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Evidence for Accelerated Decline of Functional Brain Network Efficiency in Schizophrenia

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Previous work suggests that individuals with schizophrenia display accelerated aging of white matter integrity, however, it is still unknown whether functional brain networks also decline at an elevated rate in schizophrenia. Given the known degradation of functional connectivity and the normal decline in cognitive functioning throughout healthy aging, we aimed to test the hypothesis that efficiency of large-scale functional brain networks supporting overall cognition, as well as integrity of hub nodes within those networks, show evidence of accelerated aging in schizophrenia. Using pseudo-resting state data in 54 healthy controls and 46 schizophrenia patients, in which task-dependent signal from 3 tasks was regressed out to approximate resting-state data, we observed a significant diagnosis by age interaction in the prediction of both global and local efficiency of the cingulo-opercular network, and of the local efficiency of the fronto-parietal network, but no interaction when predicting both default mode network and whole brain efficiency. We also observed a significant diagnosis by age interaction for the node degree of the right anterior insula, left dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex. All interactions were driven by stronger negative associations between age and network metrics in the schizophrenia group than the healthy controls. These data provide evidence that is consistent with accelerated aging of large-scale functional brain networks in schizophrenia that support higher-order cognitive ability.

Key words: functional connectivity/accelerated aging/cognition/graph theory/central executive networks

Introduction

Schizophrenia is associated with increased risk for a multitude of biological and physiological pathologies, many of which occur in the process of normal aging, such as cardiovascular disease and diabetes.[1] Accordingly, individuals with schizophrenia have, on average, a 20% decrease in life expectancy as compared to the general population.[2,3] Given these trends, some have hypothesized that schizophrenia is a disorder of "accelerated aging," suggesting that individuals with schizophrenia experience age-related decline in functional, clinical, and biological processes at an elevated rate[4]—a process first introduced through Kraepelin's conceptualization of schizophrenia as "dementia praecox," a chronic and deteriorating neuropsychiatric disorder.

One area of accelerated decline that has been reported in schizophrenia is white matter integrity, which has been shown to reduce even in healthy aging.[5] Friedman and colleagues[6] observed significant reductions in fractional anisotropy (FA) in chronic schizophrenia, but not in first-episode schizophrenia (compared to age-matched controls). Although findings on progressive FA decline in schizophrenia are mixed,[7–9] Friedman's study provides evidence that white matter integrity reduces at an elevated rate throughout the course of the disorder. Studies have also found significant diagnosis by age interactions in the prediction of white matter integrity,[10] such that age shows a stronger relationship to white matter decline in schizophrenia than in healthy individuals; an interaction not observed in major depressive disorder.[11]

Although the mechanisms underlying accelerated decline in white matter integrity associated with aging

or schizophrenia remain unclear, studies have found that healthy aging is associated with a disruption of myelinated fibers that connect different cortical regions.[12–14] These changes in myelination and white matter integrity have critical implications for the integrity of "functional" connectivity in the brain, which is thought to reflect a history of coordinated neural activity between different brain regions, yielding stable, intrinsic functional brain networks.[15] Although no studies, to our knowledge, have looked for age-related alterations in functional connectivity in schizophrenia, aging in healthy individuals has been associated with reductions in the functional connectivity of large-scale brain networks,[16] and these changes in functional connectivity were associated with both reductions in white matter integrity and cognitive ability.[17]

In the current study, we aimed to assess whether the diagnosis by age interaction seen in studies of white matter in schizophrenia can be observed in functional connectivity. We focused on graph analysis of functional brain networks that support higher-order cognitive ability: the cingulo-opercular network (CON), fronto-parietal network (FPN), and default mode network (DMN) and hubs within those networks (right/left anterior insula [AI], right/left dorsolateral prefrontal cortex [DLPFC], and the dorsal anterior cingulate cortex [DACC]). Research suggests that, in healthy aging, functional networks that develop the latest (eg, networks supporting higher-order cognitive ability[18]) are also the first to show age-related changes in functional connectivity,[19,20] making these networks particularly vulnerable to an accelerated rate of decline. We hypothesized that we would observe significant diagnosis by age interactions, driven by stronger negative associations between age and network measures in schizophrenia. In addition, given previous work showing that higher-order cognition, but not crystallized knowledge, declines with aging[21] and is associated with connectivity in our networks of interest,[22] we hypothesized that both age and network metrics would be associated with a measure of overall cognition, but not crystallized knowledge.

Methods

Participants

Subjects were recruited and run through identical protocols at 5 sites (Washington University in St Louis, University of Minnesota, Maryland Psychiatric Research Center, University of California at Davis, and Rutgers University) as part of the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRACS) initiative[23] (table 1). All subjects signed informed consent before beginning the study (exclusion criteria in supplementary material). Of our schizophrenia patients (SCZ), 85% were taking an atypical antipsychotic, 4% were taking a typical antipsychotic, and 7% were taking both. Medication information was not available for 2 patients. Final analyses included 54 healthy controls (HC) and 46 SCZ, the same sample used in a previous study from our group.[22]

Procedure

Subjects completed the Hopkins Verbal Learning Task (HVLT[24]) and the Symbol-Coding task from the Brief Assessment of Cognition in Schizophrenia (BACSsc[25]) outside of the functional magnetic resonance imaging (fMRI) scanner. In the scanner, subjects completed the Dot Probe Expectancy task (DPX[26]), the Relational and

Table 1. Subject Demographics Split by Group and Median Age

Demographics, Mean (SD)	Young Healthy Controls, $N = 27$	Older Healthy Controls, $N = 27$	Young Schizophrenia, $N = 23$	Older Schizophrenia, $N = 23$	Young vs Older Healthy Controls	Young vs Older Schizophrenia
Gender (male/female)	23/4	16/11	21/2	16/7	$X^2 = 4.52$, $P = .03$	$X^2 = 3.45$, $P = .06$
Ethnicity (%Caucasian/% African American)	44/37	74/26	52/30	65/26	$X^2 = 7.5$, $P = .06$	$X^2 = 3.4$, $P = .49$
Subject education (y)	15.6 (2.4)	15.2 (2.8)	14.2 (2.2)	14.0 (2.3)	$F(1,52) = .33$, $P = .57$	$F(1,44) = .04$, $P = .85$
Subject SES	33.7 (12.3)	38.5 (12.0)	24.4 (5.2)	24.7 (6.5)	$F(1,52) = 3.1$, $P = .08$	$F(1,44) = .13$, $P = .72$
Father education (y)	15.2 (2.9)	13.5 (3.1)	14.7 (2.6)	14.4 (3.7)	$F(1,49) = 4.4$, $P = .04$	$F(1,44) = .09$, $P = .77$
Mother education (y)	14.4 (3.7)	13.1 (2.7)	14.5 (2.3)	13.5 (2.3)	$F(1,52) = 2.4$, $P = .13$	$F(1,44) = 1.96$, $P = .17$
Positive symptoms	—	—	10.4 (5.5)	9.9 (5.4)	—	$F(1,44) = .09$, $P = .77$
Negative symptoms	—	—	7.5 (2.5)	7.4 (2.2)	—	$F(1,44) = .04$, $P = .85$
Disorganized symptoms	—	—	4.7 (1.4)	5.5 (2.2)	—	$F(1,44) = 2.6$, $P = .11$
Depressive symptoms	—	—	7.4 (3.0)	8.0 (4.1)	—	$F(1,44) = .38$, $P = .54$
Manic symptoms	—	—	4.8 (1.3)	4.7 (1.7)	—	$F(1,44) = .08$, $P = .78$

Note: Younger healthy controls were significantly more likely to be male than in the older healthy control group. Otherwise, no significant differences in subject demographics were found between the old and young subjects within each diagnostic group. SES = socioeconomic status, measured using the Hollingshead Index as updated using occupational prestige ratings based on the 1989 general social survey (Hollingshead, 1958); Symptom scores within the schizophrenia group were calculated using the Brief Psychiatric Rating Scale (BPRS).

Item-Specific Encoding task (RISE[27]), and the Jittered Orientation Visual Integration task (JOVI[28]), yielding behavioral data from 5 domains: verbal learning, processing speed, goal maintenance, episodic memory, and visual integration. Overall cognition was approximated as the shared variance from a principle axis factor analysis that included performance from all 5 tasks. This factor analysis was performed using data from all subjects and revealed a single factor with an eigenvalue >1 that explained 40% of the variance. Subjects also completed the Wechsler Test of Adult Reading (WTAR[29]), a word-reading task, used to estimate crystallized knowledge.

Imaging data were collected in a single session using a consistent imaging protocol across sites (supplementary material). FMRI data were processed using in-house software that included slice timing correction, rigid body motion correction, normalization, and co-registration of functional volumes to a structural image in Talairach space (Washington University 711-2b atlas). Additional preprocessing steps were completed using custom code in MATLAB to improve the signal-to-noise ratio and minimize sources of artifactual correlation between brain regions (supplementary material). Task-dependent signal was modeled and regressed out using a generalized linear model to yield "pseudo-resting state" data. Residualized data from all 3 tasks runs (DPX, RISE, and JOVI) were then concatenated to yield a single, 60-minute timecourse of "pseudo-resting state" data. As discussed previously,[22] concatenated task residuals have been shown to provide an approximation of resting state data, allowing us to observe each subject's stable, intrinsic functional networks.[30] This pseudo-resting state data timeseries was subject to robust motion-correction[31] (supplementary material).

Graph Analysis

Node coordinates and network membership were defined based on the atlas of 264 region of interests (ROIs) published by Power and colleagues.[32] A priori node assignments for the FPN, CON, and DMN were used to construct our network graphs. ROIs for each node were 6 mm spheres. Freesurfer was used to segment tissue from our structural image to define a 264-ROI gray matter mask for each individual. Nine nodes did not overlap with our gray matter mask and were excluded (supplementary material), yielding a 255 × 255 whole brain matrix.

Blood-oxygen–dependent (BOLD) timecourses for each node were computed by averaging the timeseries for all voxels within each node for each subject. These average timeseries were then inter-correlated to yield a 255 × 255 whole brain correlation matrix of functional connectivity values. Individual subject whole brain matrices were thresholded to retain the top 10% to 5% strongest connections, with weak or negative correlation coefficients replaced by 0s. Nodes were extracted from the thresholded whole brain network, for each subject, to create network-specific weighted graphs for the FPN, CON, and the DMN.

Graph Metrics

Global and local efficiency were calculated for whole brain, FPN, CON, and DMN, as described in the supplementary material. Global efficiency measures a network's functional integration. Local efficiency measures the efficiency of a node's neighbors, following removal of that node, and therefore represents fault tolerance of nodes within a network.[33]

We measured "hub-ness" in 2 ways: participation coefficient and node degree. Participation coefficient measures the distribution of a node's edges among the various modules (communities) of a graph[34] and was calculated as described in the supplementary material (also see Rubinov and Sporns[33]). Node degree is the number of connections (ie, edges) that a node has within the whole brain network. A greater number of edges suggests a more connected node that is, therefore, important for integration of information across the whole brain network. Thus, participation coefficient measures how important that node is for inter-network communication, while degree instead quantifies how generally connected that node is, whether that is within or between networks.

Data Analysis

Graph metrics were computed in MATLAB using the Brain Connectivity Toolbox 2013_12_25.[33] Statistical analyses were completed in SPSS v20. Diagnosis by age interactions were calculated in linear regression analyses that included diagnosis, age, and a diagnosis by age interaction variable in the prediction of graph metrics and cognitive measures. Bonferroni procedures were used to adjust significance levels for each a priori graph metric, depending on the number of networks/nodes tested (global efficiency: 0.05/4 = 0.017; local efficiency: 0.05/4 = 0.017; participation coefficient: 0.05/5 = 0.01; degree: 0.05/5 = 0.01). Significant differences in correlation coefficients were determined using formulas provided by Meng and colleagues.[35] Group differences in graph metrics for older and younger subjects (based on median-split) were calculated through multivariate analysis of variances (MANOVAs; results presented in supplementary material). Group differences in cognitive variables were calculated using one-way ANOVAs. Correlation analyses were performed using a Pearson's correlation coefficient, and mediation analysis was performed using macros provided by Preacher and Hayes.[36]

Results

Diagnosis by Age Effects for Global Efficiency of Functional Networks

Regression analysis revealed a significant main effect of age ($\beta = -.31$, $t(99) = -3.19$, $P = .002$), but no significant

main effect of diagnosis (β = .19, $t(99) = 0.63$, $P = .53$) or diagnosis by age interaction (β = .01, $t(99) = 0.02$, $P = .98$) in the prediction of whole brain global efficiency, suggesting that both SCZ and HC experienced a similar reduction in whole brain global efficiency with age (figure 1A). Similarly, although global efficiency of the DMN was significantly negatively associated with age (β = −.39, $t(99) = -4.17$, $P < .001$), no main effect of diagnosis (β = .18, $t(99) = .62$, $P = .54$) or diagnosis by age interaction was observed (β = .01, $t(99) = 0.04$, $P = .97$; figure 1B).

Analysis of the cognitive networks, however, revealed significant main effects of age (β = −.45, $t(99) = -5.01$, $P < .001$) and diagnosis (β = .81, $t(99) = 2.88$, $P = .005$; HC > SCZ) for CON, that were modified by a significant diagnosis by age interaction (β = −.82, $t(99) = -2.93$, $P < .01$; figure 1C). This interaction was driven by a significantly stronger negative correlation ($z = -2.85$, $P = .004$) between age and CON global efficiency in SCZ ($r = -.66$, $P < .001$) than in HC ($r = -.20$, $P = .15$). A similar pattern was observed in the FPN (figure 1D); global efficiency of the FPN was significantly negatively associated with age (β = −.37, $t(99) = -3.94$, $P < .001$), though not with diagnosis (β = .47, $t(99) = 1.6$, $P = .11$), with a trend toward a diagnosis by age interaction (β = −.56, $t(99) = -1.88$, $P = .06$), again reflecting a stronger negative association between age and FPN global efficiency in SCZ ($r = -.46$, $P = .001$) than HC ($r = -.24$, $P = .08$).

Within SCZ, the correlation between age and CON global efficiency was significantly stronger than for whole brain ($z = -2.65$, $P = .004$) or DMN ($z = -2.64$, $P = .004$). These significant differences in correlation magnitude were not observed for HC (zs < 1.54, Ps > .06).

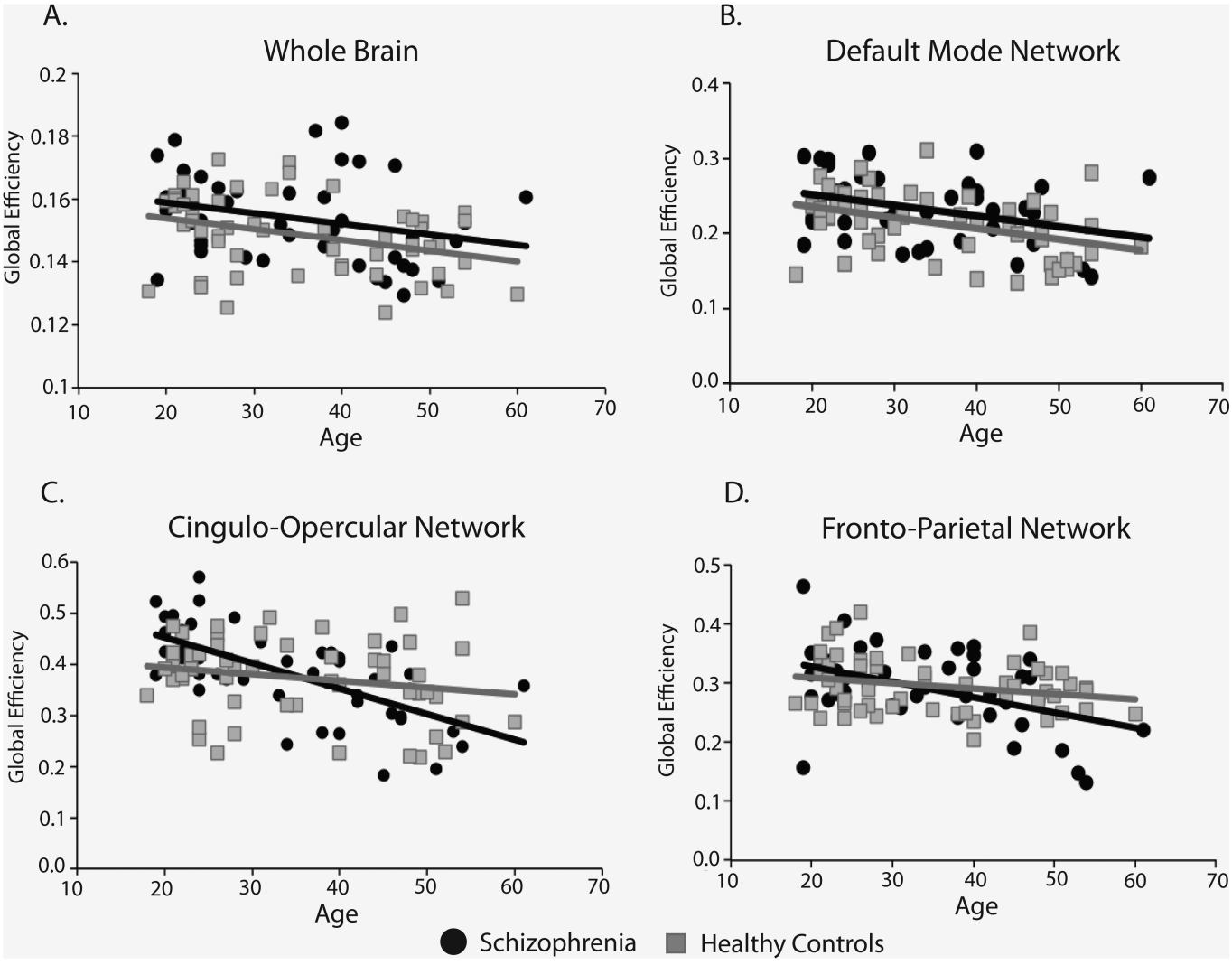

Fig. 1. Associations between global efficiency and age. Diagnosis by age interactions were nonsignificant for (A) the whole brain (β = .01, $P = .98$) and (B) the default mode network (β = .01, $P = .97$), but reached significance for (C) the cingulo-opercular network (CON; β = −.82, $P < .01$) and trended for (D) the fronto-parietal network (β = −.56, $P = .06$). A significantly stronger negative association between age and CON global efficiency was observed in schizophrenia, compared to healthy controls.

Diagnosis by Age Effects for Local Efficiency of Functional Networks

All functional networks showed significant negative associations between age and local efficiency across groups (all *t*s > 3.78, all *P*'s<.001), and there was a significant main effect of diagnosis for the CON (β = .76, $t(99) = 2.70$, $P = .008$; HC > SCZ), but not the whole brain ($P = .20$), FPN ($P = .08$), or DMN ($P = .37$). However, there was a significant diagnosis by age interaction for the CON (β = −.90, $t(99) = -3.20$, $P = .002$; figure 2C) and trending for the FPN (β = −.63, $t(99) = -2.11$, $P = .04$; figure 2D). The diagnosis by age interaction in the CON was again driven by a significantly stronger negative association between age and local efficiency in SCZ than HC ($z = -2.80$, $P = .005$). There were no significant interactions for the whole brain (β = −.24, $t(99) = -0.84$, $P = .40$; figure 2A) or the DMN (β = −.11, $t(99) = -.39$, $P = .70$; figure 2B).

Diagnosis by Age Effects for a priori Hubs

When looking at the degree of our a priori nodes, we observed significant main effects of diagnosis for right AI, DACC, and left DLPFC (all *P*s < .02, HC > SCZ for AI and DLPFC, SCZ > HC for DACC), which were modified by significant diagnosis by age interactions for right AI (β = −.88, $t(99) = -2.86$, $P = .005$), DACC (β = −.88, $t(99) = -2.91$, $P = .005$) and left DLPFC (β = −1.08, $t(99) = -3.63$, $P < .001$; figure 3). The interactions in right AI and DACC were driven by stronger negative associations between degree and age in SCZ (right AI: $r = -.35$, $P = .017$; DACC: $r = -.45$, $P < .01$) as compared to the HC (right AI: $r = .20$, $P = .15$; DACC: $r = .07$, $P = .61$). Surprisingly, the diagnosis by age interaction in the left DLPFC was driven by a negative correlation with age in SCZ ($r = -.38$, $P < .01$) but a significant positive correlation with age in the HC ($r = .31$, $P = .03$). There were no significant effects of age or age by diagnosis interactions for participation coefficients for any of our hub nodes.

Associations With Cognitive Ability

In previous work, we found that efficiency of the FPN and CON significantly predicted overall cognition across this sample of SCZ and HC.[22] Here, we expanded on these findings by assessing relationships between age, graph metrics, and both crystallized and overall cognition, in part to determine whether or not FPN or CON graph metrics mediated any relationships between age and cognition in SCZ or HC. SCZ had significantly impaired overall cognition ($F(1,98) = 34.34$, $P < .001$), but not crystallized knowledge ($F(1,98) = 1.34$, $P = .24$), when compared to the HC group. This was also true when comparing either young SCZ and HC ($F(1,48) = 17.04$, $P < .001$), or older SCZ and HC ($F(1,48) = 25.24$, $P < .001$).

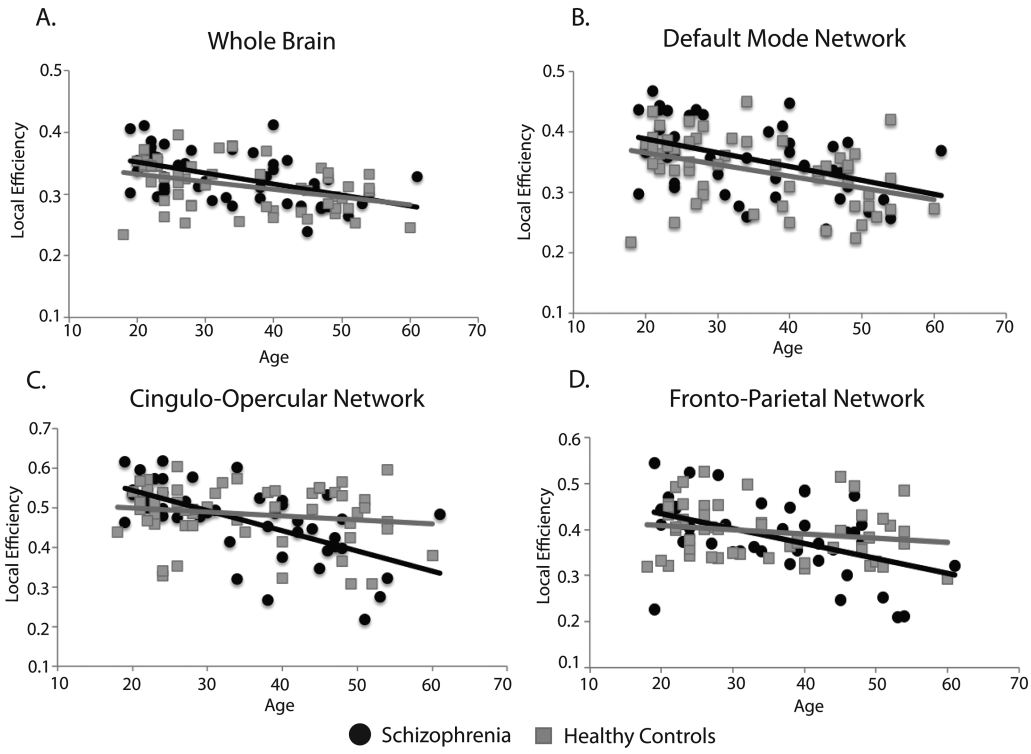

Fig. 2. Associations between local efficiency and age. Diagnosis by age interactions were nonsignificant for (A) the whole brain (β = −.24, $P = .40$) and (B) the default mode network (β = −.11, $P = .70$), but reached significance for (C) the cingulo-opercular network (CON; β = −.90, $P < .01$), and (D) the fronto-parietal network (β = −.63, $P < .05$). A significantly stronger negative association between age and CON local efficiency was observed in schizophrenia, compared to healthy controls.

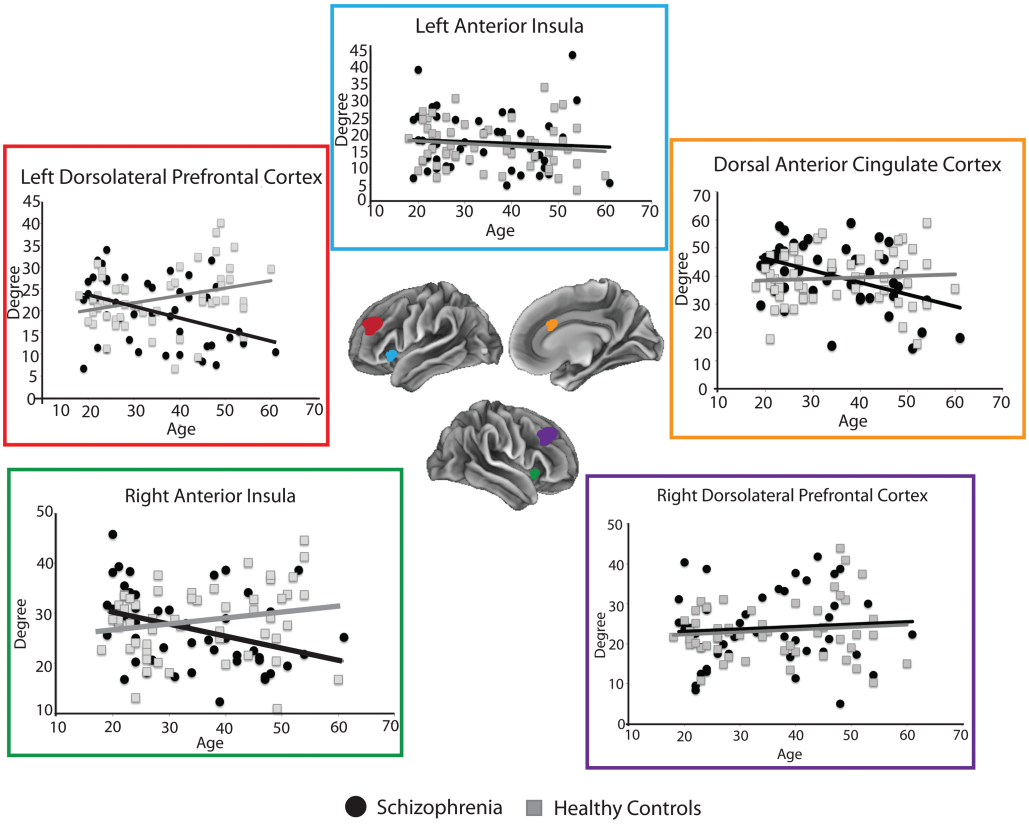

Fig. 3. Associations between node degree and age. A significant diagnosis by age interaction was observed for the left dorsolateral prefrontal cortex (DLPFC; β = −1.08, $P < .001$), right anterior insula (AI; β = −.88, $P < .01$), and the dorsal anterior cingulate cortex (DACC; β = −.88, $P < .01$), but not for the right DLPFC (β = −.002, $P = .99$) or the left AI (β = .19, $P = .85$).

Using separate linear regressions with group, graph metric, and their interaction predicting cognition, we found significant positive associations between overall cognition and global efficiency of both FPN (β = .23, $t(99) = 2.67$, $P < .01$) and CON (β = .24, $t(99) = 2.85$, $P < .01$), but not with crystallized knowledge (FPN: β = −.18, $t(99) = -1.82$, $P = .07$; CON: β = .00, $t(99) = -.04$, $P = .97$). A similar pattern was observed for local efficiency (overall cognition: FPN: β = .21, $t(99) = 2.43$, $P = .017$; CON: β = .15, $t(99) = 1.78$, $P = .08$; crystallized knowledge: FPN: β = −.16, $t(99) = -1.61$, $P = .11$; CON: β = −.07, $t(99) = -.73$, $P = .47$). There were no significant main effects or interactions with group (Ps > .07). However, we observed a significant diagnosis by degree interaction for left DLPFC when predicting overall cognition (β = .81, $t(99) = 3.13$, $P < .01$), driven by a stronger association between hub degree and cognitive ability in SCZ ($r = .45$, $P < .01$) than HC ($r = -.16$, $P = .25$). No other hubs showed associations with overall cognition, and left DLPFC degree was not associated with crystallized knowledge in either group (rs < .10, Ps > .50).

Additionally, age was negatively associated with overall cognition (β = −.41, $t(99) = -5.17$, $P < .001$) but not crystallized knowledge (β = 0.10, $t(99) = .96$, $P = .34$) in all subjects, when diagnosis was in the model. However, no diagnosis by age interaction was observed when predicting overall cognition (β = −.13, $t(99) = -.53$, $P = .60$). Further, CON and FPN global efficiency were not significant mediators of the relationship between age and overall cognition, in all subjects combined or in either diagnostic group separately.

Discussion

These data reveal a significant diagnosis by age interaction in relationship to the functional integration and fault tolerance of 2 brain networks that support higher-order cognitive ability, as well as the connectedness of several hub nodes within those networks, in individuals with schizophrenia. Our findings are consistent with the hypothesis that age-related reductions in functional network efficiency and hub degree may occur at an accelerated rate in patients with schizophrenia, as compared to healthy individuals. Interestingly, these differences in higher-order network and hub metrics occur in the context of "normal" age-related differences in whole brain network efficiency, suggesting that central executive networks may be particularly vulnerable to accelerated aging in the context of schizophrenia.

As we have previously reported,[22] efficiency of the FPN and CON, as well as degree of the left DLPFC, were also significantly positively associated with overall

cognition, suggesting that this decline in functional network integrity negatively impacts higher-order cognition. However, we did not find that these graph metrics significantly "mediated" the association between age and overall cognition, and we did not observe a significant diagnosis by age interaction in the prediction of overall cognition. Given that SCZ already showed significantly impaired overall cognition at younger ages, this suggests that although functional network integrity is an important factor in cognitive deficits, it does not fully explain cognitive dysfunction in schizophrenia.

In the healthy aging literature, there is evidence of alterations in functional brain networks in elderly individuals, including reductions in both global and local efficiency of the whole brain,[37,38] findings that are consistent with our current results. Functional connectivity of the CON and the FPN has also been found to decrease with age,[39] particularly in terms of within-network connectivity,[40,41] a finding that is in line with our observed reduction in the local and global efficiency of these networks—metrics that are weighted by the strength of functional connections for within-network nodes. Several studies have also reported reductions in functional connectivity of the DMN with age.[42] Accordingly, we found that local and global efficiency of the DMN were negatively associated with age in both patients and controls, but with no differential relationship. Our findings of reduced global and local efficiency with age suggests that functional networks (as well as the whole brain network) experience reductions in functional integration, as well as reduced fault tolerance (ie, a network's resiliency to the removal of nodes) as individuals get older.

In addition to accelerated decline of CON and FPN efficiency in patients with schizophrenia, we also observed a diagnosis by age interaction when predicting the integrity of network hubs. Hubs were assessed using 2 different metrics—hub degree and participation coefficient. Participation coefficient reflects inter-network connectivity, whereas degree quantifies the number of edges a node has, and therefore reflects a node's connections regardless of network or module membership. We observed a significant diagnosis by age interaction for the degree of the right AI, DACC, and left DLPFC, but did not observe any significant interactions or associations with age for participation coefficient. One interpretation of why node degree was associated with age while participation coefficient was not, is that node degree is more sensitive to subtle changes in network structure with aging, particularly in terms of connections within its own network. Given that both patients and controls showed only moderate reductions in whole brain efficiency with age, but efficiency of the CON and FPN were strongly negatively associated with age in the patients, reductions in degree may reflect within-network alterations in functional integration as patients get older.

Aging-related alterations in white matter connectivity have been much more deeply explored than in resting state functional networks, and can guide our understanding of the current results. Previous work in healthy individuals estimating the maturation rate of white matter tracts has shown that associative, cerebral tracts, which mature slower than sensory and motor tracts, have earlier age-related decline,[43] suggesting that white matter tracts whose myelination peaks later are the first to experience a decrease in myelin integrity. Accordingly, it has been shown that these same associative white matter pathways that connect multimodal regions are vulnerable to the process of accelerated aging in patients with schizophrenia.[11] Interestingly, the white matter tracts found to have the slowest maturation rates (and therefore the earliest age-related decline) were the genu and body of the corpus collosum, which connect prefrontal regions, and the cingulum, which supports connections with the cingulate gyrus. These 2 white matter pathways, therefore, support many nodes within the FPN and the CON, including DLPFC and DACC, providing evidence consistent with degeneration of the structural connectivity that would support functional integration, and therefore, efficiency, of the FPN and CON.[17] Although evidence of decreased FA in schizophrenia is mixed, we posit that the degeneration of myelin that appears to occur at an accelerated rate in schizophrenia,[10,11] which recent evidence suggests is due to an accelerated reduction in the permeability of axonal fibers leading to reduced signal propagation,[44] may lead to the observed reduction in functional efficiency and hub degree of critical higher-order functional brain networks. However, this hypothesis needs to be tested in a dataset that includes both diffusion tensor imaging (DTI) and fMRI data in the same group of schizophrenia subjects—an interesting avenue for future research.

Higher-order cognition, but not crystallized knowledge, was negatively associated with age in both patients and controls, consistent with previous work on alterations in cognitive functioning with age.[21] As previously reported by our group, local and global efficiency of the FPN and CON, and left DLPFC degree, are negatively associated with higher-order cognition. The FPN and CON are central executive networks, meaning that nodes within these networks increase activity during the performance of higher-order cognitive tasks, implying their critical role in supporting cognitive ability across multiple domains of cognition.[45] We were surprised that none of these network metrics significantly mediated the association between age and overall cognition, and that we did not observe a significant diagnosis by age interaction in the prediction of overall cognition. At this point, we must conclude that efficiency of the FPN and CON, and degree of the left DLPFC, do not fully explain cognitive alterations in schizophrenia.

Several limitations exist within the current dataset. We used pseudo-resting state data, as opposed to data from a "pure" resting state scan. Although previous work has

shown strong similarities in functional connectivity matrices from pseudo-resting state and resting state scans,[30] it is possible that our findings are more specific to pseudo-resting state data. These data are cross-sectional, limiting our ability to make causal inferences about active decline in functional network integration across the lifespan of individuals with schizophrenia. The young HC group included significantly more males than the older HC, however, our results were unchanged when gender was included in our linear regressions. The majority of our SCZ were taking antipsychotic medications and we do not have data available for the duration of illness for each participant, making it difficult to rule out the impact of long-term antipsychotic use. Additionally, changes in white and gray matter that are associated with the illness-state of schizophrenia are likely to interact with aging-related changes in these brain measures, particularly within the context of vascular disease. Vascular disease can occur for many reasons, but in schizophrenia may be more associated with smoking and antipsychotic use than in the general population.[46] Therefore, to control for these confounds and more clearly test the hypothesis of accelerating aging in schizophrenia, future studies should compare SCZ to other (nonpsychiatric) populations that are enriched for cardiovascular risk factors. Of note, however, our findings of accelerated decline in network efficiency were fairly specific to the CON and FPN, in the context of "normal" decline in whole brain functional efficiency. If vascular disease or antipsychotics were driving our results, we would expect those variables to impact the entire brain and manifest in whole brain-wide alterations, not just those observed in the central executive networks.

Given these limitations, it is important to note that accelerated aging is just one of many possible interpretations of the presented data. As noted above, vascular abnormalities as related to smoking and antipsychotic drug use may be influencing our results, and the cumulative effect of these drugs could explain accelerated decline in functional connectivity, which is measured using the BOLD signal. Our findings are also in line with the cognitive reserve hypothesis, which posits that individuals with higher levels of IQ, education, and occupational attainment are more resilient to age and disease-related brain changes, due to a "cognitive reserve" of greater and more efficient neural capacity.[47] SCZ not only have lower IQ, but also have on average lower educational and occupational attainment,[48] suggesting that any "reserve" that healthy individuals may have to combat age-related decline in functional network efficiency is reduced in patients with schizophrenia, which could lead to more robust reductions in functional network efficiency with age.

Conclusions

We presented evidence that the age-related decline in functional efficiency of 2 brain networks that support higher-order cognitive ability, the FPN and CON, as well as the connectedness of hubs within those networks, occurs at an accelerated rate in patients with schizophrenia, as compared to nonpsychiatric healthy controls. In the context of several studies showing accelerated decline of white matter integrity in schizophrenia, our findings reveal a potentially related accelerated degradation of functional connectivity in schizophrenia, that may be subject to the same neurobiological processes that result in white matter changes over time. Future research looking at fMRI and DTI data in the same subjects will hopefully elucidate these associations and point to potential neurobiological mechanisms for an accelerated aging process in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org

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