11DS-psychosis+ vs. 22q11DS-psychosis- study and type of diffusivity measures altered. D). Direction of effects for largest diffusion-weighted imaging study to date of idiopathic schizophrenia vs. healthy controls and type of diffusivity measures altered (159).

A. Region	**B. Anatomical brain structures known to be connected by this white matter tract**	**C. 22q11DS-psychosis+ vs. 22q11Ds-psychosis-**	**D. Idiopathic schizophrenia vs. healthy controls**
Anterior limb of internal capsule	anterior and medial thalamic nuclei⇔ prefrontal cortex (160) pons⇔frontal cortex	↓ AD	↓ FA, ↓ AD, ↑ RD
Posterior limb of internal capsule	Pons/cerebellum⇔premotor and primary motor cortex Ventral thalamus⇔premotor and primary motor cortex	↓ MD	No measures statistically significant
posterior thalamic radiation	pulvinar and lateral geniculate thalamic nuclei ⇔ posterior parietal and occipital cortex (161)	↓ AD	↓ FA, ↑ MD, ↑ RD
sagittal stratum	Thalamus and brainstem ⇔ parietal, occipital, cingulate, and temporal regions of cortex (162)	↓ AD	↓ FA, ↑ MD, ↑ RD
cingulum of cingulate gyrus	Orbitofrontal cortex ⇔ cingulate gyrus ⇔ temporal lobes (163)	↓ AD	↓ FA, ↑ MD, ↑ RD
superior longitudinal fasciculus	Parietal lobes ⇔ frontal lobes (164)	↓ AD	↓ FA, ↑ MD, ↑ RD
Genu of the corpus callosum	Callosal fibers (interhemispheric)	↓ RD, ↓ MD	