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Commentary

The Duration of Untreated Psychosis and Frontostriatal Connectivity: Toward Understanding the Impact of Untreated Psychosis on Brain Function

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Understanding the impact of the duration of untreated psychosis (DUP) on outcomes and brain health is a major priority in the field. The median DUP in the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study was a shocking 74 weeks (1). One can only imagine the outcry if young people with acute, life-threatening, non–mental health conditions went untreated for longer than 1 year. While it is increasingly clear that a longer DUP is associated with a poorer outcome, clear evidence of the effect of the DUP on brain structure or function has the potential for major public health impact and potential advocacy for better systems of care.

Well-designed studies examining the effects of DUP on brain structure or function are few and far between. We attempted a meta-analysis and systematic review of the effects of DUP on brain structure (2). However, the lack of high-quality study designs and the lack of consistent approaches prevented a meta-analysis. Disappointingly, the main conclusion we could draw from the systematic review was that studies were insufficiently well-designed to achieve any major advance in knowledge.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Manivannan *et al.* (3) examine the association between DUP and frontostriatal connectivity during maintenance of visuospatial working memory. Manivannan *et al.* (3) included 37 patients with a first episode of psychosis (FEP). As is typical of FEP studies, patients' DSM-IV diagnoses ranged from schizophrenia to psychotic disorder not otherwise specified. However, Manivannan *et al.* (3) did not include individuals with a concurrent mood disorder in order to make it less likely that an affective psychotic disorder would be included. This decision diminishes the generalizability of the findings. Similarly, those with a substance-induced psychotic disorder were not included. Recent epidemiological data suggest that nearly 50% of patients with cannabis-induced psychosis go on to develop either schizophrenia or bipolar disorder (4). While it is perhaps more rigorous from a research method point of view to include only those patients with FEP that is immediately tied to a primary psychotic disorder, the real-world situation is different. In emergency departments and the growing number of first-episode clinics in the United States, and those established elsewhere—in Canada and Australia, for example—FEPs from different disorders that manifest psychosis are often initially indistinguishable. Moving forward, for imaging to become clinically useful as a prognostic or even mechanistic tool, scientists should work to adapt to real-world realities rather than the other way around.

Nevertheless, Manivannan *et al.* (3) should be commended for conducting such a study because it is well-known that scanning antipsychotic-naïve patients, or those who are even minimally exposed, is challenging. The DUP was characterized based on clinical records and on structured interviews with patients and families. It is not clear how many of the patients had family members present. However, the presence of family members is extremely helpful to more accurately gather information from the interview. Despite the North American emphasis on individual independence and responsibility, the assessment of a patient with FEP is a time when family involvement is crucial and can be helpful both in the clinical context of a single patient and in advancing knowledge through research.

To advance our understanding of the impact of the DUP on brain function, Manivannan *et al.* (3) chose a spatial working memory (WM) task. The specific task and approach that they chose is relatively noncontroversial, and they used the number of correct responses and the reaction time of correct responses to assess WM. They chose to use conventional preprocessing and analytic pipelines. Their main imaging outcome measures were bilateral dorsolateral prefrontal cortex (DLPFC) activation and functional connectivity between the DLPFC and dorsal caudate of the striatum, which they termed frontostriatal connectivity. Some of the co-authors have previously shown that frontostriatal connectivity is associated with antipsychotic treatment response in FEP (5). WM activation was examined using contrast combinations of task phase (i.e., encoding, maintenance, and retrieval) and load (i.e., low and high). Functional connectivity analysis was examined using a psychophysiological interaction, with a psychological factor (task-specific context) and a physiological factor (time course of seed region of interest). Part of the quality of the analyses presented here relate to their simplicity and clear explication.

In contrast to their decision regarding diagnostic eligibility, Manivannan *et al.* (3) used a liberal threshold for movement in the scanner and for the removal of motion-related artifacts. Volumes with a framewise displacement (FD) value > 0.9 and/or DVARS > 20 were removed to reduce motion-related artifacts. An FD > 0.5 is considered lenient (6) and is associated with within-subject elevations in short-distance correlations. Not surprisingly, the FEP cohort displayed significantly greater movement than the healthy control subjects based on average FD (a matched group of $n = 25$ that is a strength of the study). At face value, the high FD value threshold could be a weakness of

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the study because of the inclusion of some potentially low-quality imaging data. Could it be that the inclusion of data from patients who moved more artifactually changed correlation values? It is becoming clearer that acutely ill, poorer neurocognitive performers, or patients with a poorer outcome, are those who move more than their less ill or higher-performing counterparts (7). The importance of this issue cannot be overstated. As a field, how can we help those who need it most if we exclude their data from study? How can we suggest that our work is generalizable to those with a given disorder if we do not include those who are most ill, or those with the poorest outcomes? The present study does not provide a solution to this issue, but it is incumbent on us, while rightly interested to ensure that the data are of high quality, to also consider how we can accommodate and include the data of those who are suffering the most and who have given their time and trust to research.

Consistent with the published literature, Manivannan *et al.* (3) found that the healthy control subjects were more accurate and had lower reaction time than the FEP participants on the visual WM task. Activation of canonical WM regions was found. However, there was no association of DUP with activation of the DLPFC in each phase of the task. There was an association of longer DUP with less frontostriatal functional connectivity strength in the direct comparison of low versus high load maintenance in the psychophysiological interaction analyses. Connectivity estimates of maintenance of higher WM load by itself also revealed a negative correlation within the same DLPFC cluster. Connectivity at each WM load was not significantly related to negative symptom subscore, total psychopathology score, or medication exposure. Parental socioeconomic status also did not appear to influence these results.

Manivannan *et al.*'s results (3) shed some early light on the potential neural mechanisms associated with the DUP. Providing further credibility to this notion is the fact that WM is a main driver of functional outcome, and there is solid evidence for a relationship between longer DUP and poorer outcome. However, there was a missed opportunity here for longitudinal measurement, which Manivannan *et al.* (3) acknowledge; in particular, a consideration of functional outcome at the time of scan and months later would have elevated the clinical impact of this investigation. It would also have told us if the particular mechanism found here is clinically meaningful. Manivannan *et al.* (3) discuss potential neurochemical underpinnings of their finding, focusing on altered dopaminergic or glutamatergic signaling or tone. A multimodal imaging study combining functional magnetic resonance imaging with magnetic resonance spectroscopy, or positron emission tomography, could further help our mechanistic understanding of the effect of DUP on frontostriatal connectivity during WM performance.

Subsequent studies could benefit our understanding of the effects of DUP on brain structure and function through the application of current best practices of clinical neuroimaging. Specifically, large-sample-size, ideally multicenter, computational, and data-driven approaches could provide us with results that are more generalizable with the potential opportunity for within-study replication. Furthermore, the use of data-driven techniques can leverage heterogeneity within those with an FEP with the visual WM task or other tasks. Large *n* studies are showing different patterns or neural strategies during task engagement among people with the same diagnosis (8). Neural engagement based on these strategies may have different associations with the DUP, different associations with different prognostic value, and different associations with different approaches to target engagement in therapeutic interventions. The multicenter approach is a likely necessity to enhance the clinical impact in FEP neuroimaging studies given the challenges of recruiting large numbers of individuals at a single site. At present, however, the findings reported here represent an admirable starting point in our understanding of the effects of DUP on brain function.

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Article Information

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