Title

Robust Brain Correlates of Cognitive Performance in Psychosis and Its Prodrome.

Journal

Biological Psychiatry, 97(2)

Authors

Ward, Heather
Beermann, Adam
Xie, Jing
et al.

Publication Date

2025-01-15

DOI

10.1016/j.biopsych.2024.07.012

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2025 January 15.

Published in final edited form as:

Biol Psychiatry. 2025 January 15; 97(2): 139–147. doi:10.1016/j.biopsych.2024.07.012.

Robust Brain Correlates of Cognitive Performance in Psychosis and its Prodrome

Heather Burrell Ward, MD[1], **Adam Beermann, MA**[2], **Jing Xie, BA**[2], **Gulcan Yildiz, MD**[2], **Karlos Manzanarez Felix, BS**[2], **Jean Addington, PhD**[3], **Carrie E. Bearden, PhD**[4], **Kristin Cadenhead, MD**[5], **Tyrone D. Cannon, PhD**[6], **Barbara Cornblatt, PhD, MBA**[7], **Matcheri Keshavan, MD**[2,8], **Daniel Mathalon, MD, PhD**[9], **Diana O. Perkins, MD, MPH**[10], **Larry Seidman, PhD**[2,8], **William S. Stone, PhD**[2,8], **Ming T. Tsuang, MD, PhD, DSc**[5], **Elaine F. Walker, PhD**[11], **Scott Woods, MD**[12], **Michael J. Coleman, MA**[13], **Sylvain Bouix, PhD**[14], **Daphne J. Holt, MD, PhD**[15], **Dost Öngür, MD, PhD**[16], **Alan Breier, MD**[17], **Martha E. Shenton, PhD**[13], **Stephan Heckers, MD**[1], **Mark A. Halko, PhD**[16], **Kathryn E. Lewandowski, PhD**[16,*], **Roscoe O. Brady Jr., MD, PhD**[2,8,16,*]

[1.] Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center

[2.] Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA

[3.] Department of Psychiatry, University of Calgary, Alberta, Canada

[4.] Semel Institute for Neuroscience and Human Behavior, Departments of Psychiatry and Behavioral Sciences and Psychology, University of California, Los Angeles, Los Angeles, CA, USA

[5.] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

[6.] Department of Psychology and Psychiatry, Yale University, New Haven, CT, USA

[7.] Department of Psychiatry, Zucker Hillside Hospital and Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, NY, USA

[8.] Harvard Medical School, Boston, MA

[9.] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

[10.] Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[11.] Department of Psychology, Emory University, Atlanta, GA, USA

[12.] Department of Psychiatry, Yale University, New Haven, CT, USA

[13.] Department of Psychiatry, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

Corresponding Authors: Heather Burrell Ward, MD, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, 1601 23rd Ave S, Nashville, TN 37212, heather.b.ward@vumc.org, Roscoe O. Brady, Jr., MD, PhD, Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, 375 Longwood Ave, Boston, MA 02215, robrady@bidmc.harvard.edu.

*Co-last authors

Competing Interests

The authors have no competing interests to disclose.

[14] Department of Software Engineering and Information Technology, École de technologie supérieure, Montréal, QC, Canada

[15] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School Boston, MA

[16] McLean Hospital and Harvard Medical School, Boston, MA

[17] Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA

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 fMRI. We hypothesized 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 Human Connectome Project for Early Psychosis (n=183) to identify links between connectivity and ACPT performance. We then analyzed the North American Prodrome Longitudinal Study 2 (n=345), a multi-site 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 controls.

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 controls (n=132).

Conclusions: This connectome-wide association study identified reproducible links between connectivity and cognition in separate samples of 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.

Keywords

psychosis; resting-state fMRI; cognitive performance; clinical high risk; early psychosis; auditory

Introduction

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, to understand its predictive value regarding conversion to psychosis or illness course post-onset, and to 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, 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), as the strength of these correlations is often so weak as to be of dubious value for clinical translation.

While one popular explanation for lack of robust brain-behavior associations is limitations of MRI signals (14), another explanation is that heterogenous 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, allows for 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 in the current study (21).

The early phase of psychosis represents a unique window into 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, 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 those at CHR as well, perhaps most robustly in those 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. We then 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 are stronger in people at CHR who go on to develop a psychotic disorder based on longitudinal follow-up data. We 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 those participants who later develop psychosis. If successful, this would identify a potential target for intervention.

Materials & Methods

This project included data from two separate studies. First, we sought to identify brain-cognition relationships using data from the Human Connectome Project for Early Psychosis (HCP-EP), a large, multisite study of individuals with early psychosis and healthy controls. We then aimed to validate the brain-cognition association using data from the North American Prodrome Longitudinal Study (NAPLS2), 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 healthy controls 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 (now MGB sIRG, which served as the single IRB of record for Boston sites).

Validation.—Data from 213 individuals at CHR and 132 healthy controls 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 (SIPS) (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 (Figure 1). We used ACPT total score as a summary measure of cognitive performance. 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 3.0-T MRI systems (Munich, Germany). 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 (Munich, Germany) or GE 3.0-T 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 (>3mm translation or >3 degrees rotation) were discarded. Individual time points with framewise displacement >0.2mm were discarded, and scans with >50% of volumes removed for framewise displacement were discarded. All data were preprocessed to remove motion (24-parameter), CSF 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 (MNI) space and smoothed with an 8-mm full-width half-maximum kernel. Voxels within a pre-defined (MNI) gray matter mask were used for further analysis. Data were resampled into 4mm isotropic resolution prior to multivariate distance matrix regression.

Network identification was conducted with multivariate distance matrix regression (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 voxel-wise maps.

MRI Analysis

Multivariate Distance Matrix Regression—We conducted an assessment in the *discovery* sample (HCP-EP) across all participants (early psychosis and healthy control)

to identify shared and diagnosis-specific circuits of cognitive performance (ACPT). We performed the multivariate pattern analysis of whole-connectome data (multivariate distance matrix regression) to identify the strongest links between cognitive performance (ACPT total score) and functional connectivity (27). In previous work, multivariate distance matrix regression has been used to identify reliable relationships between psychiatric pathology and connectivity (28–30) that have been validated with noninvasive neuromodulation (31). Critically, multivariate distance matrix regression does not rely on group-derived parcellations, which have increasingly been shown to be inaccurate (32). Briefly, this analysis occurs in two steps: the first step identifies any regions where cognitive performance correlates with 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 fMRI data were analyzed with multivariate distance matrix regression (27). This method allows for an unbiased, data-driven approach to identifying phenotype-connectivity relationships. Multivariate distance matrix regression 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, multivariate distance matrix regression tests every voxel to determine if 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 5,000 such permutations (27). This voxelwise threshold was selected to maximize the replicability potential.

We conducted the multivariate distance matrix regression to identify anatomical regions where connectivity significantly varied 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 multivariate distance matrix regression, we then conducted seed-based connectivity (see Seed-Based Connectivity Analysis) analysis to examine the spatial distribution of these connectivity differences as in prior multivariate distance matrix regression analyses (27, 33–35). See Supplemental Methods for additional detail.

Seed-Based Connectivity Analysis—To visualize spatial patterns of connectivity driving the results of multivariate distance matrix regression, maps of connectivity to the region identified in multivariate distance matrix regression were generated. This step identifies the spatial pattern of connectivity to the region identified in the multivariate distance matrix regression analysis (27, 33–35). The time course of the BOLD signals from rsfMRI scans in the region identified in the multivariate distance matrix regression process was extracted and whole brain connectivity maps were generated using Data Processing and Analysis for Brain Imaging. Using SPM12 (SPM – Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm) we regressed the z-transformed Pearson's correlation coefficient connectivity maps against ACPT total score, using age, sex, and site as

covariates, to generate spatial maps of how whole functional brain connectivity to the region varies with ACPT total score. We then measured region to seed connectivity at this step by measuring BOLD correlation between the multivariate distance matrix regression-identified region and a 6mm sphere (seed) placed at the location of maximal connectivity-cognition association. We then correlated connectivity between the multivariate distance matrix regression-identified region and the seeds placed at maximal connectivity-cognition association with 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 in 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 two Pearson's correlation coefficients by first transforming r with Fisher's z_r transformation into z values. T-tests were used to compare continuous outcomes based on dichotomous variables. ANOVAs were used to compare continuous outcomes based on three or more groups. All analyses were conducted in RStudio (Version 2023.03.1+446) using alpha<.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 healthy controls (Supplemental Table 1). Age (p<.0001) and race (p<.001) were significantly different between the psychosis and control 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 354 participants with data available for analysis, including 213 individuals at-risk for psychosis and 132 healthy controls (Supplemental Table 2). In the at-risk group (n=213), 17 converted to psychosis (i.e. developed a psychotic disorder) during the 2-year study duration. There were no significant differences in age, sex, or race/ethnicity between individuals at-risk for psychosis, healthy controls, converters, and nonconverters.

Individuals Across the Psychosis Spectrum Show Impairment on the Auditory Continuous Performance Task

In both HCP-EP and NAPLS2, individuals in the early psychosis and at-risk for psychosis groups performed worse on the ACPT compared to healthy controls (Figure 2, Supplemental Tables 3 and 4). In HCP-EP, the non-affective psychosis group performed worse than the affective psychosis group for ACPT total score (230.5 vs. 254.5, $p=6\times10^{-13}$, Cohen's d = 0.48). In NAPLS2, there were no differences in 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 = −0.95, df = 16.7, p = 0.36, Cohen's d = 0.30).

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

When we performed the data-driven analysis using multivariate distance matrix regression 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 healthy control 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 MNI x = −16, y = 46, z = 42) in the left medial prefrontal cortex where functional connectivity correlated with ACPT total score (p <.005, Figure 3F). We did not identify any regions in healthy controls where functional connectivity significantly correlated with ACPT total score.

In the follow-up analysis to determine the spatial pattern of how connectivity to the prefrontal cluster correlates 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 healthy controls (r = −0.11, p = 0.44, Cohen's d = −0.22, Figure 4). The correlations between ACPT performance and connectivity were significantly different between 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 = 0.003, Cohen's d = 0.80).

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

We then 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 healthy comparison participants. We did not observe significant relationships between connectivity and cognitive performance in healthy comparison participants (r = −0.14, p = 0.11, 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 = 0.09, Cohen's d = 0.24, Figure 5). The connectivity-cognition relationship was significantly stronger in CHR individuals at risk for psychosis than in healthy controls (p = .02, Cohen's q = 0.26).

Within 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 = 0.006, 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 the HCP-EP *discovery* sample ($p = 0.014$, Cohen's $q = 0.375$). We did not observe significant relationships between connectivity and cognitive performance in at-risk individuals who would not go on to develop psychosis ($r = 0.074$, $p = 0.31$, 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 two independent, multisite samples. We first used a data-driven, agnostic analysis of the entire connectome to identify a region where functional connectivity significantly correlates 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 healthy controls.

We then 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 healthy controls. We observed the same connectivity-cognition relationship, but only in those in individuals who subsequently developed psychosis during the follow-up period. This relationship was neither present in CHR individuals who did not develop psychosis nor was it present in healthy controls. By using a data-driven analytic method and a disease-informed cognitive task, we identified a novel relationship between prefrontal-somatomotor connectivity and cognitive performance that is 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 instance, 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 two curated populations: 1) HCP-EP (*discovery*), a group of individuals in the first 5 years of psychotic illness, a time period critical to understanding 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 like NAPLS require multiple sites (NAPLS has 8) and require enrollment of hundreds of individuals just to capture a small group who develop a psychotic disorder during the study period. Our replication of our connectivity-cognition result from HCP-EP only in the high-risk participants in 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 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 into 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, as it indicates 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 controls (21).

Notably these associations between connectivity and cognitive performance were observed only in individuals with psychosis or future convertors to psychosis, not in controls. 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, 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., ACPT) designed specifically for psychotic disorders, an agnostic, data-driven connectome-wide analysis, and the replication of our results using two independent, multisite datasets. When the ACPT was designed, Seidman et al. proposed that this task could potentially serve as an endophenotypic illness marker which could be used to monitor the progression of neurocognitive impairment from the premorbid to prodromal phase and 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 lifespan 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 such brain-cognition relationships have been consistently demonstrated across the lifespan of psychosis.

The primary limitation of this analysis is that the ACPT is not a widely disseminated cognitive assessment, so available ACPT data is limited. Although several studies have combined the ACPT with fMRI, they only included healthy participants (38–40). To our knowledge, our *discovery* and *validation* analyses used the largest datasets of ACPT collected in 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 if 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). Indeed, this is a challenge for the field, as 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 was its correlational nature, which limits our ability to determine the causality of brain-cognition relationships. From our data, it is unclear if 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 to disentangle these relationships (42).

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 non-invasive neuromodulation probes of the prefrontal or somatomotor regions we identified (42).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Sidney R. Baer, Jr. Foundation and Harvard Medical School Department of Psychiatry Norman E. Zinberg Fellowship in Addiction Psychiatry Research to Dr. Ward, by National Institutes of Health (NIH) grants K23DA059690 and KL2TR002245 to Dr. Ward, U01 MH066134 to Dr. Addington, P50 MH066286 to Dr. Bearden, 1R01MH120588–01A1 to Dr. Breier, U01 MH081902 to Dr. Cannon, U01 MH081857 to Dr. Cornblatt, R01 MH117012 to Dr. Lewandowski, U01 MH109977 to Drs. Breier and Shenton, U01 MH82022 to Dr. Woods, U01 MH081944 to Dr. Cadenhead, U01 MH066069 to Dr. Perkins, R01 MH076989 to Dr. Mathalon, U01 MH081928 to Dr. Stone, and U01 MH081988 to Dr. Walker, and R01 MH116170 to Dr. Brady.

References

1. Mirsky AF. Neuropsychological bases of schizophrenia. Annu Rev Psychol. 1969;20:321–48. [PubMed: 4181098]
2. Seidman LJ. Schizophrenia and brain dysfunction: an integration of recent neurodiagnostic findings. Psychol Bull. 1983;94(2):195–238. [PubMed: 6356196]
3. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, et al. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry. 2006;59(9):863–71. [PubMed: 16325151]
4. Carrión RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, et al. Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry. 2013;70(11):1133–42. [PubMed: 24006090]
5. Goff DC, Hill M, Barch D. The treatment of cognitive impairment in schizophrenia. Pharmacol Biochem Behav. 2011;99(2):245–53. [PubMed: 21115035]

6. Catalan A, Salazar de Pablo G, Aymerich C, Damiani S, Sordi V, Radua J, et al. Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis. JAMA psychiatry. 2021;78(8):859–67. [PubMed: 34132736]
7. Catalan A, Radua J, McCutcheon R, Aymerich C, Pedruzo B, Gonzalez-Torres MA, et al. Examining the variability of neurocognitive functioning in individuals at clinical high risk for psychosis: a meta-analysis. Transl Psychiatry. 2022;12(1):198. [PubMed: 35551176]
8. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatry. 2008;165(2):203–13. [PubMed: 18172019]
9. Wechsler D Wechsler Adult Intelligence Scale-Third Edition. San Antonio, TX: The Psychological Corporation; 1997.
10. Reitan RM. Manual for the Administration of Neuropsychological Test Batteries for Adults and Children. Tucson, AZ1979.
11. Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Beck LH. A continuous performance task of brain damage. Journal of Consulting Psychology. 1956;20:343–50. [PubMed: 13367264]
12. Sheffield JM, Barch DM. Cognition and resting-state functional connectivity in schizophrenia. Neurosci Biobehav Rev. 2016;61:108–20. [PubMed: 26698018]
13. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. Nature. 2022;603(7902):654–60. [PubMed: 35296861]
14. Richtel M Brain-Imaging Studies Hampered by Small Data Sets, Study Finds. The New York Times. 2022.
15. Stone W, Seidman L. Neuropsychological and Structural Neuroimaging Endophenotypes in Schizophrenia. In: Cicchetti D, editor. Developmental Psychopathology. II. Third ed: John Wiley & Sons; 2016. p. 931–65.
16. Nuechterlein KH, Parasuraman R, Jiang Q. Visual sustained attention: image degradation produces rapid sensitivity decrement over time. Science. 1983;220(4594):327–9. [PubMed: 6836276]
17. Gur RC, Braff DL, Calkins ME, Dobie DJ, Freedman R, Green MF, et al. Neurocognitive performance in family-based and case-control studies of schizophrenia. Schizophr Res. 2015;163(1–3):17–23. [PubMed: 25432636]
18. Lopez-Luengo B, Gonzalez-Andrade A, Garcia-Cobo M. Not All Differences between Patients with Schizophrenia and Healthy Subjects Are Pathological: Performance on the Conners' Continuous Performance Test. Arch Clin Neuropsychol. 2016;31(8):983–95. [PubMed: 27620627]
19. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res. 1988;26(2):223–38. [PubMed: 3237915]
20. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophrenia bulletin. 1994;20(1):31–46. [PubMed: 8197420]
21. Seidman LJ, Meyer EC, Giuliano AJ, Breiter HC, Goldstein JM, Kremen WS, et al. Auditory working memory impairments in individuals at familial high risk for schizophrenia. Neuropsychology. 2012;26(3):288–303. [PubMed: 22563872]
22. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl. 1998;172(33):53–9. [PubMed: 9764127]
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. Duration of active psychosis during early phases of the illness and functional outcome: The PAFIP 10-year follow-up study. Schizophr Res. 2020;220:240–7. [PubMed: 32276867]
24. Addington J, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan TH, Perkins DO, et al. North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. Schizophr Res. 2012;142(1–3):77–82. [PubMed: 23043872]
25. McGlashan TH, Walsh BC, Woods SW. The Psychosis Risk Syndrome: Handbook for Diagnosis and Follow-up. New York: Oxford University Press; 2010.
26. Yan CG, Wang XD, Zuo XN, Zang YF. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics. 2016;14(3):339–51. [PubMed: 27075850]

27. Shehzad Z, Kelly C, Reiss PT, Cameron Craddock R, Emerson JW, McMahon K, et al. A multivariate distance-based analytic framework for connectome-wide association studies. Neuroimage. 2014;93 Pt 1:74–94. [PubMed: 24583255]

28. Ward HB, Beermann A, Nawaz U, Halko MA, Janes AC, Moran LV, et al. Evidence for Schizophrenia-Specific Pathophysiology of Nicotine Dependence. Front Psychiatry. 2022;13:804055. [PubMed: 35153877]

29. Ling G, Lee I, Guimond S, Lutz O, Tandon N, Nawaz U, et al. Individual variation in brain network topology is linked to emotional intelligence. Neuroimage. 2019;189:214–23. [PubMed: 30630078]

30. Nawaz U, Lee I, Beermann A, Eack S, Keshavan M, Brady R. Individual Variation in Functional Brain Network Topography is Linked to Schizophrenia Symptomatology. Schizophr Bull. 2020.

31. Brady RO Jr., Gonsalvez I, Lee I, Ongur D, Seidman LJ, Schmahmann JD, et al. Cerebellar-Prefrontal Network Connectivity and Negative Symptoms in Schizophrenia. Am J Psychiatry. 2019:appiajp201818040429.

32. Hermosillo RJM, Moore LA, Feczko E, Miranda-Domínguez Ó, Pines A, Dworetsky A, et al. A precision functional atlas of personalized network topography and probabilities. Nat Neurosci. 2024.

33. Sharma A, Wolf DH, Ciric R, Kable JW, Moore TM, Vandekar SN, et al. Common Dimensional Reward Deficits Across Mood and Psychotic Disorders: A Connectome-Wide Association Study. Am J Psychiatry. 2017;174(7):657–66. [PubMed: 28135847]

34. Shanmugan S, Wolf DH, Calkins ME, Moore TM, Ruparel K, Hopson RD, et al. Common and Dissociable Mechanisms of Executive System Dysfunction Across Psychiatric Disorders in Youth. Am J Psychiatry. 2016;173(5):517–26. [PubMed: 26806874]

35. Satterthwaite TD, Vandekar SN, Wolf DH, Bassett DS, Ruparel K, Shehzad Z, et al. Connectome-wide network analysis of youth with Psychosis-Spectrum symptoms. Mol Psychiatry. 2015;20(12):1508–15. [PubMed: 26033240]

36. Kebets V, Holmes AJ, Orban C, Tang S, Li J, Sun N, et al. Somatosensory-Motor Dysconnectivity Spans Multiple Transdiagnostic Dimensions of Psychopathology. Biol Psychiatry. 2019;86(10):779–91. [PubMed: 31515054]

37. Mittal VA, Bernard JA, Northoff G. What Can Different Motor Circuits Tell Us About Psychosis? An RDoC Perspective. Schizophr Bull. 2017;43(5):949–55. [PubMed: 28911048]

38. Goldstein JM, Jerram M, Poldrack R, Anagnoson R, Breiter HC, Makris N, et al. Sex differences in prefrontal cortical brain activity during fMRI of auditory verbal working memory. Neuropsychology. 2005;19(4):509–19. [PubMed: 16060826]

39. Huang S, Seidman LJ, Rossi S, Ahveninen J. Distinct cortical networks activated by auditory attention and working memory load. Neuroimage. 2013;83:1098–108. [PubMed: 23921102]

40. Seidman LJ, Breiter HC, Goodman JM, Goldstein JM, Woodruff PW, O'Craven K, et al. A functional magnetic resonance imaging study of auditory vigilance with low and high information processing demands. Neuropsychology. 1998;12(4):505–18. [PubMed: 9805320]

41. Collins MA, Ji JL, Chung Y, Lympus CA, Afriyie-Agyemang Y, Addington JM, et al. Accelerated cortical thinning precedes and predicts conversion to psychosis: The NAPLS3 longitudinal study of youth at clinical high-risk. Mol Psychiatry. 2023;28(3):1182–9. [PubMed: 36434057]

42. Ward HB, Brady RO, Halko MA. Bridging the Gap: Strategies to Make Psychiatric Neuroimaging Clinically Relevant. Harv Rev Psychiatry. 2021;29(3):185–7. [PubMed: 33882534]

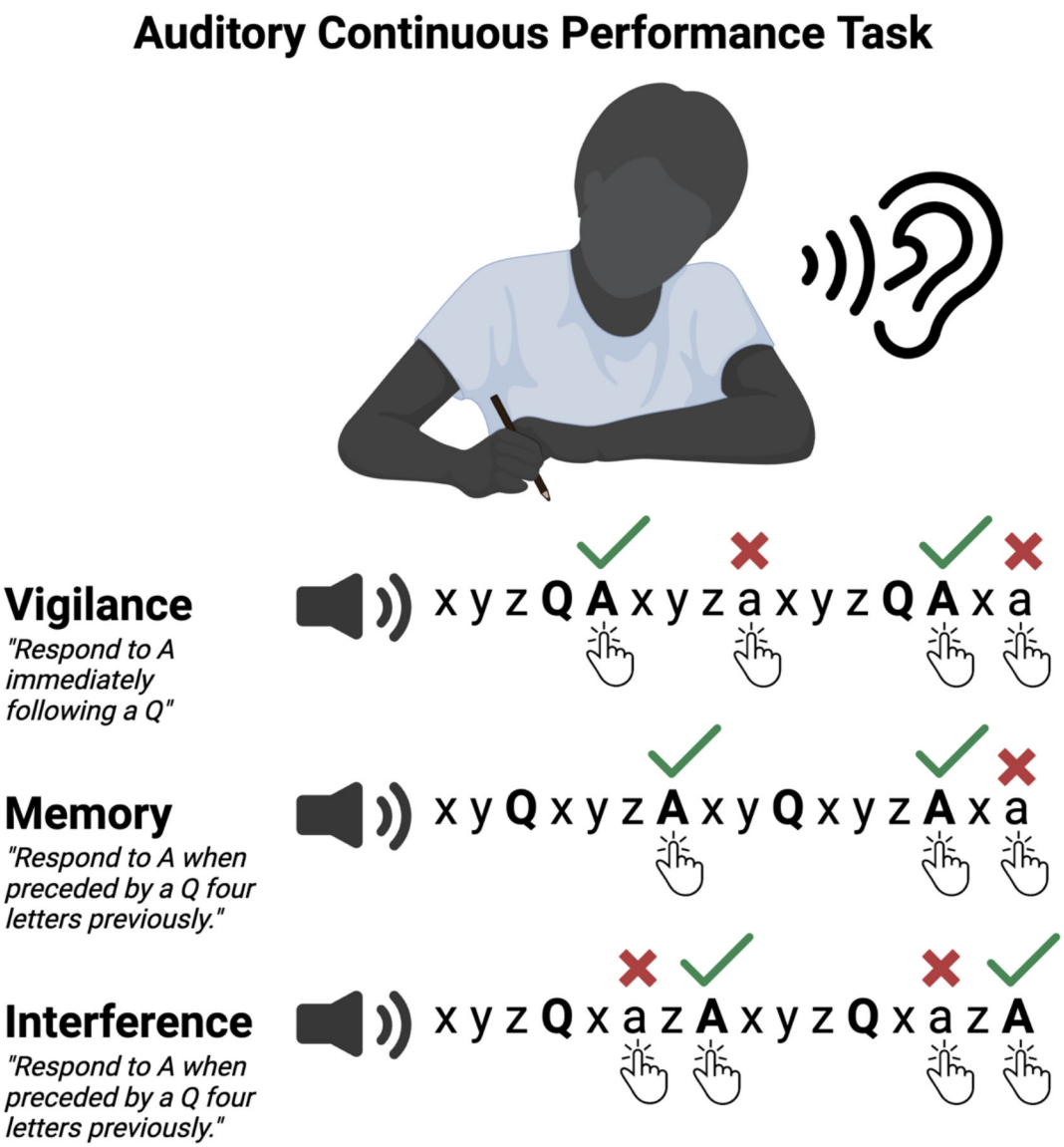

Figure 1. The Seidman Auditory Continuous Performance Task (ACPT).

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 which 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 ACPT total score as a summary measure of cognitive performance. ACPT total score was calculated by summing the vigilance, memory, and interference subscores.

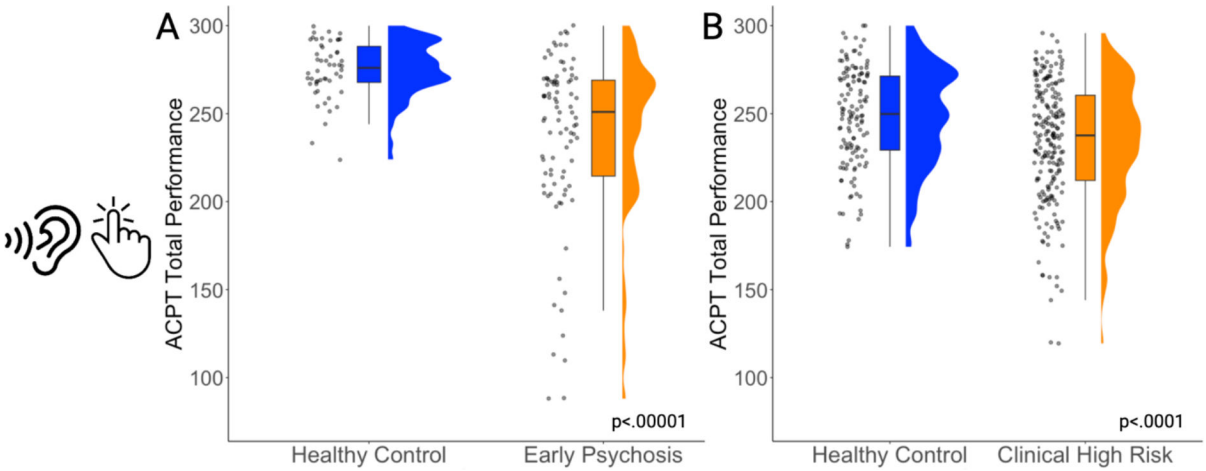

Figure 2. Individuals Across the Psychosis Spectrum Show Impairment on the Auditory Continuous Performance Task (ACPT).

In both HCP-EP (A, n=183) and NAPLS2 (B, n=345), individuals in the early psychosis and clinical high risk groups performed significantly worse than control groups on the ACPT. We used ACPT total score as a summary measure of cognitive performance. 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.

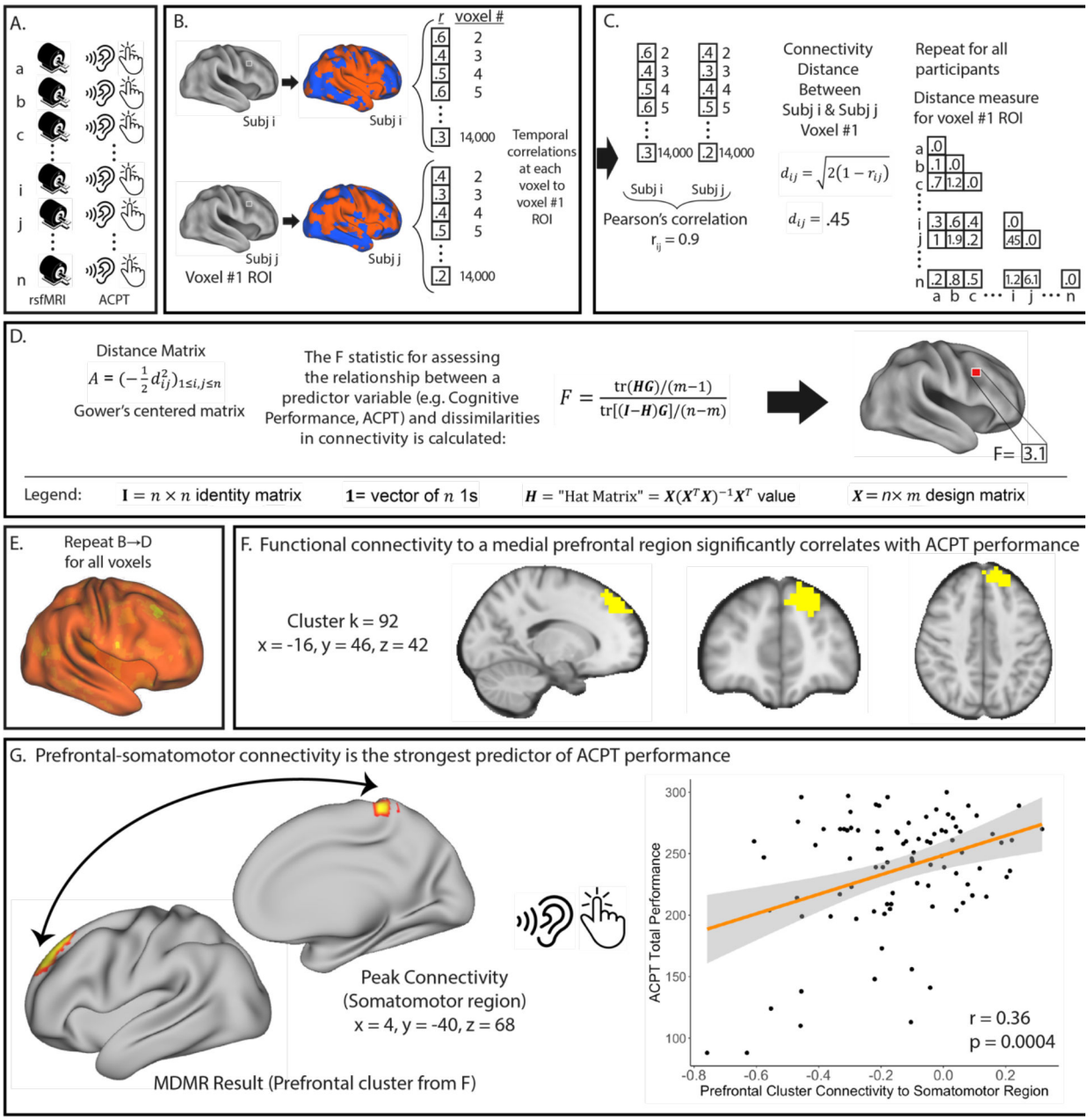

Figure 3. Connectome-wide analysis links cognitive performance to prefontal-somatomotor connectivity in psychosis.

Performance on the Auditory Continuous Performance Task (ACPT) and resting-state functional MRI (rsfMRI) data were collected for each participant (1A). For each voxel in the brain, the voxel was used as a seed region to create a connectivity map for each participant (1B). These maps were compared with each other to create a subject-wise similarity matrix (1C). 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 (1D). This is repeated for all voxels (1E). Each multivariate distance matrix regression voxel-wise 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 subjects' labels is used to test the significance of this pseudo-F statistic. This analysis identified a left medial prefrontal region (cluster k = 92 centered at MNI x = −16, y = +46, z = +42) where functional connectivity to this region significantly correlates with performance on the ACPT (1F). The strongest correlation was between the prefrontal cluster (Multivariate Distance Matrix Regression Result) and a region in the right somatomotor cortex (x = 4, y = −40, z = 68, Peak Connectivity) in the psychosis group (1G). The prefrontal cluster (Multivariate Distance Matrix Regression Result) and somatomotor region (Peak Connectivity) are shown in lateral and medial views.

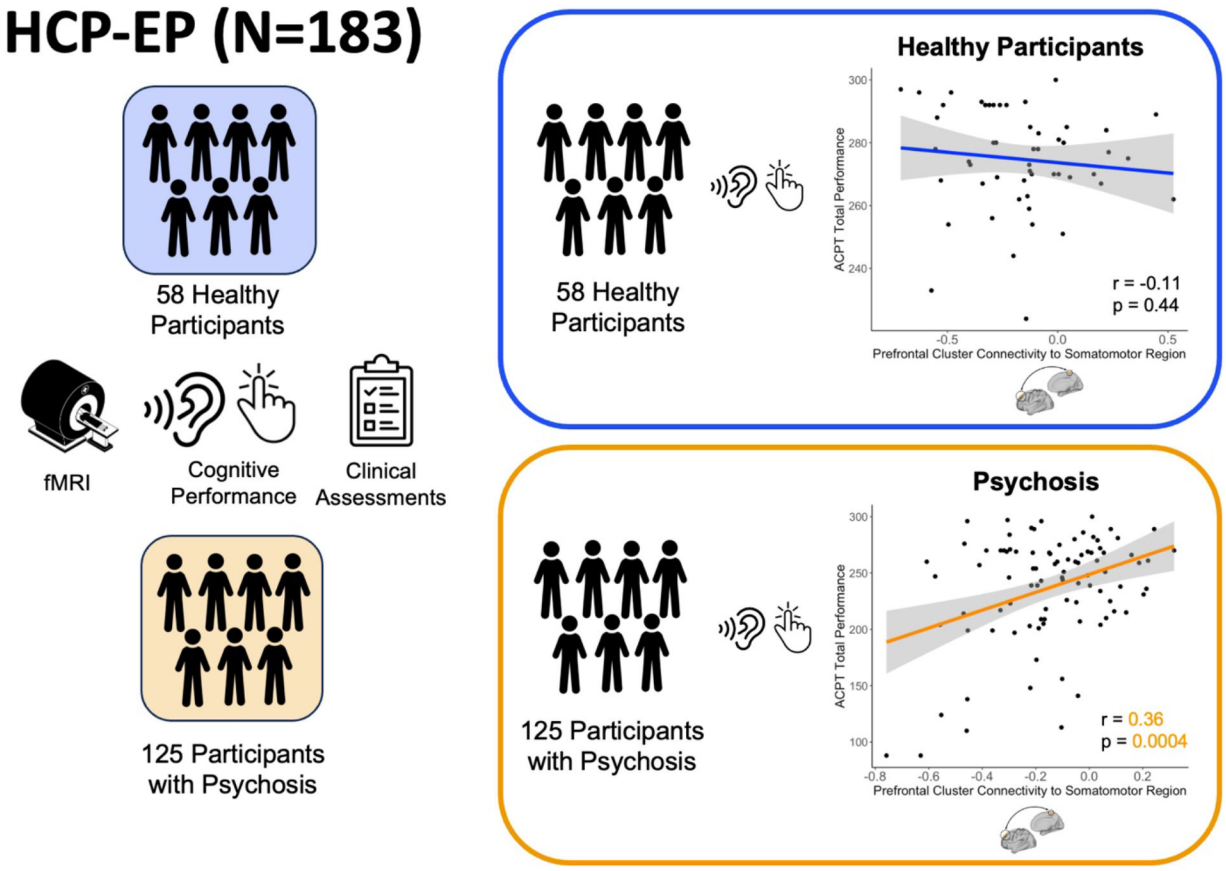

Figure 4. Prefrontal-somatomotor connectivity is uniquely linked to cognitive performance in psychosis.

Our data-driven connectome-wide association study identified a psychosis-specific brain correlate of cognitive performance using data from the Human Connectome Project for Early Psychosis (HCP-EP, n=183). In individuals with early psychosis, connectivity between the prefrontal cluster and 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 not observed in healthy controls (Healthy Participants: r = −0.11, p = 0.44).

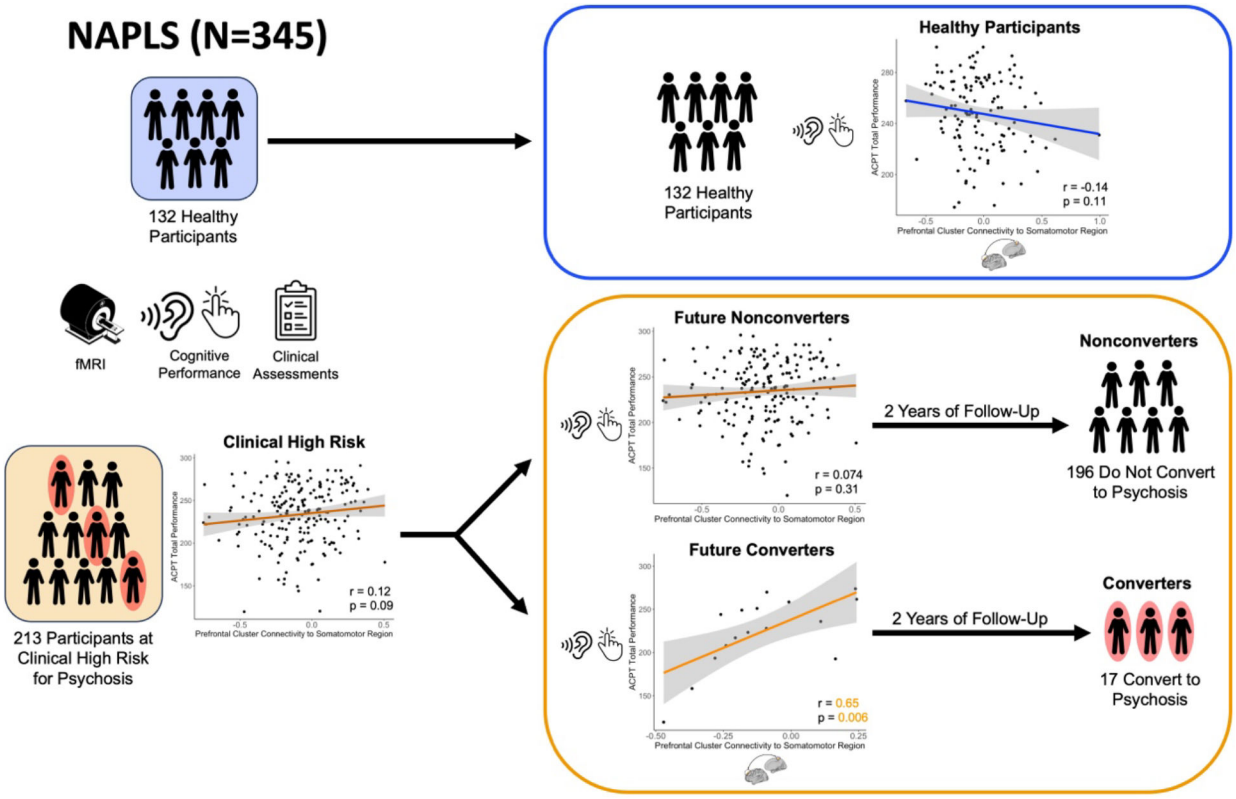

Figure 5. This brain-cognition link is reproducible across the psychosis spectrum, even in the prodrome.

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 North American Prodrome Longitudinal Study (NAPLS2, 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: $r = 0.65$, $p = 0.006$). This relationship was neither present in clinical high risk individuals who did not convert to psychosis (Future: $r = 0.074$, $p = 0.31$) nor in healthy controls (Healthy Participants: $r = -0.14$, $p = 0.11$).