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Are You Maximizing Your Multimodal, Longitudinal Dataset? Toward an Integrated Framework for Advancing Psychosis Research

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Psychosis represents a cluster of symptoms that includes alterations in thoughts and perceptions, often leading to a loss of contact with reality. It is characterized by hallucinations (sensory experiences that lack an external stimulus), delusions (fixed false beliefs that persist in the face of counterevidence and are not consistent with the person's cultural norms), and disorganized thinking, speech, and behavior. It is also a core feature of schizophrenia spectrum disorder and other psychotic disorders (1). Although the precise neural mechanisms of psychosis remain elusive, dysconnectivity—disruptions in structural and functional interactions between brain regions—has consistently been hypothesized to be a key mechanism underlying psychotic symptoms (2). Indeed, empirical evidence from earlier structural and functional connectivity studies has revealed a significant association between dysconnectivity among various brain regions and psychotic symptoms in schizophrenia (3). However, most previous studies adopted a unimodal approach and treated structural and functional connectivity as distinct entities. While these studies provided valuable insights, separating functional and anatomical information largely overlooked the fact that brain function is influenced, to a significant extent, by the underlying brain structure, such as white matter pathways (4). Moreover, there is evidence that coupling strengths between structure and function vary across different brain regions and functional domains (5). Therefore, multimodal approaches that integrate structural and functional information could potentially offer biologically plausible insights into the neural mechanisms of psychosis.

Various approaches have been developed by researchers to relate structural and functional measures obtained from different neuroimaging techniques, such as diffusion-weighted imaging, which could reveal white matter pathways (i.e., structural connectivity), and functional magnetic resonance imaging (fMRI), which could reveal neuronal activity patterns (i.e., functional connectivity). For example, drawing on the graph signal processing framework, Preti and Van De Ville (5) applied classical signal processing techniques within a graph-based context to analyze human brain imaging data and introduced a metric known as the structural-decoupling index (SDI) to quantify the coupling strength between structure and function in brain regions.

In 2022, Bortolin *et al.* (6) explored how regional functional-structural dependency (FSD), measured by SDI, contributes to positive psychotic symptoms (PPS) in adults with 22q11.2 deletion syndrome (22q11.2DS)—a multisystem neurogenetic disorder recognized as one of the greatest genetic risk factors for developing psychosis (7). Individuals with 22q11.2DS have an elevated risk of developing psychosis compared with the general population, with approximately 20% to 25% of these individuals being diagnosed with schizophrenia by adulthood. Compared with healthy control individuals, 22q11.2DS carriers with more severe PPS exhibited stronger FSD in the parahippocampal gyrus and subcortical dopaminergic regions, and weaker dependency within the cingulate cortex. These findings revealed neurological alterations in 22q11.2DS that would not have been identified by examining the 2 modalities independently, underscoring the value in integrating multimodal information in similar investigations.

In addition to a heightened risk for psychosis, 22q11.2DS is often associated with developmental abnormalities such as congenital heart diseases, dysmorphic facial features, and a weakened immune system (7). As a result, 22q11.2DS is typically diagnosed early in life. This early diagnosis offers researchers a unique and valuable opportunity to follow these individuals from a young age to study the emergence of psychotic symptoms and neurological alterations. In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Forrer *et al.* (8) extended their investigation of FSD alterations in adults with 22q11.2DS (6) to study the emergence and development of FSD in a longitudinal sample of 22q11.2DS carriers.

Forrer *et al.* (8) mapped the neurodevelopmental trajectory of function-structure coupling from childhood to adulthood (7–34 years of age) in both healthy control individuals and individuals with 22q11.2DS and examined the relationship between FSD maturation patterns and positive psychotic symptoms. Clinical and multimodal imaging (T1 MRI, resting-state fMRI, and diffusion-weighted imaging) data were collected from 125 healthy control individuals and 108 22q11.2DS carriers over the course of 12 years. Each participant completed 1 to 5 study sessions, resulting in a total of 391 scans. Forrer *et al.* quantified the FSD of each scan by calculating the SDI using the resting-state fMRI and diffusion-weighted imaging data and applied longitudinal multivariate partial least squares correlation (PLSC) to investigate FSD alterations across the 2 groups and among 22q11.2DS carriers with and without mild to moderate PPS (Figure 1).

PLSC is a multivariate statistical method widely applied in human neuroimaging research to explore relationships between 2 sets of data (usually denoted as matrices **X** and **Y**) from different modalities within the same set of observations, such as behavioral and brain measures collected in a study. PLSC identifies shared information between the 2 matrices by decomposing them using singular value decomposition and extracting latent variables that are linear combinations of the original variables with maximal covariance (9). In the study, the brain data matrix (**X**) consisted of regional SDI values from selected regions of interest

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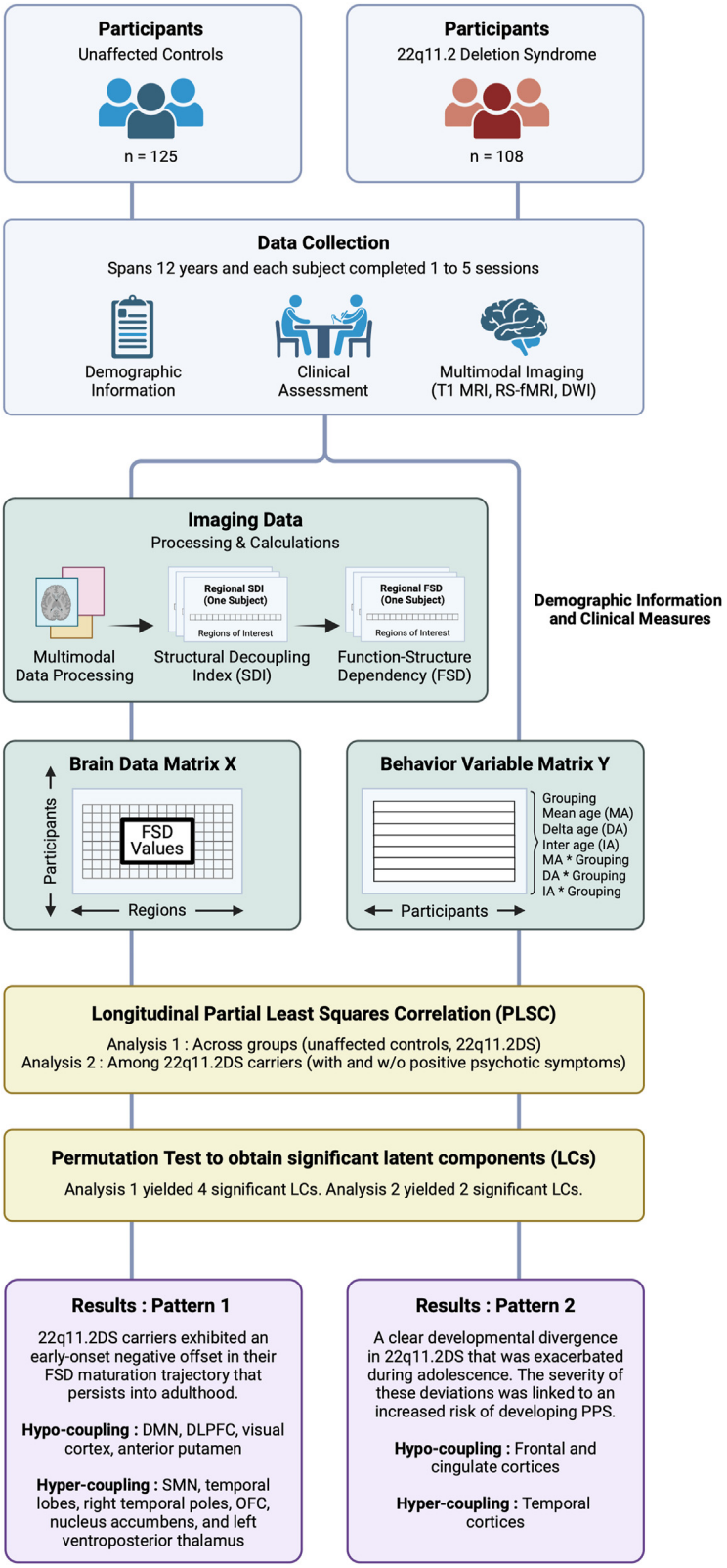

Figure 1. Schematic diagram summarizing the experimental pipeline and highlighted findings in Forrer *et al.* (8). 22q11.2DS, 22q11.2 deletion syndrome; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network (precuneus, parahippocampus, retrosplenial cortex, superioparietal cortex, and temporal lobe); DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PPS, positive psychotic symptoms; RS-fMRI, resting-state functional MRI; SMN, somatomotor network (motor, premotor, sensorimotor, and auditory).

across all participant visits. The authors took the longitudinal aspect into account by including mean age, delta age, and interage constructs in the behavior variable matrix (**Y**).

The PLSC analyses demonstrated altered FSD development in 22q11.2DS and revealed deviation patterns in FSD that were associated with PPS. Specifically, individuals with 22q11.2DS exhibited an early-onset negative offset in their FSD maturation trajectory that persisted into adulthood, indicating a continuous developmental gap between 22q11.2DS carriers and healthy control individuals. A diverse array of brain regions of hyper- and hypocoupling was implicated, including areas within the default mode network, somatomotor network, prefrontal cortex, and various subcortical regions. These regions are broadly involved in higher cognition and motor coordination, aligning with behavioral deficits commonly experienced by 22q11.2DS carriers. In addition, there was a clear developmental divergence in individuals with 22q11.2DS, with regions including the frontal and cingulate cortices exhibiting less coupling and areas such as the temporal cortices showing increased coupling relative to healthy control individuals. Notably, this pattern was exacerbated during adolescence, and the severity of these deviations was linked to an increased risk of developing PPS.

Overall, the results presented by Forrer *et al.* (8) offer crucial insights into the neurodevelopmental trajectory of function-structure coupling in 22q11.2DS and its relevance to the emergence of psychotic symptoms. Their longitudinal analysis, spanning childhood to adulthood, provides compelling evidence of abnormal developmental trajectories of region-specific FSD in 22q11.2DS that are consistent with functional deficits experienced by 22q11.2DS carriers. Furthermore, by demonstrating that the divergence in FSD maturation is exacerbated during adolescence, particularly among 22q11.2DS participants with mild to moderate PPS, the study supports the notion that psychosis could stem from atypical neurodevelopment during this crucial developmental stage. Such findings not only deepen our understanding of the neural mechanisms underlying psychotic symptoms but also provide valuable insights into potential early detection and sensitive periods for intervention.

Psychosis is a complex condition that lies at the core of several disorders and can also manifest due to other underlying conditions, and the findings from this study examining psychotic symptoms in 22q11.2DS may not generalize broadly to the larger population affected by psychosis. A promising future direction to advance our understanding of the neuropathology of psychosis is to apply similar methods to investigate the relationship between FSD and PPS across different populations affected by psychosis. As SDI is computed as a ratio of multimodal MRI data collected under the same condition (usually in the same scanning session), aggregating SDI from multiple studies is less sensitive to issues associated with directly combining raw data from different sites, scanners, and studies. Therefore, this approach is less prone to methodological challenges and has the potential to reveal shared patterns or differences across various disorders affected by psychosis.

Lastly, the work by Forrer *et al.* (8) highlights the value of integrating multiple neuroimaging modalities to capture biologically plausible brain alternations in the investigation of brain-behavior relationships. Despite the collection of multimodal data in many studies, analyses often remain unimodal due to logistical and methodological challenges. However, the growing application of multivariate techniques in neuroimaging research, such as PLSC as used in this study, as well as canonical correlation analysis, graph-based methods, and deep learning approaches, demonstrates the feasibility and benefits of integrated analyses (10). Moving toward an integrated framework allows researchers to leverage the complementary strengths of different modalities, providing a more holistic understanding of brain function and dysfunction across various conditions. This framework not only enhances the robustness of findings but also holds promise for uncovering novel biomarkers and therapeutic targets for personalized medicine in psychiatry.

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Article Information

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