

## Accelerated Aging of Functional Brain Networks Supporting Cognitive Function in Psychotic Disorders

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### ABSTRACT

**BACKGROUND:** Across networks, connectivity within the frontoparietal network (FPN) and cingulo-opercular network (CON) exhibits reductions earliest during healthy aging, contributing to cognitive impairment. Individuals with psychotic disorders demonstrate evidence of accelerated aging across multiple biological systems. By leveraging a large sample of patients with psychosis from early to chronic illness stages, this study sought to determine whether the CON and FPN exhibit evidence of accelerated aging in psychotic disorders, confirm associations between network efficiency and cognition, and determine whether reduced network efficiency is observed in early-stage psychosis.

**METHODS:** Resting-state functional magnetic resonance imaging and cognitive data were obtained on 240 patients with psychotic disorder and 178 healthy control participants (HCs). Global efficiency, a measure of functional integration, was calculated for the CON, FPN, subcortical network, and visual network. Associations with age and cognition were assessed and compared between groups.

**RESULTS:** Consistent with accelerated aging, significant group by age interactions reflected significantly stronger relationships between efficiency and age in patients with psychosis than in HCs for both the CON (psychosis:  $r = -.37$ ; HC:  $r = -.16$ ) and FPN (psychosis:  $r = -.31$ ; HC:  $r = -.05$ ). Accelerated aging was not observed in either the subcortical or visual network, suggesting specificity for cognitive networks that decline earliest in healthy aging. Replicating prior findings, efficiency of both the CON and FPN correlated with cognitive function across all participants ( $r_s > .11$ ,  $p_s < .031$ ). Furthermore, patients with chronic psychosis ( $p = .004$ ), but not patients with early psychosis ( $p = .553$ ), exhibited significantly lower FPN efficiency compared with HCs.

**CONCLUSIONS:** Functional integration of higher-order cognitive networks is intact in early psychosis but exhibits evidence of accelerated aging, suggesting the potential for intervention targeting cognition within the early psychosis period.

**Keywords:** Accelerated aging, Cingulo-opercular network, Cognition, Early psychosis, Fronto-parietal network, Global efficiency

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Psychotic disorders typically manifest during late adolescence or early adulthood as the end result of an abnormal neurodevelopmental process (1) likely shaped by a combination of genetic risk (2), pre- and perinatal factors (3,4), and environmental stress (5). While neurodevelopmental in nature, psychotic disorders are also characterized by accelerated aging, indicating more rapid aging processes following illness onset (6). Markers of accelerated aging in psychosis span biological systems and include shorter telomere length (7), increased inflammatory markers (8), and functional deterioration in the context of cognitive decline (9). Patients with psychotic disorder also demonstrate accelerated brain aging, as demonstrated by a sharper decline in gray matter volume (10) and white matter integrity (10,11), and increased brain age gap (12,13) compared with healthy individuals and patients with depression.

Another marker of brain aging is resting-state functional connectivity, which estimates the degree of interconnectivity between brain regions. Resting-state functional connectivity declines throughout healthy aging, particularly for connections within networks (14). Age-related reductions in functional connectivity occur earliest in higher-order cognitive networks, such as the frontoparietal network (FPN) and cingulo-opercular network (CON), which support domain-general cognitive ability (15–18). Reduced FPN and CON connectivity occurs in the context of stable visual network connectivity (15,17), suggesting that cognitive networks are most vulnerable to age-related decline in the healthy population (19).

Abnormal resting-state functional connectivity has been widely reported in psychotic disorders (20–22). While average functional connectivity is the most commonly used metric of

network connectivity, efficiency, which reflects integration of information transfer within a given network (23), is a potentially more sensitive measure of network alterations and vulnerability to aging abnormalities (24–26). Older adults with vascular dementia, for instance, exhibit lower global efficiency, which is associated with greater cognitive impairment (27). Patients with stroke with lesions in nodes critical for highly efficient network connectivity exhibit greater cognitive and functional impairment compared with patients with lesions in areas less critical for network integration (28). Network efficiency is therefore sensitive to alterations in neurodegenerative disorders and localized brain lesions.

The only prior study of accelerated aging of functional networks in schizophrenia, by Sheffield *et al.* (29), found that functional network efficiency of the CON and FPN declines at an accelerated rate in schizophrenia. However, limitations of this study, including modest sample sizes (especially for a study on age effects), a focus on individuals in the chronic stage of schizophrenia, and use of regressed task effects to estimate resting-state functional connectivity that yields different estimates of functional connectivity than pure resting-state functional magnetic resonance imaging (fMRI) (30) and drives heterogeneous findings in clinical populations (31), raise concerns about reproducibility and generalization. Moreover, growing evidence indicates that accelerated aging processes observed in schizophrenia are also present in bipolar disorder, including reduced telomere length (32), altered immune functioning (33), and increased oxidative stress (34). However, whether accelerated aging of functional networks extends to psychotic bipolar disorder has not been investigated.

The current investigation used a large sample of individuals with schizophrenia and bipolar disorder, including a significant number of individuals in the early stage of psychosis, to address the limitations and knowledge gaps described above. The primary goal of this study was to determine whether accelerated aging of the FPN and CON, identified in an earlier smaller study of largely chronic patients, replicates in a substantially larger independent dataset and, if so, to confirm the specificity of differential aging effects compared with other networks. Secondary goals were to 1) determine whether bipolar disorder is associated with similar patterns of accelerated aging as schizophrenia, 2) replicate prior associations between network efficiency and cognition, and 3) examine the effect of illness stage (i.e., chronic or early stage) on CON and FPN efficiency.

## METHODS AND MATERIALS

### Participants

A total of 506 individuals who participated in one of three MRI studies (CT00762866, 1R01MH070560, or 1R01MH102266) were included in this investigation. This included 197 healthy control participants (HCs) and 309 individuals with a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, or schizophreniform) or bipolar disorder type I with psychotic features (i.e., psychotic bipolar disorder). Patients with psychotic disorder were recruited from the Psychotic Disorders Program in the Department of Psychiatry and Behavioral Sciences at Vanderbilt University Medical Center. HCs were recruited from Nashville, Tennessee, and the

surrounding area via advertisements and word of mouth. The studies were approved by the Vanderbilt Institutional Review Board, and all study participants provided written informed consent.

Diagnosis was confirmed using the Structured Clinical Interview of the DSM-IV (35). Exclusion criteria were similar across the three studies, including age under 16 years or over 65 years (55 years in 1R01MH102266); estimated premorbid IQ less than 70 based on the Wechsler Test of Adult Reading (36); history of significant head trauma, medical illness, or central nervous system disorder; pregnancy or lactation; substance abuse within the last 1 month for patients (3 months in 1R01MH102266) or lifetime history of substance abuse/dependence in HCs; first-degree relative with a psychotic illness (HCs only); and MRI contraindications.

Of the 506 individuals included in the study, 48 were excluded for neuroimaging processing failures (e.g., segmentation/normalization errors due to poor-quality structural scans), 38 resting-state scans (32 patients with psychosis and 6 HCs) did not meet our quality assurance threshold described below, and 2 subjects were identified as multivariate outliers (age and network efficiency were tested using Mahalanobis distance). Thus, the final sample included 240 patients with psychosis and 178 HCs (Table 1).

### Cognitive Testing

All participants completed the Screen for Cognitive Impairment in Psychiatry (SCIP) (37), a brief (10- to 15-minute) measure that assesses immediate verbal memory, working memory, verbal fluency, delayed verbal memory, and processing speed [see (21) for a description of the SCIP]. General cognitive ability was estimated as the first factor of an exploratory principal axis factor analysis including SCIP subscores across all final subjects and explained 57% of the variance in performance across tasks. The first factor was the only factor with an eigenvalue > 1.

### Neuroimaging Data Acquisition and Preprocessing

Neuroimaging data were collected on one of two identical 3T Philips Intera Achieva scanners (Philips Healthcare, Andover, MA) located at the Vanderbilt Institute for Imaging Sciences. Scanning parameters, number of participants scanned under each protocol, and imaging preprocessing steps are described in detail in the Supplement. Briefly, a 7-minute (eyes closed) or 10-minute (eyes open, fixation) echo-planar imaging resting-state fMRI scan and T1-weighted anatomical images (1-mm isotropic resolution) were collected on each subject. fMRI data preprocessing was performed using the SPM12 package (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) and included correction for head motion using rigid body motion correction, spatial coregistration to T1-weighted anatomical images, spatial normalization to Montreal Neurological Institute space, and spatial smoothing (6-mm full width at half maximum kernel).

### Functional Connectivity

Following preprocessing, fMRI data were bandpass filtered (0.01–0.10 Hz), and blood oxygen level–dependent time-series data were extracted from 264 regions of interest (ROIs) [6-mm spheres corresponding to the Power Atlas (38)]. Following

**Table 1. Demographics and Participant Characteristics**

Demographics	Healthy Control Subjects ( <i>n</i> = 178)	Patients With Psychosis ( <i>n</i> = 240)	Omnibus Statistic
Age, Years	28.99 (10.45)	28.71 (10.73)	$t_{416} = 0.267, p = .790$
Gender, M/F	109/69	155/85	$\chi^2 = 0.492, p = .483$
Race, C/AA/O	124/42/12	174/52/13	$\chi^2 = 2.55, p = .467$
Parental Education, Years	14.46 (2.24)	14.73 (2.65)	$t_{372} = 1.02, p = .308$
Personal Education, Years	15.15 (2.22)	13.52 (2.16)	$t_{391} = 7.26, p < .001$
WTAR	111.28 (11.20)	102.33 (15.14)	$t_{415} = 6.63, p < .001$
Cognitive Factor Score	0.535 (0.56)	-0.392 (0.94)	$t_{413} = 11.71, p < .001$
Duration of Illness, Months	-	87.88 (111.96)	-
PANSS Positive	-	16.29 (8.01)	-
PANSS Negative	-	14.03 (6.48)	-
PANSS General	-	29.64 (8.22)	-
PANSS Total	-	59.64 (18.56)	-
Montgomery-Åsberg Depression Rating Scale	-	8.83 (8.52)	-
Young Mania Rating Scale	-	4.67 (7.39)	-
Chlorpromazine Equivalent	-	390.10 (237.07)	-
Schizophrenia/Psychotic Bipolar Disorder	-	177/63	-
Early Psychosis/Chronic Psychosis	-	110/130	-

Values are *n* or mean (SD).

AA, African American; C, Caucasian; F, female; M, male; O, other race; PANSS, Positive and Negative Syndrome Scale; WTAR, Wechsler Test of Adult Reading.

removal of nuisance signals related to head motion, white matter, cerebrospinal fluid, and the global gray matter signal regression, the ROI-to-ROI correlation matrix was calculated. A priori power network assignments for each ROI were used to define the CON, FPN, subcortical network, and visual network (29) (Supplement).

Multiple steps were taken to minimize the effects of head motion on functional connectivity estimates (Supplement). Briefly, 12 nuisance regressors, anatomical CompCor (39), and signal-to-noise ratio calculations were applied. Subjects with median temporal signal-to-noise ratios below the 5th percentile or median intraframe voxel displacements above the 95th percentile of the entire sample were excluded from further analysis.

### Global Efficiency

Network efficiency was calculated using the Brain Connectivity Toolbox (23) in MATLAB (The Mathworks, Inc., Natick, MA). A priori network ROIs were extracted from thresholded whole-brain graphs (5%–10% strongest positive connections) (see Supplement), resulting in a CON, FPN, subcortical, and visual subgraph for each subject at each threshold. The global efficiency algorithm was then applied to network-specific subgraphs. Global efficiency yields a single metric estimating the potential for information transfer within a network and reflects network integration (23). Efficiency metrics calculated at each threshold (5%–10%) were averaged to produce a single estimate for each network used in data analysis.

### Statistical Analysis

Similar to previous work (29), presence of accelerated network aging was tested using linear regression analysis. Age, group

(patients with psychosis or HCs), gender, race, study, and group by age interaction terms were entered as predictors of network efficiency. Significant interactions reflecting accelerated aging were further explored by examining within-group bivariate correlations and comparing correlations between groups using Fisher *r*-to-*z* transformation and subsequent one-tailed independent-samples *t* test of *z*-transformed coefficients. Relationships between age and efficiency were followed up, controlling for chlorpromazine (CPZ) equivalent and duration of illness, to help determine whether medication use and illness chronicity were driving accelerated aging effects. The accelerated aging hypothesis was tested on efficiency of the visual and subcortical networks to determine specificity of our CON/FPN results.

The association between network efficiency and overall cognition was examined using linear regression with cognition (i.e., SCIP factor score) entered as the dependent variable and diagnostic group, gender, race, protocol, network metric, and metric by group interaction entered as predictors, allowing for analysis of behavioral consequences related to changes in efficiency.

Group differences in efficiency for illness stage (early psychosis, chronic psychosis, or HCs) were analyzed through repeated-measures analysis of variance (ANOVA) and follow-up univariate ANOVA, controlling for age, gender, race, and protocol. These analyses were included to determine whether network efficiency is already reduced at illness onset compared with HCs to aid in our interpretation of the accelerated aging results [e.g. (40)]. Follow-up analyses comparing just early and chronic psychosis, controlling for age, were also explored because group differences that remain after controlling for age would suggest a substantial impact of illness wear and tear on the accelerated aging findings. Subcortical efficiency was included in these analyses to test for further

replication of previously published findings (41). Early psychosis was defined as study participation within 2 years following onset of psychosis.

## RESULTS

### Accelerated Aging of Functional Networks

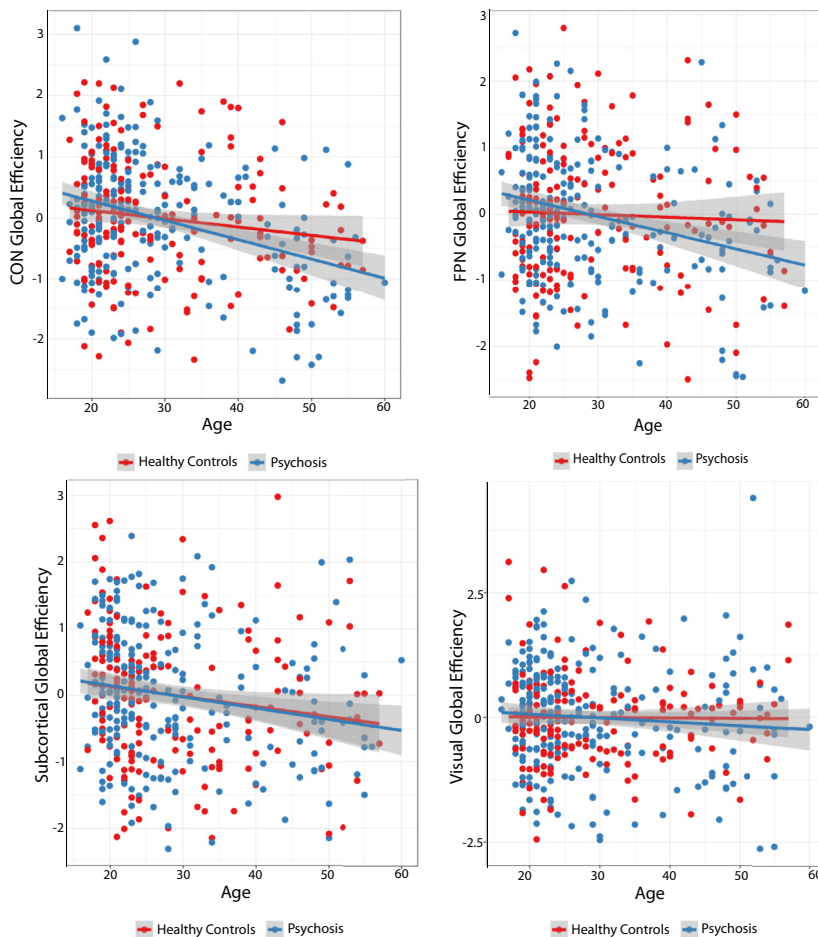
CON efficiency was significantly negatively associated with age across all subjects ( $t_{416} = -5.61, p < .001$ ). A significant group by age interaction ( $t_{416} = -2.15, p = .034$ ) (Figure 1) was due to a stronger association ( $z = 2.34, p = .019$ ) between age and CON efficiency in patients with psychosis ( $r = -.37, p < .001$ ) than in HCs ( $r = -.16, p = .036$ ).

Age was also negatively associated with FPN efficiency ( $t_{416} = -3.627, p < .001$ ), with a significant group by age interaction ( $t_{416} = -2.33, p = .02$ ) also due to a stronger negative association ( $z = 2.66, p = .008$ ) between age and FPN efficiency in patients with psychosis ( $r = -.31, p < .001$ ) than in HCs ( $r = -.05, p = .489$ ).

To determine the impact of disorder chronicity on our findings, we examined the effect of CPZ equivalent and duration of illness on associations between efficiency and age. Age remained significantly associated with efficiency when

controlling for CPZ equivalent (CON:  $t_{193} = -6.75, p < .001$ ; FPN:  $t_{193} = -3.80, p < .001$ ). CPZ equivalent was not significantly associated with efficiency (CON:  $t_{193} = 0.33, p = .739$ ; FPN:  $t_{193} = -0.55, p = .580$ ). Furthermore, both CON ( $t_{227} = -4.15, p < .001$ ) and FPN ( $t_{227} = -2.39, p = .018$ ) were significantly associated with age after controlling for duration of illness.

To assess specificity of accelerated aging to higher-order cognitive networks, we tested for accelerated aging in two additional networks: the subcortical network, which may be influenced by antipsychotic drug use; and the visual network, which has shown preserved connectivity in healthy aging (16). Although age was significantly negatively associated with subcortical efficiency ( $t_{416} = -3.68, p < .001$ ), no significant group interaction was observed ( $t_{416} = -0.270, p = .787$ ). In the psychosis group alone, the relationship between age and subcortical efficiency ( $t_{193} = -2.52, p = .012$ ) was attenuated when controlling for CPZ equivalent ( $t_{193} = -1.74, p = .083$ ), and CPZ equivalent was significantly associated with efficiency ( $t_{193} = -2.69, p = .008$ ). Visual network efficiency was not associated with age across subjects ( $t_{416} = -1.11, p = .267$ ), with no significant group interaction ( $t_{416} = -0.761, p = .447$ ). Accelerated aging effects of the CON and FPN in



**Figure 1.** Differential association between age and diagnosis for cingulo-opercular network (CON) and frontoparietal network (FPN) efficiency. A significant age by diagnosis interaction was observed when predicting CON global efficiency ( $t_{416} = -2.15, p = .034$ ) and FPN global efficiency ( $t_{416} = -2.33, p = .02$ ) but not subcortical network efficiency ( $t_{416} = -0.270, p = .787$ ) or visual network efficiency ( $t_{416} = -0.761, p = .447$ ), controlling for age, group, race, gender, and protocol. Shaded areas represent 95% confidence intervals. Global efficiency values are marginal means after controlling for covariates of no interest.

patients with psychosis remained when controlling for subcortical and visual network efficiency (CON:  $t_{416} = -2.15$ ,  $p = .032$ ; FPN:  $t_{416} = -2.30$ ,  $p = .022$ ).

We repeated the analysis of the CON and FPN considering psychotic disorder diagnosis to determine whether patients with schizophrenia and psychotic bipolar disorder demonstrate similar patterns of accelerated aging (results discussed in detail in the Supplement). Briefly, in each group, age was similarly associated with efficiency of the CON (bipolar disorder:  $r = -.41$ ; schizophrenia:  $r = -.36$ ) and FPN (bipolar disorder:  $r = -.23$ ; schizophrenia:  $r = -.33$ ).

### Network Efficiency and Cognitive Ability

CON efficiency was significantly associated with cognition across all subjects ( $t_{413} = 2.17$ ,  $p = .03$ ) in the context of a significant group interaction ( $t_{413} = 2.39$ ,  $p = .018$ ) driven by a positive association between CON efficiency and cognition in participants with psychosis ( $r = .16$ ,  $p = .012$ ) but not in HCs ( $r = -.06$ ,  $p = .420$ ) (Figure 2).

FPN efficiency was also associated with cognition across all subjects ( $t_{413} = 3.26$ ,  $p = .001$ ), with no significant group interaction ( $t_{413} = -0.22$ ,  $p = .830$ ); the correlations were similar in patients with psychosis ( $r = .12$ ,  $p = .066$ ) and HCs ( $r = .23$ ,  $p = .002$ ).

Subcortical network efficiency was not associated with cognition across all subjects ( $t_{413} = 1.58$ ,  $p = .114$ ), and there was no group interaction ( $t_{413} = 1.18$ ,  $p = .239$ ; patients with psychosis:  $r = .18$ ,  $p = .005$ ; HCs:  $r = .10$ ,  $p = .185$ ).

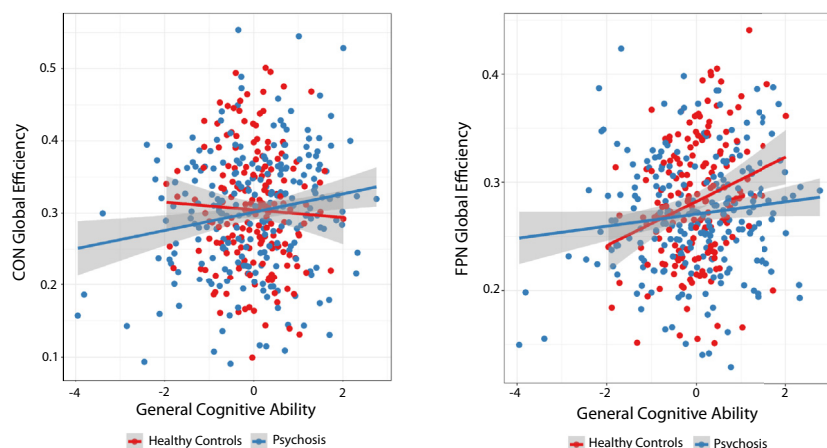
We further examined the group by age interaction when predicting higher-order cognition to better elucidate our findings. This interaction was not significant ( $t_{413} = -1.04$ ,  $p = .301$ ) because age was similarly related to cognition in both patients with psychosis ( $r = -.27$ ,  $p < .001$ ) and HCs ( $r = -.30$ ,  $p < .001$ ).

Finally, to test specificity of FPN and CON efficiency with current cognitive ability, relationships with premorbid crystallized knowledge from the Wechsler Test of Adult Reading were assessed. Analyses revealed nonsignificant associations between CON/FPN efficiency and crystallized knowledge and continued relationships with current cognitive ability when controlling for crystallized knowledge (Supplement).

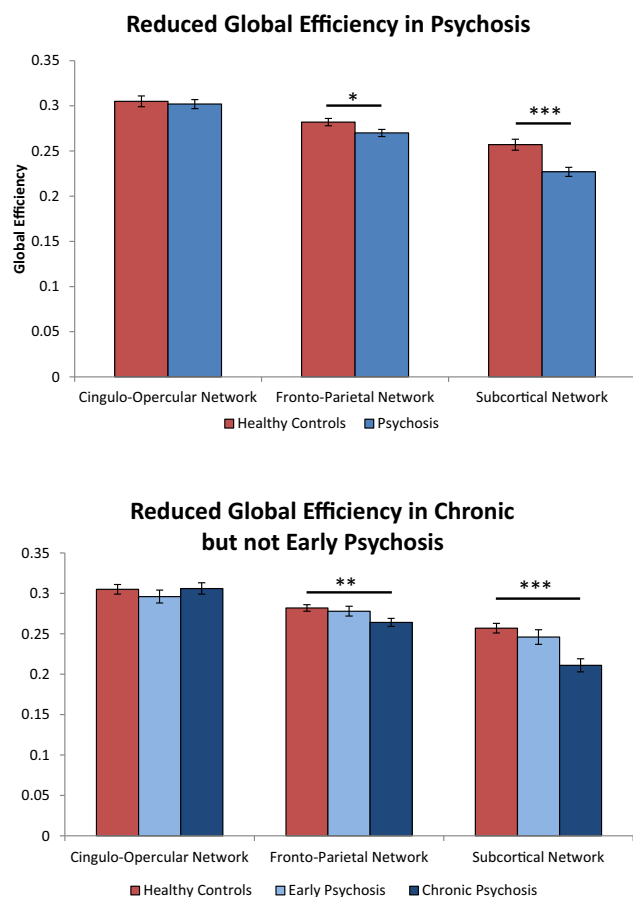
### Group and Illness Stage Effects on Network Efficiency

While regression analysis revealed significantly different slopes between age and efficiency in each group (an estimate of rate of decline in our cross-sectional sample), we aimed to determine 1) whether there were group differences in overall network efficiency and 2) whether accelerated aging could be further understood through group differences based on illness stage to aid in inference about trajectory. In a repeated-measures ANOVA with network (FPN, CON, or subcortical) as a within-subjects factor and group (HCs or patients with psychosis) as a between-subjects factor, participants with psychosis demonstrated significant overall reduction in network efficiency compared with HCs ( $F_{1,411} = 11.52$ ,  $p = .001$ ) (Figure 3, top) a significant main effect of network ( $F_{2,822} = 37.52$ ,  $p < .001$ ), and a significant group by network interaction ( $F_{2,822} = 3.54$ ,  $p = .029$ ). A follow-up univariate ANOVA revealed that FPN efficiency ( $F_{1,411} = 5.06$ ,  $p = .025$ ) and subcortical efficiency ( $F_{1,411} = 12.76$ ,  $p < .001$ ), but not CON efficiency ( $F_{1,411} = 0.16$ ,  $p = .688$ ), were significantly reduced in patients with psychosis.

Regarding illness stage, there was a significant overall group difference in network efficiency ( $F_{1,410} = 7.89$ ,  $p < .001$ ) (Figure 3, bottom), a significant main effect of network ( $F_{2,820} = 43.75$ ,  $p < .001$ ), and a significant group by network interaction ( $F_{2,820} = 4.08$ ,  $p = .003$ ). Univariate ANOVAs revealed no main effect of group for CON global efficiency ( $F_{2,410} = 0.44$ ,  $p = .643$ ) and no differences between HCs and both early-stage patients ( $p = .398$ ) and chronic patients ( $p = .888$ ). FPN efficiency, however, showed a significant main effect of group ( $F_{2,410} = 4.27$ ,  $p = .015$ ), with reduced FPN efficiency in patients with chronic psychosis ( $p = .004$ ) but similar FPN efficiency in patients with early psychosis ( $p = .553$ ) compared with HCs. Subcortical efficiency also significantly differed between groups ( $F_{2,410} = 10.66$ ,  $p < .001$ ), with chronic patients ( $p < .001$ ) but not early-stage patients ( $p = .317$ ) demonstrating reduced subcortical efficiency compared with HCs. After controlling for age, early and chronic patients did not significantly differ on CON efficiency ( $F_{2,237} = 2.68$ ,  $p = .103$ ), FPN efficiency ( $F_{2,237} = 1.12$ ,  $p = .291$ ), or subcortical efficiency ( $F_{2,237} = 3.58$ ,  $p = .06$ ).



**Figure 2.** General cognitive ability is associated with cingulo-opercular network (CON) and frontoparietal network (FPN) efficiency. General cognitive ability was significantly positively associated with CON global efficiency ( $t_{413} = 2.17$ ,  $p = .03$ ) and FPN global efficiency ( $t_{413} = 3.26$ ,  $p = .001$ ) across all subjects when controlling for age, group, gender, race, and protocol. A significant group by efficiency interaction was observed in the CON owing to a significant positive association in patients with psychosis ( $r = .16$ ,  $p = .012$ ) not observed in healthy control subjects ( $r = -.06$ ,  $p = .420$ ). Shaded areas represent 95% confidence intervals.



**Figure 3.** Group differences in network efficiency. Group differences in network efficiency were tested in a repeated-measures analysis of variance with three networks as within-subject factors. A significant main effect of group was found for both healthy control subjects vs. patients with psychosis ( $F_{1,411} = 11.52, p = .001$ ) (top) and healthy control subjects vs. patients with early psychosis vs. patients with chronic psychosis ( $F_{2,410} = 7.89, p < .001$ ) (bottom). Follow-up univariate analyses of variance demonstrated that this omnibus group difference was driven by reduced global efficiency in the frontoparietal network and subcortical network, primarily in patients with chronic psychosis. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .

Finally, while connectivity of the whole brain was lower in patients with psychosis ( $t_{415} = 1.88, p = .06$ ), group differences in efficiency were largely unchanged when including whole-brain connectivity as a covariate, suggesting that graph results are minimally influenced by overall connectivity differences (42) (Supplement).

## DISCUSSION

In a large sample of patients with psychotic disorder and HCs, we confirmed evidence of accelerated functional network aging in psychosis. Accelerated aging was observed in the FPN and CON, two networks that have shown the earliest evidence of connectivity decline in prior studies of healthy aging (15,18). Furthermore, prior findings of stable visual network connectivity were confirmed in both HCs and patients with psychosis, strengthening the evidence that differential associations

between network efficiency and age in the CON and FPN are due to an accelerated aging process as opposed to a general reduction in network efficiency. When controlling for CPZ equivalent, relationships between efficiency and age remained for the CON and FPN but were attenuated in the subcortical network, arguing against a general medication effect on network topology. Accelerated aging of FPN and CON efficiency has real-world consequences because lower efficiency of these networks was associated with worse general cognition. Finally, FPN and CON efficiency was intact in early psychosis, but FPN efficiency was significantly reduced in the chronic state, providing additional validation for efficiency reductions following illness onset. This implies that intervention even after the first episode of psychosis may provide significant benefits.

Typically, functional network connectivity declines with age, occurring earliest within higher-order cognitive networks (15,18). In older versus younger adults, FPN and CON efficiency, but not visual or somatosensory network efficiency, is reduced (17) in the context of reduced whole-brain modularity, suggesting that lower within-network efficiency results in a less segregated whole-brain system. Older adults' functional networks are also more susceptible to perturbation, with a larger decline in network efficiency following computational lesioning (i.e., node removal) than is seen in younger adults (43). Comparing cognitive and emotion processing networks, only cognitive networks exhibit reduced functional connectivity in older adults, which is associated with poorer cognitive performance (44). Furthermore, effective connectivity between the anterior insula and dorsal anterior cingulate cortex, two hub nodes of the CON, is reduced in older adults and associated with worse cognition (39). In the current study, CON efficiency was also significantly associated with age in our healthy cohort; however, the magnitude of this relationship was significantly less than in patients with psychosis. This suggests that a normative pattern of decline in network integrity occurs in psychotic disorders, but the rate of decline is more rapid than expected in healthy aging.

Accelerated decline of resting-state network integrity in psychotic disorders occurs in the context of abnormal resting-state functional connectivity throughout the life course. Ultra-high-risk patients demonstrate significantly reduced anticorrelation between the default mode network and regions comprising the FPN and CON (45–47), and there is reduced within- and between-network connectivity of the FPN and CON in chronic states (48–50). Furthermore, reduced connectivity and efficiency of the CON occurs across the psychosis spectrum, including in youths on the psychosis spectrum (51) and individuals in the general population who endorse psychotic-like experiences (52). In our data, CON efficiency was not reduced in either chronic or early psychosis, even in the context of accelerated aging, suggesting that CON efficiency is intact, and possibly even slightly greater in patients with early psychosis than in HCs, although the difference was nonsignificant. Given the presence of connectivity alterations in high-risk youths and youths on the psychosis spectrum, we were surprised to find intact CON and FPN efficiency in our patients with early psychosis; however, there is growing evidence that dysconnectivity of higher-order cognitive networks is not present in early psychosis. For instance,

functional connectivity within the FPN and CON is normal in medication-naïve, first-episode patients (53,54), global efficiency abnormalities were not present at baseline or 12 months later in an early psychosis sample (55), and analysis of network topology during a cognitive control task revealed intact global efficiency in subjects with first-episode psychosis versus healthy control subjects (56). Findings of intact network efficiency in early psychosis, and nonsignificant differences in network efficiency for early and chronic patients when controlling for age, aid our understanding of network trajectories (40); together, they suggest that network efficiency is intact in early psychosis and that the network alterations more reliably observed in chronic states may be manifestations of an accelerated aging process.

Accelerated aging in psychotic disorders is a growing literature based on mounting evidence that processes observed in healthy aging are occurring earlier and/or at a more rapid rate in patients with psychosis (57). A recent review reported fairly consistent evidence of increased inflammation, oxidative stress, prolactin, and insulin resistance in schizophrenia (58). While the influence of environmental factors on accelerated aging have yet to be fully explored, abnormal glucose tolerance and metabolic profiles have been observed in antipsychotic-naïve patients with schizophrenia after controlling for a multitude of environmental confounds (59,60). Furthermore, gray matter volume and white matter integrity demonstrate evidence of accelerated aging in multiple studies and are unrelated to antipsychotic drug use (10,11) or smoking (61). Our finding that CON and FPN efficiency was not related to CPZ equivalent, but subcortical efficiency was, fits well with previous literature demonstrating that antipsychotics exert the greatest effect in subcortical regions (62) and chronic administration of antipsychotics decreases striatal neuron firing (63). Therefore, specificity of accelerated aging in the CON and FPN, but not in the subcortical network, suggests that medication use is not driving accelerated aging of higher-order networks. Although still an open question, degradation of gray matter volume and white matter pathways may contribute to alterations in functional connectivity observed in the current study, a hypothesis recently supported by accelerated decline of white matter tracts associated with higher-order cognitive functioning in schizophrenia not seen in tracts supporting sensorimotor information (61).

Finally, accelerated aging of FPN and CON efficiency has important implications for cognitive functioning in a population already affected by significant cognitive impairment. Activation in the FPN and CON supports domain-general cognitive ability, with regions in the FPN modulating activity for adaptive task control (e.g., error cues) and regions in the CON maintaining activation for stable task control (64). Reduced efficiency of these networks has now been associated with poorer general cognition in four independent datasets (41,52,65), providing strong evidence that the functional topology of these networks supports cognitive ability. It is notable, however, that a similar relationship between age and cognitive ability was observed in both groups, indicating that more rapid decline in FPN and CON efficiency in psychosis is not leading to a significantly steeper decline in cognition. Although speculative, this discrepancy may be due to our use of a relatively brief cognitive screen (SCIP), such that differential age effects may have been detected using a more comprehensive cognitive battery. Lastly,

we showed specific associations between FPN/CON efficiency and fluid cognitive ability as opposed to crystallized cognitive ability. This finding mirrors data in older adults, who typically show stable crystallized knowledge, such as word reading, and declining higher-order cognitive abilities, such as processing speed and verbal learning (66). Given the recently shown impact of accelerated aging on functional outcome (9), accelerated decline of information integration within higher-order cognitive networks implies an accelerated decline of functional outcome, which may in turn contribute to the increased mortality rates in schizophrenia recently reported (67).

The current study has several limitations. First, the data presented are cross-sectional and therefore cannot speak directly to changes in network efficiency over each individual's lifetime. Review of accelerated aging studies has noted this as a major limitation of most accelerated aging reports (58); however, given the relatively gradual changes in markers of aging, longitudinal studies over decades may be necessary to appropriately address this issue. Another limitation is the potential influence of confounding factors, for instance, antipsychotic drug use and metabolic disease. While not directly addressable here, the lack of accelerated aging in the subcortical network, continued accelerated aging in the CON and FPN when CPZ equivalent was included as a covariate, and the normative relationship between age and visual network efficiency in psychosis argue against a strong influence of antipsychotics, metabolic disease, or smoking on our results because cardiovascular risk factors should influence connectivity across the whole brain, not within specific networks. We also had several limitations for data collection; for instance, we cannot rule out that some subjects fell asleep during their resting-state scans, and we also used slightly different scanning protocols across studies, which we addressed by including protocol as a covariate. Finally, the age range for our sample was <65 years, truncating our ability to detect influences of age on efficiency in older adults.

## Conclusions

Here, in a cross-sectional study, we presented compelling evidence that functional integration of the FPN and CON, which support general cognitive ability, are subject to differential age effects in individuals with a primary psychotic disorder. These findings may explain network abnormalities observed in chronic patients that are often not observed in first-episode psychosis. What is hopeful about these findings is that efficiency of these critical networks may be responsive to intervention during the early stages of a psychotic disorder. In fact, both moderate aerobic exercise and cognitive training have been found to increase functional connectivity within the FPN and CON in older adults (68,69), and exercise increases some areas of cognition in patients with schizophrenia (70). If connectivity and cognition can be increased or protected during early stages of psychosis, functional outcome and ultimately mortality have the potential for improvement even following the diagnosis of a psychotic disorder.

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### ARTICLE INFORMATION

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