Archival Report

Biological Psychiatry

Robust Brain Correlates of Cognitive Performance in Psychosis and Its Prodrome

Heather Burrell Ward, Adam Beermann, Jing Xie, Gulcan Yildiz, Karlos Manzanarez Felix, Jean Addington, Carrie E. Bearden, Kristin Cadenhead, Tyrone D. Cannon, Barbara Cornblatt, Matcheri Keshavan, Daniel Mathalon, Diana O. Perkins, Larry Seidman, William S. Stone, Ming T. Tsuang, Elaine F. Walker, Scott Woods, Michael J. Coleman, Sylvain Bouix, Daphne J. Holt, Dost Öngür, Alan Breier, Martha E. Shenton, Stephan Heckers, Mark A. Halko, Kathryn E. Lewandowski, and Roscoe O. Brady Jr.

ABSTRACT

BACKGROUND: Neurocognitive impairment is a well-known phenomenon in schizophrenia that begins prior to psychosis onset. Connectome-wide association studies have inconsistently linked cognitive performance to resting-state functional magnetic resonance imaging. We hypothesized that a carefully selected cognitive instrument and refined population would allow identification of reliable brain-behavior associations with connectome-wide association studies. To test this hypothesis, we first identified brain-cognition correlations via a connectome-wide association study in early psychosis. We then asked, in an independent dataset, if these brain-cognition relationships would generalize to individuals who develop psychosis in the future.

METHODS: The Seidman Auditory Continuous Performance Task (ACPT) effectively differentiates healthy participants from those with psychosis. Our connectome-wide association study used the HCP-EP (Human Connectome Project for Early Psychosis) (n = 183) to identify links between connectivity and ACPT performance. We then analyzed data from the NAPLS2 (North American Prodrome Longitudinal Study 2) (n = 345), a multisite prospective study of individuals at risk for psychosis. We tested the connectome-wide association study–identified cognition-connectivity relationship in both individuals at risk for psychosis and control participants.

RESULTS: Our connectome-wide association study in early-course psychosis identified robust associations between better ACPT performance and higher prefrontal-somatomotor connectivity ($p < .005$). Prefrontal-somatomotor connectivity was also related to ACPT performance in at-risk individuals who would develop psychosis (n = 17). This finding was not observed in nonconverters (n = 196) or control participants (n = 132).

CONCLUSIONS: This connectome-wide association study identified reproducible links between connectivity and cognition in separate samples of individuals with psychosis and at-risk individuals who would later develop psychosis. A carefully selected task and population improves the ability of connectome-wide association studies to identify reliable brain-phenotype relationships.

https://doi.org/10.1016/j.biopsych.2024.07.012

Neurocognitive impairment is a well-established core symptom of psychotic disorders (1–3) and is among the strongest predictors of functional outcomes (4), but current treatments for cognitive deficits are limited (5). These impairments have also been observed in individuals at high risk for developing a psychotic disorder even prior to the onset of psychosis (6,7). Accordingly, considerable efforts have been made to characterize cognitive impairment, understand its predictive value regarding conversion to psychosis or illness course postonset, and develop effective, targeted interventions to ameliorate these symptoms.

Several cognitive domains found to be reliably impaired in psychotic disorders such as schizophrenia have received intensive study, such as overall cognitive ability (i.e., IQ) and the domains chosen for inclusion in the MATRICS Consensus Cognitive Battery (8). To measure cognitive impairment in psychosis, most studies have utilized cognitive tasks originally designed and validated in control populations (9–11). These tests have identified reliable and robust cognitive domains of impairment in populations diagnosed with psychosis (8), but a separate and distinct question is, "Do these cognitive constructs map onto quantifiable brain substrates?" Without reliable brain-behavior links, our ability to identify and correct pathophysiology is limited.

Noninvasive neuroimaging has been widely embraced as a tool to identify brain correlates of cognitive, behavioral, and pathological phenotypes. For clinical neuroscience, an implicit premise is that localization of pathology may inform diagnosis,

ISSN: 0006-3223

prognosis, and intervention. Many of these efforts rely on associations between imaging signals and diagnosis or variation in cognitive and behavioral variables. Studies using hypothesis-driven approaches have identified associations without converging on reliable findings [reviewed in (12)]. An alternative approach, data-driven analyses of whole connectomes, could identify novel and reliable brain-cognition relationships. This approach has recently been challenged by the observation that for some phenotypes, connectome-wide association studies may require thousands of participants to identify reproducible associations (13) because the strength of these correlations is often so weak as to be of dubious value for clinical translation.

While one popular explanation for the lack of robust brain-behavior associations is limitations of magnetic resonance imaging (MRI) signals (14), another explanation is that heterogeneous behavioral measures that combine multiple cognitive domains (e.g., IQ) do not map onto brain substrates. Another possibility is that heterogeneity in clinical populations (e.g., from medication and disease progression) confounds attempts at replication. We hypothesized that connectome-wide association studies applied in a carefully selected early psychosis population and combined with a behavioral task developed specifically for use in psychosis research would allow for the identification of robust, reproducible brain-behavior associations with particular relevance to psychosis.

The cognitive domain of attention is among the most central cognitive difficulties observed in schizophrenia and is among the most extensively studied (15). Sustained attention has been measured using several different forms of continuous performance tasks (8,16–20). Among these, the Seidman Auditory Continuous Performance task (ACPT) (Figure 1) was specifically developed to assess sustained attention in individuals with or at risk for schizophrenia, as well as other clinical conditions marked by difficulties sustaining attention. The particular sensitivity of Seidman's ACPT in relating cognitive performance to liability for psychosis guided our decision to select Seidman's ACPT for the current study (21).

The early phase of psychosis represents a unique window for identification of the underlying mechanisms and long-term outcomes of the illness with fewer confounding effects such as age-related degeneration, chronic illness, and long-term antipsychotic treatment (22,23). As noted above, cognitive impairments are also present and detectable in people who will develop schizophrenia well prior to illness onset, and people at clinical high risk (CHR) who go on to convert to psychosis have more significant cognitive impairments prior to onset than those at CHR who do not convert (6,7). Thus, it would be expected that brain-behavior associations identified in early psychosis would be present in individuals at CHR as well, perhaps most robustly in individuals who go on to develop psychosis.

We aimed to explore associations between brain connectivity and attention using the Seidman ACPT in a cross-sectional sample of people in the early course of psychosis. Then we aimed to test whether this same brain-cognition relationship was detectable in people at CHR for psychosis. Lastly, we aimed to examine whether these associations were stronger in people at CHR who went on to develop a psychotic disorder based on longitudinal follow-up data. We

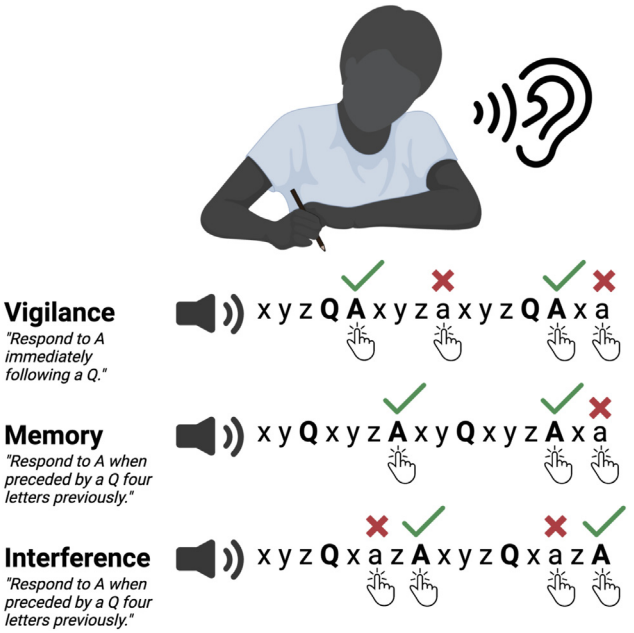

Figure 1. The Seidman Auditory Continuous Performance Task (ACPT). In the ACPT, individuals are presented with an auditory sensory stimulus (letters). There is a target response signal (the letter "A") and a warning/cue signal (the letter "Q"). The ACPT contains several conditions that differ based on their degree of working memory and interference load. Working memory load is defined as the number of letters between the warning/cue and the target. To make the task more difficult, competing information (i.e., "interference") is added to increase task demands within a continuous cognitive updating (i.e., CPT) framework. Interference load is defined by the number of distracters (Q's and A's) embedded between the cue and the target (21). Additional methodological details are presented in the Supplement. We used the ACPT total score as a summary measure of cognitive performance. The ACPT total score was calculated by summing the vigilance, memory, and interference subscores.

hypothesized that a fully data-driven approach would identify a robust circuit associated with attention and that this association would be replicable in a CHR sample and stronger in participants who later developed psychosis. If successful, this would identify a potential target for intervention.

METHODS AND MATERIALS

This project included data from 2 separate studies. First, we sought to identify brain-cognition relationships using data from the HCP-EP (Human Connectome Project for Early Psychosis), a large multisite study of individuals with early psychosis and healthy control (HC) participants. Then we aimed to validate the brain-cognition association using data from the NAPLS2 (North American Prodrome Longitudinal Study 2), a large multisite study of young people identified as being at high risk for developing psychosis (CHR).

Participants

Discovery. Data from 125 people with early-course psychosis and 58 matched HC participants recruited to the HCP-EP were included in the study. Prior to participation, all participants provided written informed consent in accordance with

the institutional review boards of Indiana University, Indianapolis, Indiana, and Partners Institutional Review Board Committee, which served as the single institutional review board of record for Boston sites.

Validation. Data from 213 individuals at CHR and 132 HC participants who were recruited to the NAPLS2 were included in the study (24). Individuals at CHR were included if they met the Criteria of Prodromal Syndromes (COPS), based on the Structured Interview for Psychosis-Risk Syndromes (25). If individuals were younger than 19 years, they were included based on criteria for schizotypal personality disorder or COPS. Prior to participation, all participants provided written informed consent in accordance with the institutional review boards of Beth Israel Deaconess Medical Center, Boston, Massachusetts; Emory University, Atlanta, Georgia; University of Calgary, Alberta, Canada; University of California, Los Angeles; University of California, San Diego; The University of North Carolina at Chapel Hill; Yale University, New Haven, Connecticut; and Zucker Hillside Hospital, Queens, New York.

Cognitive Performance

Participants were assessed using the ACPT in both the discovery (HCP-EP) and validation (NAPLS2) cohorts (Figures 1 and 2). We used the ACPT total score as a summary measure of cognitive performance. The ACPT total score was calculated by summing the vigilance, memory, and interference subscores. Additional methodological details are presented in the Supplement. Although both HCP-EP and NAPLS2 assess cognitive performance on a variety of tasks, the ACPT was the only shared cognitive task performed in both the HCP-EP and NAPLS2 cohorts.

MRI Acquisition

For discovery (HCP-EP), imaging was conducted on Siemens 3.0T MRI systems. Briefly, 0.8-mm^3 T1-weighted anatomical scans were acquired, and resting-state functional runs of approximately 6 minutes were acquired from all participants (420 time points, 0.8-second repetition time, 2-mm^3 voxels).

For validation (NAPLS2), imaging was conducted on either Siemens 3.0-T MRI systems or GE 3T MRI systems. Briefly, 1-mm^3 T1-weighted anatomical scans were acquired, and resting-state functional runs of approximately 5 minutes were acquired from all participants (154 time points, 2-second repetition time, 3-mm^3 voxels).

MRI Data Processing

All analyses were preprocessed using the Data Processing and Analysis for Brain Imaging toolbox [(26); http://rfmri.org/dpabi]. As a quality control metric, scans that exceeded motion thresholds (>3-mm translation or >3° rotation) were discarded. Individual time points with framewise displacement > 0.2 mm were discarded, and scans with >50% of volumes removed for framewise displacement were discarded. All data were preprocessed to remove motion (24-parameter), cerebrospinal fluid signals, white matter signals, and an overall linear trend. A bandpass filter was applied (0.01–0.08 Hz). Data were normalized using the DARTEL toolbox into Montreal Neurological Institute space and smoothed with an 8-mm full width at half maximum kernel. Voxels within a predefined (Montreal Neurological Institute) gray matter mask were used for further analysis. Data were resampled into 4-mm isotropic resolution prior to multivariate distance matrix regression (MDMR).

Network identification was conducted with MDMR (Figure 3). Time courses from regions identified with the network identification method were extracted using the Data Processing and Analysis for Brain Imaging toolbox for the validation cohort and then correlated with *z*-transformed Pearson's correlation coefficients. An additional analysis was conducted with SPM12 for voxelwise maps.

MRI Analysis

Multivariate Distance Matrix Regression. We conducted an assessment in the discovery sample (HCP-EP) across all participants (early psychosis and HC groups) to identify shared and diagnosis-specific circuits of cognitive performance (ACPT). We performed the multivariate pattern analysis of whole-connectome data (MDMR) to identify the strongest links between cognitive performance (ACPT total score) and functional connectivity (27). In previous work, MDMR has been used to identify reliable relationships between psychiatric pathology and connectivity (28–30) that have been validated with noninvasive neuromodulation (31). Critically, MDMR does not rely on group-derived parcellations, which have increasingly been shown to be inaccurate (32). Briefly, this analysis occurs in 2 steps: the first step identifies any regions where cognitive performance is correlated with

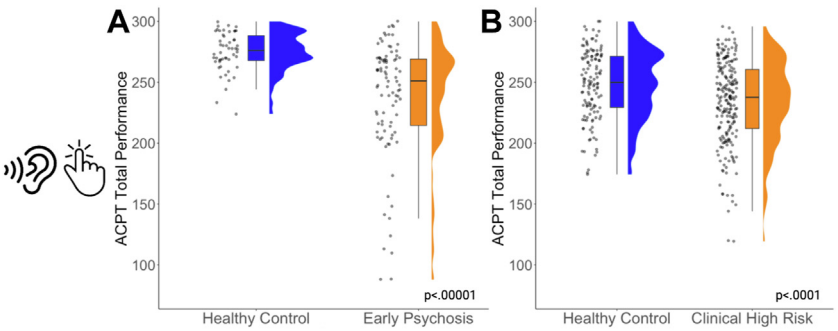

Figure 2. Individuals across the psychosis spectrum show impairment on the Auditory Continuous Performance Task (ACPT). In both **(A)** HCP-EP (Human Connectome Project for Early Psychosis) (n = 183) and **(B)** NAPLS2 (North American Prodrome Longitudinal Study 2) (n = 345), individuals in the early psychosis and clinical high-risk groups performed significantly worse than control groups on the ACPT. We used the ACPT total score as a summary measure of cognitive performance. The ACPT total score was calculated by summing the vigilance, memory, and interference subscores. ACPT total scores range from 0 to 300, with a higher number indicating better performance.

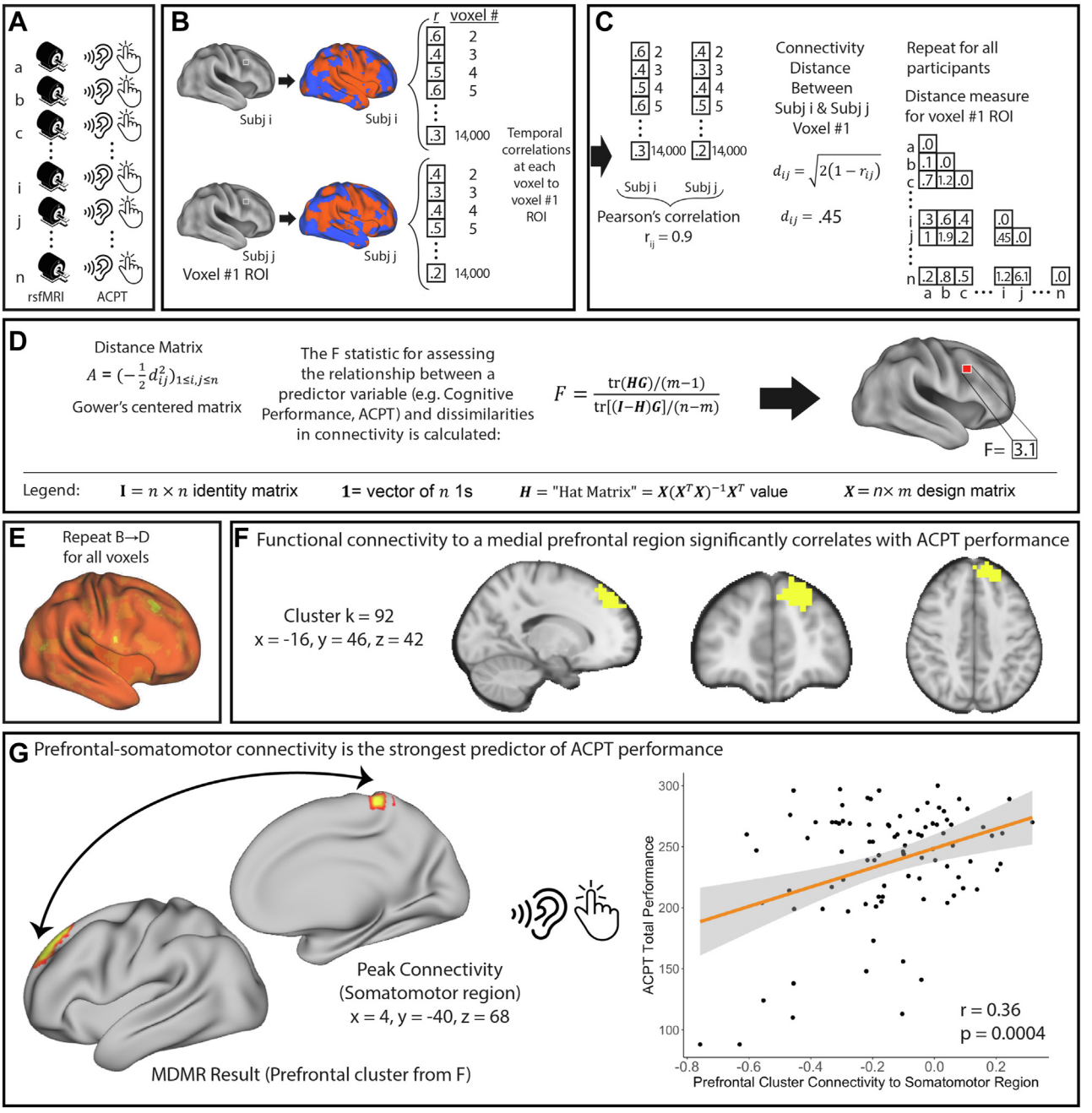

Figure 3. Connectome-wide analysis links cognitive performance to prefrontal-somatomotor connectivity in psychosis. **(A)** Performance on the Auditory Continuous Performance Task (ACPT) and resting-state functional magnetic resonance imaging (rsfMRI) data were collected for each participant. **(B)** For each voxel in the brain, the voxel was used as a seed region to create a connectivity map for each participant. **(C)** These maps were compared with each other to create a participant-wise similarity matrix. **(D)** The ACPT total score for each participant was then combined with the connectivity similarity matrix to produce a pseudo-*F* statistic, which characterizes how individual variation in ACPT performance explains individual variation in functional connectivity. **(E)** This was repeated for all voxels. **(F)** Each multivariate distance matrix regression (MDMR) voxelwise result was then combined to produce a map of the ability of the connectivity pattern to predict an ACPT total score in each voxel. A permutation test of the study participants' labels was used to test the significance of this pseudo-*F* statistic. This analysis identified a left medial prefrontal region (cluster $k = 92$ centered at Montreal Neurological Institute x = −16, y = +46, z = +42) where functional connectivity to this region was significantly correlated with performance on the ACPT. **(G)** The strongest correlation was between the prefrontal cluster (MDMR result) and a region in the right somatomotor cortex (x = 4, y = −40, z = 68, peak connectivity) in the psychosis group. The prefrontal cluster (MDMR result) and somatomotor region (peak connectivity) are shown in lateral and medial views. ROI, region of interest; Subj, subject.

functional connectivity, and the second step involves seed-based analysis of the identified region (see Seed-Based Connectivity Analysis) to determine the spatial pattern of connectivity it represents (27–30).

After preprocessing, resting-state functional MRI data were analyzed with MDMR (27). This method allows for an unbiased, data-driven approach to identifying phenotype-connectivity relationships. MDMR allows quantification of how a variable of interest (ACPT total score) is reflected in the distributed connectivity of individual voxels to the whole brain (i.e., at the finest resolution possible) without parcellating the brain into regions defined a priori (Figure 3). In brief, MDMR tests every voxel to determine whether whole-brain connectivity to that voxel is more similar in individuals with similar values on an independent measure (ACPT total score) than in individuals with dissimilar values. To correct for multiple comparisons, a nonparametric permutation is calculated for voxels that exceed the significance threshold of $p < .005$ and clusters of such with an extent threshold of $p < .05$, with a null distribution calculated from 5000 such permutations (27). This voxelwise threshold was selected to maximize the replicability potential.

We conducted the MDMR to identify anatomical regions where connectivity varied significantly with cognitive performance (ACPT total score). We modeled the effect of cognitive performance (ACPT total score) on functional connectivity while covarying for effects of age, sex, and site. After identifying any regions with MDMR, we then conducted seed-based connectivity analysis (see Seed-Based Connectivity Analysis) to examine the spatial distribution of these connectivity differences as in prior MDMR analyses (27,33–35). See Supplemental Methods for additional details.

Seed-Based Connectivity Analysis. To visualize spatial patterns of connectivity driving the results of MDMR, maps of connectivity to the region identified in MDMR were generated. This step identifies the spatial pattern of connectivity to the region identified in the MDMR analysis (27,33–35). The time course of the blood oxygen level–dependent signals from resting-state functional MRI scans in the region identified in the MDMR process was extracted, and whole-brain connectivity maps were generated using Data Processing and Analysis for Brain Imaging. Using SPM12 (http://www.fil.ion.ucl.ac.uk/spm), we regressed the *z*-transformed Pearson's correlation coefficient connectivity maps against the ACPT total score, using age, sex, and site as covariates, to generate spatial maps of how whole functional brain connectivity to the region varied with ACPT total score. Then we measured region to seed connectivity at this step by measuring the blood oxygen level–dependent correlation between the MDMR-identified region and a 6-mm sphere (seed) placed at the location of maximal connectivity–cognition association. Then we correlated connectivity between the MDMR-identified region and the seeds placed at maximal connectivity–cognition association with the ACPT total score.

In the validation analysis of the psychosis at-risk sample (NAPLS2), we constrained our imaging analyses to the significant connectivity-task performance relationships identified during the discovery phase (HCP-EP). See Supplemental Methods for details.

Statistical Approach. Pearson's correlation coefficients were used to determine the relationships between functional connectivity and cognitive performance. Correlation coefficients were compared using a Fisher's *z* test (R package cocor, version 1.1-4), where Cohen's *q* is used to compare 2 Pearson's correlation coefficients by first transforming *r* with Fisher's z_r transformation into *z* values. To compare continuous outcomes based on dichotomous variables, *t* tests were used. Analyses of variance were used to compare continuous outcomes based on ≥3 groups. All analyses were conducted in RStudio (version 2023.03.1+446) using $\alpha < 0.05$.

RESULTS

A total of 182 HCP-EP participants had complete neuroimaging and behavioral data. After completing quality control analyses, there were 151 HCP-EP participants with data available for analysis for discovery, including 96 individuals with early psychosis and 55 HC participants (Table S1). Age ($p < .0001$) and race ($p < .001$) were significantly different between the psychosis and HC groups included in these analyses. The nonaffective and affective psychosis groups were significantly different on sex ($p < .01$) and race ($p < .01$).

In the validation (NAPLS2) cohort, a total of 435 participants had complete neuroimaging and behavioral data. After performing quality control analyses, there were 345 participants with data available for analysis, including 213 individuals at-risk for psychosis and 132 HC participants (Table S2). In the at-risk group ($n = 213$), 17 converted to psychosis (i.e., developed a psychotic disorder) during the 2-year study period. There were no significant differences in age, sex, or race/ethnicity between individuals at-risk for psychosis, HC participants, converters, and nonconverters.

Individuals Across the Psychosis Spectrum Show Impairment on the ACPT

In both HCP-EP and NAPLS2, individuals in the early psychosis and at-risk for psychosis groups performed worse on the ACPT compared with HC participants (Figure 2 and Tables S3 and S4). In HCP-EP, the nonaffective psychosis group performed worse than the affective psychosis group for the ACPT total score (230.5 vs. 254.5, $p = 6 \times 10^{-13}$, Cohen's $d = 0.48$). In NAPLS2, there were no differences in the ACPT total score between individuals at-risk for psychosis who later developed a psychotic disorder and those who did not develop psychosis (224.0 vs. 234.3, $t_{16.7} = -0.95$, $p = .36$, Cohen's $d = 0.30$).

Cognitive Performance in Psychotic Disorders Is Related to Prefrontal-Somatomotor Connectivity

When we performed the data-driven analysis using MDMR in the discovery (HCP-EP) sample, we identified significant relationships between functional connectivity and performance on the ACPT total score in the psychosis group, but not in the HC group.

When we performed a multivariate pattern analysis of the entire connectome in the early psychosis group ($n = 96$), we identified a single region (cluster $k = 92$, centered at Montreal Neurological Institute x = −16, y = 46, z = 42) in the left medial prefrontal cortex, where functional connectivity correlated with

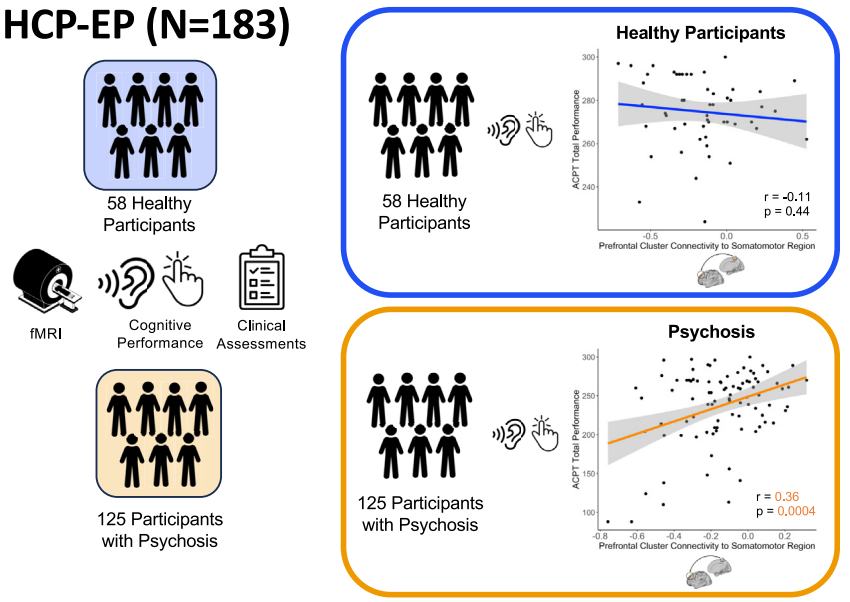

Figure 4. Prefrontal-somatomotor connectivity is uniquely linked to cognitive performance in psychosis. Our data-driven connectome-wide association study identified a psychosis-specific brain correlate of cognitive performance using data from the HCP-EP (Human Connectome Project for Early Psychosis) (n = 183). In individuals with early psychosis, connectivity between the prefrontal cluster and the somatomotor region was significantly related to performance on the Seidman Auditory Continuous Performance task (ACPT). This relationship was specific to the psychosis group (psychosis: r = 0.36, p = .0004) and was not observed in healthy control participants (healthy participants: r = −0.11, p = .44). fMRI, functional magnetic resonance imaging.

the ACPT total score ($p < .005$) (Figure 3F). We did not identify any regions in the HC group where functional connectivity significantly correlated with the ACPT total score.

In the follow-up analysis to determine the spatial pattern of how connectivity to the prefrontal cluster correlated with ACPT total performance in the early psychosis group, we observed that the strongest correlation was between the prefrontal cluster and a right somatomotor region (x = 4, y = −40, z = 68) in the early psychosis group (r = 0.36, p = .0004, Cohen's d = 0.77) (Figures 3G and 4). We did not observe a significant relationship between prefrontal-somatomotor connectivity and ACPT total performance in the HC group (r = −0.11, p = .44, Cohen's d = −0.22) (Figure 4). The correlations between ACPT performance and connectivity were significantly different in the early psychosis and control groups (p = .006, Cohen's q = 0.487).

When we correlated functional connectivity and ACPT total performance among participants confirmed to be on antipsychotics with known dosages (n = 65), a significant relationship remained (r = 0.37, p = .003, Cohen's d = 0.80).

Cognitive Performance in Psychosis Risk Syndromes Is Related to Prefrontal-Somatomotor Connectivity

Then we tested whether connectivity between the prefrontal cluster and somatomotor region identified in the early psychosis discovery cohort was related to ACPT performance in an independent validation sample of individuals at risk for psychosis (CHR, NAPLS2) and HC participants. We did not observe significant relationships between connectivity and cognitive performance in HC participants (r = −0.14, p = .11, Cohen's d = −0.28) (Figure 5). In the CHR sample, there was a trend-level association between connectivity and cognition (r = 0.12, p = .09, Cohen's d = 0.24) (Figure 5). The connectivity-cognition relationship was significantly stronger in individuals at CHR than in HC participants (p = .02, Cohen's q = 0.26).

In the CHR group, we observed a highly significant relationship between connectivity and cognition in the subset of at-risk individuals who would subsequently develop psychosis (r = 0.65, p = .006, Cohen's d = 1.7) (Figure 5). The strength of this association was even stronger in the at-risk individuals who would later develop psychosis than in individuals already diagnosed with psychosis in the HCP-EP discovery sample (p = .014, Cohen's q = 0.375). We did not observe significant relationships between connectivity and cognitive performance in at-risk individuals who did not go on to develop psychosis (r = 0.074, p = .31, Cohen's d = 0.15) (Figure 5).

DISCUSSION

In this data-driven, connectome-wide analysis, we identified novel and reproducible links between functional connectivity and a disease-informed measure of cognitive performance in 2 independent multisite samples. First, we used a data-driven, agnostic analysis of the entire connectome to identify a region where functional connectivity significantly correlated with performance on the ACPT. This analysis identified a prefrontal cluster whose connectivity to a somatomotor region was most correlated with ACPT performance only in individuals with psychotic disorders (discovery, HCP-EP). This relationship was not present in the HC group.

Then we tested whether the relationship between prefrontal-somatomotor connectivity was also related to ACPT performance in an independent validation dataset of individuals at-risk for psychosis and HC participants. We observed the same connectivity-cognition relationship, but only in individuals who subsequently developed psychosis during the follow-up period. This relationship was not present in CHR individuals who did not develop psychosis or in HC participants. By using a data-driven analytic method and a

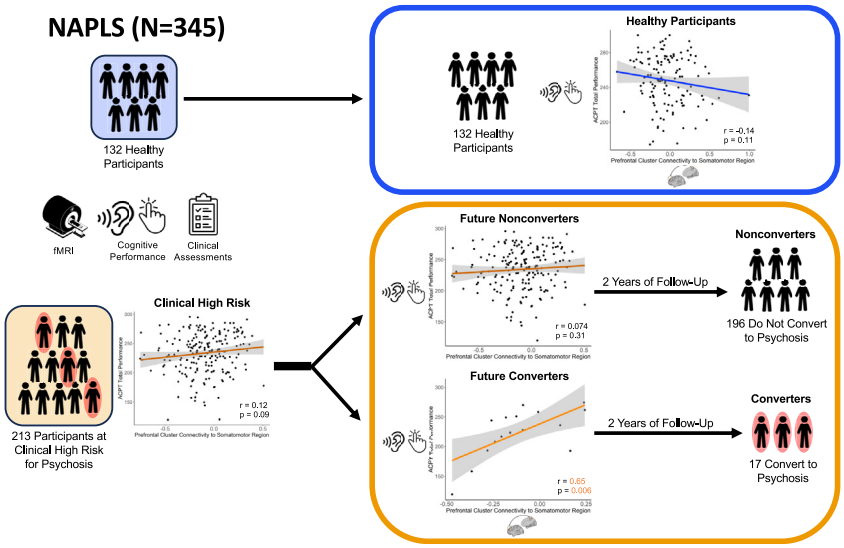

Figure 5. This brain-cognition link is reproducible across the psychosis spectrum, even in the prodrome. We observed a robust, reproducible relationship between prefrontal-somatomotor connectivity and performance on the Seidman Auditory Continuous Performance task (ACPT) in an independent psychosis spectrum sample. Using a sample of individuals at clinical high risk for psychosis in the NAPLS2 (North American Prodrome Longitudinal Study 2) (n = 345), we observed an even stronger relationship between prefrontal-somatomotor connectivity and ACPT performance that was specific to individuals who went on to develop a psychotic disorder (future converters: r = 0.65, p = .006). This relationship was present neither in clinical high-risk individuals who did not convert to psychosis (future: r = 0.074, p = .31) nor in healthy control participants (healthy participants: r = −0.14, p = .11). fMRI, functional magnetic resonance imaging.

disease-informed cognitive task, we identified a novel relationship between prefrontal-somatomotor connectivity and cognitive performance that was reproducible across multiple independent, multisite datasets and is specific to psychotic disorders. To our knowledge, this is the first connectivity-cognition link to be identified both in the prodrome and in individuals with a psychotic disorder.

These results are consistent with our hypothesis that connectome-wide association studies can identify reliable brain-cognition/behavior associations under specific experimental conditions. In this case, our behavioral measure (ACPT performance) was designed for use in populations with or at risk for psychotic disorders. Another likely contributor to our finding was the use of carefully selected populations. Our analyses used 2 curated populations: 1) HCP-EP (discovery), a group of individuals in the first 5 years of psychotic illness, a time period critical to understanding the underlying pathophysiology of illness without confounding effects of age-related degeneration, chronic medical illness, or decades of antipsychotic treatment; and 2) NAPLS2 (validation), a sample of hundreds of individuals at high risk for psychosis.

Individuals in the psychosis prodrome are difficult to identify and challenging to image. Cohorts such as the NAPLS require multiple sites (NAPLS has 8) and require enrollment of hundreds of individuals just to capture a small group who will develop a psychotic disorder during the study period.

Our replication of our connectivity-cognition result from the HCP-EP only in the high-risk participants in the NAPLS who developed psychosis shows how important such resource-intensive studies are for advancing our understanding of the underlying pathophysiology of psychosis and how even a small group of converters can have powerful implications for the field.

Notably, the brain regions and networks that we identified as being most associated with ACPT performance were not in the primary auditory cortex. This is consistent with previous work identifying transdiagnostic relationships between somatosensory-motor dysconnectivity and cognitive performance (36). Our results extend this connectivity-cognition relationship to the psychosis risk syndrome, which is novel. However, our findings are consistent with existing literature that has observed disturbances in somatomotor circuits in psychotic disorders (37). Successful performance on the ACPT involves translation of a cognitive process into a motor response, consistent with the observation that ACPT performance was most related to prefrontal-somatomotor connectivity in both samples. When combined with imaging, this relationship between ACPT performance and connectivity is informative prognostically because it indicates the future development of psychosis. This discriminatory ability of the ACPT harkens back to its original purpose: to differentiate individuals at elevated risk for psychosis from HC participants (21).

Notably, these associations between connectivity and cognitive performance were observed only in individuals with psychosis or future converters to psychosis, not in HC participants. Although ACPT task performance presumably relies on coordinated activity distributed across the brain, it is possible that specific circuits serve as rate-limiting steps during certain cognitive tasks for people with schizophrenia. If this is the case, then these circuits would serve as prime targets for intervention.

Our study has several strengths, including the use of a disease-informed cognitive task (i.e., the ACPT) designed specifically for psychotic disorders; an agnostic, data-driven connectome-wide analysis; and the replication of our results using 2 independent multisite datasets. When the ACPT was designed, Seidman *et al.* proposed that the task could potentially serve as an endophenotypic illness marker that could be used to monitor the progression of neurocognitive impairment from the premorbid to prodromal phase and the first episode of psychosis (21). The results presented here are consistent with that goal. By using the ACPT, we were able to identify a robust relationship between connectivity and cognitive performance that was reproducible across the life

span of psychotic disorders using data collected from 11 different sites, including 10 different MRI scanners. Specifically, the relationship between connectivity and cognitive performance was observable in individuals even prior to their diagnosis. To our knowledge, this is the first time that such brain-cognition relationships have been consistently demonstrated across the life span of psychosis.

The primary limitation of this analysis is that the ACPT is not a widely disseminated cognitive assessment, so available ACPT data are limited. Although several studies have combined the ACPT with functional MRI, they only included HC participants (38–40). To our knowledge, our discovery and validation analyses used the largest datasets of ACPT collected from individuals with or at risk for psychotic disorders. Future work should replicate the relationship between ACPT performance and prefrontal-somatomotor connectivity in a larger sample of people with psychotic disorders and other psychiatric disorders to determine whether these relationships are transdiagnostic.

Another limitation of our analysis was the relatively small number of at-risk individuals who ultimately converted to psychosis (n = 17). This is a challenge for the field because large multisite studies of individuals at risk for psychosis have recently observed a conversion rate of approximately 10% (41). Nevertheless, the NAPLS studies are the largest studies of at-risk individuals who undergo imaging and clinical characterization and are followed prospectively.

A final limitation of our analysis is its correlational nature, which limits our ability to determine the causality of brain-cognition relationships. From our data, it is unclear whether alterations in prefrontal-somatomotor connectivity are driving cognitive performance or are a compensatory response to pathophysiology. This limitation is common to most imaging studies, but follow-up neuromodulation studies could help disentangle these relationships (42).

Conclusions

In summary, we have used the combination of a data-driven connectome-wide multivariate pattern analysis and a disease-informed cognitive assessment to identify a novel and reproducible relationship between brain connectivity and cognitive performance in psychotic disorders. Beyond the delineation of phenotypes, the localization of strong connectivity-cognition relationships suggests the possibility of a circuit that may be engaged for therapeutic ends, e.g., through noninvasive neuromodulation probes of the prefrontal or somatomotor regions that we identified (42).

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Sidney R. Baer, Jr. Foundation and a Harvard Medical School Department of Psychiatry Norman E. Zinberg Fellowship in Addiction Psychiatry Research (to HBW) and the National Institutes of Health (Grant Nos. K23DA059690 and KL2TR002245 [to HBW]), U01 MH066134 [to JA], P50 MH066286 [to CEB], 1R01MH120588-01A1 [to AB], U01 MH081902 [to TDC], U01 MH081857 [to BC], R01 MH117012 [to KEL], U01 MH109977 [to AB, MES], U01 MH82022 [to SW], U01 MH081944 [to KC], U01 MH066069 [to DOP], R01 MH076989 [to DM], U01 MH081928 [to WSS], U01 MH081988 [to EFW], and R01 MH116170 [to ROB]).

LS passed away tragically before submission of this manuscript. His colleagues wish to honor his contributions to this work posthumously.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, Tennessee (HBW, SH); Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts (AB, JX, GY, KMF, MK, LS, WSS, ROB); Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada (JA); Semel Institute for Neuroscience and Human Behavior, Departments of Psychiatry and Behavioral Sciences and Psychology, University of California, Los Angeles, Los Angeles, California (CEB); Department of Psychiatry, University of California, San Diego, La Jolla, California (KC, MTT); Department of Psychology and Psychiatry, Yale University, New Haven, Connecticut (TDC); Department of Psychiatry, Zucker Hillside Hospital and Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, New York (BC); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (MK, LS, WSS, ROB); Department of Psychiatry, University of California, San Francisco, San Francisco, California (DM); Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina (DOP); Department of Psychology, Emory University, Atlanta, Georgia (EFW); Department of Psychiatry, Yale University, New Haven, Connecticut (SW); Department of Psychiatry, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (MJC, MES); Department of Software Engineering and Information Technology, École de technologie supérieure, Montréal, Québec, Canada (SB); Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (DJH); McLean Hospital and Harvard Medical School, Boston, Massachusetts (DÖ, MAH, KEL, ROB); and Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana (AB).

KEL and ROB contributed equally to this article as joint last authors.

Address correspondence to Heather Burrell Ward, M.D., at heather.b.ward@vumc.org, or Roscoe O. Brady Jr., M.D., Ph.D., at robrady@bidmc.harvard.edu.

Received Mar 22, 2024; revised Jul 3, 2024; accepted Jul 13, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2024.07.012.

REFERENCES

1. Mirsky AF (1969): Neuropsychological bases of schizophrenia. Annu Rev Psychol 20:321–348.
2. Seidman LJ (1983): Schizophrenia and brain dysfunction: An integration of recent neurodiagnostic findings. Psychol Bull 94:195–238.
3. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA (2006): Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry 59:863–871.
4. Carrión RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, *et al.* (2013): Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry 70:1133–1142.
5. Goff DC, Hill M, Barch D (2011): The treatment of cognitive impairment in schizophrenia. Pharmacol Biochem Behav 99:245–253.
6. Catalan A, Salazar de Pablo G, Aymerich C, Damiani S, Sordi V, Radua J, *et al.* (2021): Neurocognitive functioning in individuals at clinical high risk for psychosis: A systematic review and meta-analysis. JAMA Psychiatry 78:859–867.
7. Catalan A, Radua J, McCutcheon R, Aymerich C, Pedruzo B, González-Torres MÁ., *et al.* (2022): Examining the variability of neurocognitive functioning in individuals at clinical high risk for psychosis: A meta-analysis. Transl Psychiatry 12:198.
8. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, *et al.* (2008): The MATRICS Consensus Cognitive Battery, part 1: Test selection, reliability, and validity. Am J Psychiatry 165:203–213.
9. Wechsler D (1997): Wechsler Adult Intelligence Scale, 3rd ed. San Antonio, TX: The Psychological Corporation.
10. Reitan RM (1979): Manual for Administration of Neuropsychological Test Batteries for Adults and Children. Tucson, AZ: Neuropsychology Laboratory.
11. Beck LH, Bransome ED, Mirsky AF, Rosvold HE, Sarason I (1956): A continuous performance test of brain damage. J Consult Psychol 20:343–350.

12. Sheffield JM, Barch DM (2016): Cognition and resting-state functional connectivity in schizophrenia. Neurosci Biobehav Rev 61:108–120.
13. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, *et al.* (2022): Reproducible brain-wide association studies require thousands of individuals. Nature 603:654–660.
14. Richtel M (2022): Brain-imaging studies hampered by small data sets, study finds. The New York Times. Available at: https://www.nytimes.com/2022/03/16/science/brain-imaging-research.html. Accessed March 16, 2022.
15. Stone W, Seidman L (2016): Neuropsychological and structural neuroimaging endophenotypes in schizophrenia. In: Cicchetti D, editor. Developmental Psychopathology II, 3rd ed. Hoboken, New Jersey: John Wiley & Sons, 931–965.
16. Nuechterlein KH, Parasuraman R, Jiang Q (1983): Visual sustained attention: Image degradation produces rapid sensitivity decrement over time. Science 220:327–329.
17. Gur RC, Braff DL, Calkins ME, Dobie DJ, Freedman R, Green MF, *et al.* (2015): Neurocognitive performance in family-based and case-control studies of schizophrenia. Schizophr Res 163:17–23.
18. López-Luengo B, González-Andrade A, García-Cobo M (2016): Not all differences between patients with schizophrenia and healthy subjects are pathological: Performance on the conners' continuous performance test. Arch Clin Neuropsychol 31:983–995.
19. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L (1988): The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res 26:223–238.
20. Cornblatt BA, Keilp JG (1994): Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr Bull 20:31–46.
21. Seidman LJ, Meyer EC, Giuliano AJ, Breiter HC, Goldstein JM, Kremen WS, *et al.* (2012): Auditory working memory impairments in individuals at familial high risk for schizophrenia. Neuropsychology 26:288–303.
22. Birchwood M, Todd P, Jackson C (1998): Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl 172:53–59.
23. Pardo-de-Santayana G, Vázquez-Bourgon J, Gómez-Revuelta M, Ayesa-Arriola R, Ortiz-Garcia de la Foz V, Crespo-Facorro B, *et al.* (2020): Duration of active psychosis during early phases of the illness and functional outcome: The PAFIP 10-year follow-up study. Schizophr Res 220:240–247.
24. Addington J, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan TH, Perkins DO, *et al.* (2012): North American Prodrome Longitudinal Study (NAPLS 2): Overview and recruitment. Schizophr Res 142:77–82.
25. McGlashan TH, Walsh BC, Woods SW (2010): The Psychosis Risk Syndrome: Handbook for Diagnosis and Follow-Up. New York: Oxford University Press.
26. Yan CG, Wang XD, Zuo XN, Zang YF (2016): DPABI: Data processing & analysis for (resting-state) brain imaging. Neuroinformatics 14:339–351.
27. Shehzad Z, Kelly C, Reiss PT, Cameron Craddock R, Emerson JW, McMahon K, *et al.* (2014): A multivariate distance-based analytic framework for connectome-wide association studies. Neuroimage 93:74–94.
28. Ward HB, Beermann A, Nawaz U, Halko MA, Janes AC, Moran LV, Brady RO (2022): Evidence for schizophrenia-specific pathophysiology of nicotine dependence. Front Psychiatry 13:804055.
29. Ling G, Lee I, Guimond S, Lutz O, Tandon N, Nawaz U, *et al.* (2019): Individual variation in brain network topology is linked to emotional intelligence. Neuroimage 189:214–223.
30. Nawaz U, Lee I, Beermann A, Eack S, Keshavan M, Brady R (2021): Individual variation in functional brain network topography is linked to schizophrenia symptomatology. Schizophr Bull 47:180–188.
31. Brady RO Jr, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, *et al.* (2019): Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. Am J Psychiatry 176:512–520.
32. Hermosillo RJM, Moore LA, Feczko E, Miranda-Domínguez Ó., Pines A, Dworetsky A, *et al.* (2024): A precision functional atlas of personalized network topography and probabilities. Nat Neurosci 27:1000–1013.
33. Sharma A, Wolf DH, Ciric R, Kable JW, Moore TM, Vandekar SN, *et al.* (2017): Common dimensional reward deficits across mood and psychotic disorders: A connectome-wide association study. Am J Psychiatry 174:657–666.
34. Shanmugan S, Wolf DH, Calkins ME, Moore TM, Ruparel K, Hopson RD, *et al.* (2016): Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. Am J Psychiatry 173:517–526.
35. Satterthwaite TD, Vandekar SN, Wolf DH, Bassett DS, Ruparel K, Shehzad Z, *et al.* (2015): Connectome-wide network analysis of youth with psychosis-spectrum symptoms. Mol Psychiatry 20:1508–1515.
36. Kebets V, Holmes AJ, Orban C, Tang S, Li J, Sun N, *et al.* (2019): Somatosensory-motor dysconnectivity spans multiple transdiagnostic dimensions of psychopathology. Biol Psychiatry 86:779–791.
37. Mittal VA, Bernard JA, Northoff G (2017): What can different motor circuits tell us about psychosis? An RDoC perspective. Schizophr Bull 43:949–955.
38. Goldstein JM, Jerram M, Poldrack R, Anagnoson R, Breiter HC, Makris N, *et al.* (2005): Sex differences in prefrontal cortical brain activity during fMRI of auditory verbal working memory. Neuropsychology 19:509–519.
39. Huang S, Seidman LJ, Rossi S, Ahveninen J (2013): Distinct cortical networks activated by auditory attention and working memory load. Neuroimage 83:1098–1108.
40. Seidman LJ, Breiter HC, Goodman JM, Goldstein JM, Woodruff PW, O'Craven K, *et al.* (1998): A functional magnetic resonance imaging study of auditory vigilance with low and high information processing demands. Neuropsychology 12:505–518.
41. Collins MA, Ji JL, Chung Y, Lympus CA, Afriyie-Agyemang Y, Addington JM, *et al.* (2023): Accelerated cortical thinning precedes and predicts conversion to psychosis: The NAPLS3 longitudinal study of youth at clinical high-risk. Mol Psychiatry 28:1182–1189.
42. Ward HB, Brady RO, Halko MA (2021): Bridging the gap: Strategies to make psychiatric neuroimaging clinically relevant. Harv Rev Psychiatry 29:185–187.