Common and Differential Pathophysiological Features Accompany Comparable Cognitive Impairments in Medication-Free Patients with Schizophrenia and in Healthy Aging Subjects

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Background: Dysfunction of the dorsolateral prefrontal cortex (DLPFC) and parahippocampal region along with poor working memory are common neurophysiological and behavioral features associated with schizophrenia and normal aging. It is, however, unknown whether the associated patterns of neural activation differ between these two groups when their cognitive performance is closely matched in a pairwise manner. The authors sought to pinpoint common and differential pathophysiological features that accompany comparable working memory impairments in schizophrenia and healthy aging.

Methods: Fifty-three subjects were scanned with oxygen-15 water positron emission tomography regional cerebral blood flow measurements during working memory. Seventeen medication-free patients with schizophrenia were individually matched for working memory performance with 17 healthy aging subjects. Brain activation of the two index groups were compared with each other and with 19 young healthy individuals.

Results: Patients with schizophrenia showed right DLPFC hypoactivation, both when compared with age-matched control subjects and after direct comparison with working memory performance-matched elderly subjects. Moreover, both groups with working memory deficits shared an inability to suppress parahippocampal and anterior medial prefrontal cortex activation.

Conclusions: These results provide new insights into the mechanisms by which impaired working memory performance can arise by showing that both common (parahippocampal/anterior medial PFC) and differential (DLPFC) pathophysiological features accompany similar cognitive impairments. The aging data also demonstrate that poor performance is not necessarily accompanied by the DLPFC hypofunction that was seen in schizophrenia. Finally, these results more closely link the DLPFC functional abnormalities in schizophrenia to the pathophysiology of the disorder rather than to poor performance per se.

Key Words: Aging, dorsolateral prefrontal cortex, neuroimaging, schizophrenia, working memory

Common neurophysiological and behavioral features, such as dysfunction of the dorsolateral prefrontal cortex (DLPFC) and the parahippocampal region, along with poor working memory, are associated with both schizophrenia and normal aging. In schizophrenia, decades of research in a number of different disciplines—including neuroimaging, neuropsychological, and neuropathological studies—have demonstrated that the prefrontal cortex (PFC) plays an important role. In functional neuroimaging studies of schizophrenia, one of the most well-replicated findings is prefrontal dysfunction, particularly during cognitive conditions involving the DLPFC (1–4). During working memory in schizophrenia, both decreased (2,5–7) and increased (8,9) DLPFC activation have been described, discrepancies that some have attributed to differences in performance and/or task difficulty (3,10). The mechanism and meaning of this DLPFC dysfunction has remained unclear, in part, because patients typically perform more poorly than healthy subjects, an observation that could potentially affect the imaging findings.

To circumvent this problem, a number of elegant event-related functional magnetic resonance imaging designs in which analyses are limited to correct trials only (2,3) as well as parametrically designed cognitive control paradigms that include control conditions in which patients perform as well as patients have been performed (11–14). Yet, these research strategies studying patients whose working memory performance is at or near normal do not address the mechanism of cognitive failure inherent to the disease (4,8,12,14,15).

A different strategy, comparing patients with schizophrenia with other groups who also perform poorly, has the potential to clarify mechanisms of brain dysfunction by identifying common and unique pathophysiological features. Additionally, this approach can provide information about the role of the performance of patients in the physiological findings as well as about the role of the DLPFC in the cognitive impairment of schizophrenia. In particular, if DLPFC hypofunction is due to poor performance per se, we would expect to observe it in any poorly performing group. Here we sought to compare patients with schizophrenia with healthy aging subjects, because: 1) they share overlapping features of cognitive impairment on tasks linked to PFC, and 2) both groups show neurophysiological changes in the DLPFC and the hippocampal formation (16–21). The specificity of the neurofunctional findings in the two groups has not been adequately tested, because previous findings have been based mainly on analyses of each index group compared separately to a control group and because medications have often been a confounding factor.

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Table 1. Demographic and Characteristics of All Participants

Subject Characteristics	Patients with Schizophrenia (n = 17)	Healthy Aging Subjects (n = 17)	Control Subjects (n = 19)
Age (Years)	30.7 (22–43, SD 6.3)	67.5 (54–79, SD 7.7)	27.5 (20–36, SD 5)
Men	10	9	10
% Correct, 2-Back Working Memory Performance	53% (SD 13)	49% (SD 14)	78% (SD 15)
% Correct, 0-Back Working Memory Performance	93% (SD 14)	98.9% (SD 1.1)	96.8% (SD 5.7)
Mean Duration of Illness	9 yrs (SD 7)		
PANSS Positive Score	19 (SD 8.4)		
PANSS Negative Score	18.8 (SD 9.8)		
Global PANSS Score	18.9 (SD 11.6)		
Total PANSS Score	37.6 (SD 22.9)		
2-Back RT (Correct Trials)	886 (SD 538) msec	783.6 (SD 168) msec	
0-Back RT (Correct Trials)	860 (SD 494) msec	632 (SD 123) msec	
Education Level	12.9 (SD 1.2) yrs	16.4 (SD 3.9) yrs	18.3 (2.7) yrs

PANSS, Positive and Negative Syndrome Scale.

The goal of the present study was to directly compare working-memory-related brain activity in medication-free patients with schizophrenia and healthy aging subjects, matched on a pairwise basis for cognitive performance. This approach is of particular interest in the context of age- and schizophrenia-related alterations, because it might provide a more complete understanding of the relationships between cerebral changes occurring in normal aging and in schizophrenia, while keeping constant performance levels and addressing the mechanism of cognitive failure.

Methods and Materials

Participants

Fifty-three right-handed participants consisting of three groups of subjects provided written consent after complete description of the study in accordance with the National Institutes of Health Institutional Review Board and Radiation Safety Committee. Two index groups, a cohort of patients with DSM-IV–diagnosed schizophrenia (n = 17) and a cohort of healthy older subjects (n = 17) (Table 1), were compared with each other and with a young control group (n = 19), matched in age with patients (t test, p = .21). Without reference to the positron emission tomography (PET) data, index groups were chosen from larger cohorts to be closely matched in a pairwise manner for 2-back working memory performance (Figure 1). Subjects were carefully screened with physical examination, history, and structural magnetic resonance imaging to rule out neurostructural abnormalities and risk factors for cerebrovascular diseases, with particular attention to those that might accompany the aging process. With the exception of the primary diagnosis in the schizophrenia group, participants were free of neurological, psychiatric, and medical illness and were taking no medications that affect regional cerebral blood flow (rCBF). Patients with schizophrenia were withdrawn from all medication at least 2 weeks before the experiment, and all participants abstained from caffeine and nicotine for 4 hours before the scanning sessions. Because all patients with schizophrenia had been previously treated with neuroleptics, it cannot be excluded that long-term effects of medications could affect our neuroimaging results. Participants were trained on the task and familiarized with scanning procedures before the study.

Working-Memory Task

We used a version of the N-back working-memory task previously validated in our group as a consistent and robust activator of DLPFC and deactivator of the parahippocampal region in healthy subjects (Figures S1 and S2 in Supplement 1). Briefly, subjects are presented with a diamond shape containing four circles, one in each corner. A single number appears at random in one of the four positions, with the same number (e.g., "2") always appearing at the same spatial location. Stimuli are presented for 1.5 sec, and each trial lasts 2 sec. Subjects press one of four buttons, with their right thumb, on a diamond-shaped response button box held in their right hand. In the 0-back sensorimotor control condition, subjects press the button corresponding to the current number. In the 2-back (working memory) condition, subjects press the button corresponding to the number presented two trials before. Thus, the 2-back condition requires subjects simultaneously to encode the current number/position presented, to retrieve the number/position seen two trials back, and to press the corresponding button. This task encompasses processes involved in maintenance of previous information, monitoring, updating, retrieving, and temporally and dynamically linking the contents of working memory. Chance level performance on this version of the N-back task is 25%.

Data Acquisition

Imaging data were acquired while subjects lay supine in a GE Advance, 3D PET camera (GE Medical Systems, Milwaukee, Wiscon-

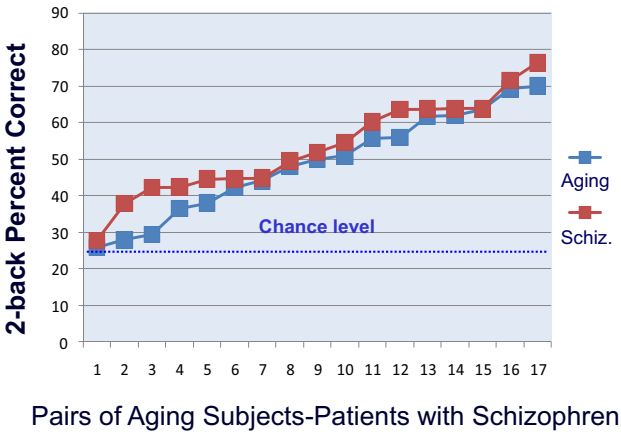

Figure 1. Behavioral results. Pairwise match between patients and healthy aging subjects: 2-back performance accuracy. See text for statistical information. Schiz., schizophrenia.

sin) with an IV bolus of 10 mCi of oxygen-15 water for each of 14 rCBF scans. The 0-back and 2-back tasks were each performed during seven scans in alternating order. Head position was maintained with individually fitted thermoplastic face masks. The scans occurred at 6-min intervals, and PET data were collected for 60 sec during 90 sec of stimulus presentation, allowing 45 trials.

Image Data Processing

The SPM99 software (http://www.fil.ion.ucl.ac.uk/spm), which is well-suited to the analysis of PET data, was used for all aspects of image processing. Images were corrected for attenuation and reconstructed into 32 planes (resolution 6.5 mm full-width-at-half-maximal), and background activity was subtracted. After registration, images were anatomically normalized to a study-specific PET template composed of the average of all subjects in the study to preclude potential confounds due to structural variation between the three groups. Data were smoothed with an isotropic Gaussian kernel filter of 10 mm^3 (full-width-at-half-maximal), and scan to scan variation in global counts was removed with proportional scaling to a global mean CBF of 50.

Statistical Analysis

rCBF Activation During Working Memory (2-back versus 0-back). To examine the main effect of task, rCBF during 2-back was compared with that during 0-back with a two-step random effects analysis across all control subjects. This random-effects analysis involved two steps: 1) a first-level voxel-wise comparison was calculated for each subject across all runs to produce one contrast image for each subject; and 2) the contrast images from each individual were entered into a one-sample t test performed across all subjects.

To identify differential pathophysiology in schizophrenia and normal aging, we next compared working memory-related brain activation between the two index groups as well as between each index group and the control group separately by using a one-way analysis of variance with three groups with a significance threshold of $p < .001$, uncorrected, and a cluster corrected threshold of $p < .05$.

To identify pathophysiology that was common across schizophrenia and aging, we also performed a conjunction analysis to localize alterations in rCBF activation that were seen in both index groups relative to the control group. The formal conjunction analysis carried out was computed by first performing the comparison 2 back > 0 back in patients with schizophrenia > control subjects (threshold of $p < .001$) and then by masking the results inclusively with the results of the same contrast (2 back > 0 back) in healthy aging subjects > control subjects.

Results

Behavior

Performance accuracy in the 2-back working memory task of older subjects and patients with schizophrenia was matched closely in a pair-wise manner (Figure 1). The mean percent correct of the aging subjects was 49% (SD 14), the mean percent correct of the patients with schizophrenia was 53% (SD 13), and that of the control group was 78% (SD 15). Although both index groups performed better than the 25% chance level on the 2-back task, they performed significantly worse than healthy young control subjects [aging vs. control subjects: $F(1,34) = 27.6$, $p < .0001$; schizophrenia vs. control subjects: $F(1,34) = 35.4$, $p < .00001$]. On the 0-back control condition, neither aging subjects (mean performance correct 98%, SD 1) nor patients with schizophrenia (mean performance correct 93%, SD 14) differed significantly from control subjects (mean performance correct 97%, SD 6); they also did not differ from each other (all p values > .1). Reaction times for correct 2-back trials did not differ between older subjects and patients with schizophrenia: mean RTs for aging subjects = 783.6 msec (SD 169); mean RTs for patients = 886.1 msec (SD 538) ($p = .51$, unpaired-test with unequal variance of the 2 samples).

Activation Analyses

Brain Regions Activated in Control Subjects. In healthy young control subjects, the 2-back versus 0-back comparison revealed activity in a large bilateral prefronto-parietal network (DLPFC: x,y,z = 46,44,20; Z score = 6.2; x,y,z = −36,36,20, Z score = 4.8; fronto-polar cortex: x,y,z = 36,56,8; Z score = 5.8; x,y,z = −32,56,12; Z score = 3.9; intra-parietal region: x,y,z = 38,−52,40, Z score = 6.8; x,y,z = −42,−46,32, Z score = 6.75) that also included the thalami (x,y,z = 10,−18,−4, Z score = 8.3; x,y,z = −10,−22,−4, Z score = 3.4) and the cerebellar hemispheres (x,y,z = −38,−56,−44, Z score = 6.45; x,y,z = 42,−60,−36, Z score = 5.7) (Figure S2 in Supplement 1, top). Conversely, relative deactivation during the 2-back task relative to the 0-back task was observed in a bilateral network that included extensive temporal (x,y,z = −52,2,−32, Z score = 6.6; x,y,z = 66,−8,−32, Z score = 6.3) and anterior medial frontal cortex areas (x,y,z = 8,64,−8, Z score = 6.7) as well as parahippocampus (x,y,z = 26,−8,−32, Z score = 8.1; x,y,z = −18,−12,−32, Z score = 8.4) and posterior cingulate cortex (x,y,z = 4,−48,24, Z score = 6.9), consistent with the default network (Figure S2 in Supplement 1, bottom).

Interactions Between Groups and Conditions. *Patients with schizophrenia versus control subjects (2-back minus 0-back).* Compared with control subjects, patients with schizophrenia showed reduced activation in regions activated by the control subjects, including the right DLPFC and fronto-polar cortex, the left premotor cortex, the pre-supplementary motor area (SMA), the thalamus and cerebellum bilaterally (Figure 2A, left, Table 3). In contrast, patients with schizophrenia showed higher activation than control subjects in regions deactivated by the control subjects, including the anterior medial prefrontal cortex (mPFC), the posterior cingulate cortex, and the left superior temporal gyrus (Figure 2A, right; Figure 3B; Table 2). Importantly, patients also deactivated the parahippocampal region less than control subjects.

Healthy aging subjects versus control subjects (2-back minus 0-back). Compared with control subjects (and in contrast to the schizophrenia vs. control results), healthy aging subjects exhibited higher activity in the lateral PFC bilaterally, particularly robust in the left hemisphere, the bilateral superior frontal gyri, bilateral fronto-polar cortices, the anterior cingulate cortex, the left middle temporal gyrus, and the left superior temporal cortex (Figure 2B, right). Like the patients with schizophrenia, aging subjects compared with control subjects also showed less deactivation in the left parahippocampal region, the anterior medial PFC, and the posterior cingulate cortex. Moreover, older subjects showed less activation in the motor cortex bilaterally, the SMA/medial frontal gyrus, and the cerebellum, as compared with control subjects (Figure 2B, left).

Healthy aging subjects versus patients with schizophrenia (2-back minus 0-back). Direct comparison between the aging group and performance-matched patients with schizophrenia revealed that older subjects showed higher activation in the right DLPFC, left premotor cortex, and anterior cingulate cortex. More robust activation in aging was also found in the fronto-polar cortices bilaterally, right inferior frontal cortices, left inferior temporal gyrus, and cerebellar hemispheres bilaterally (Figure 3A, left).

In contrast, there were no prefrontal regions where activation for patients with schizophrenia exceeded that of aging subjects.

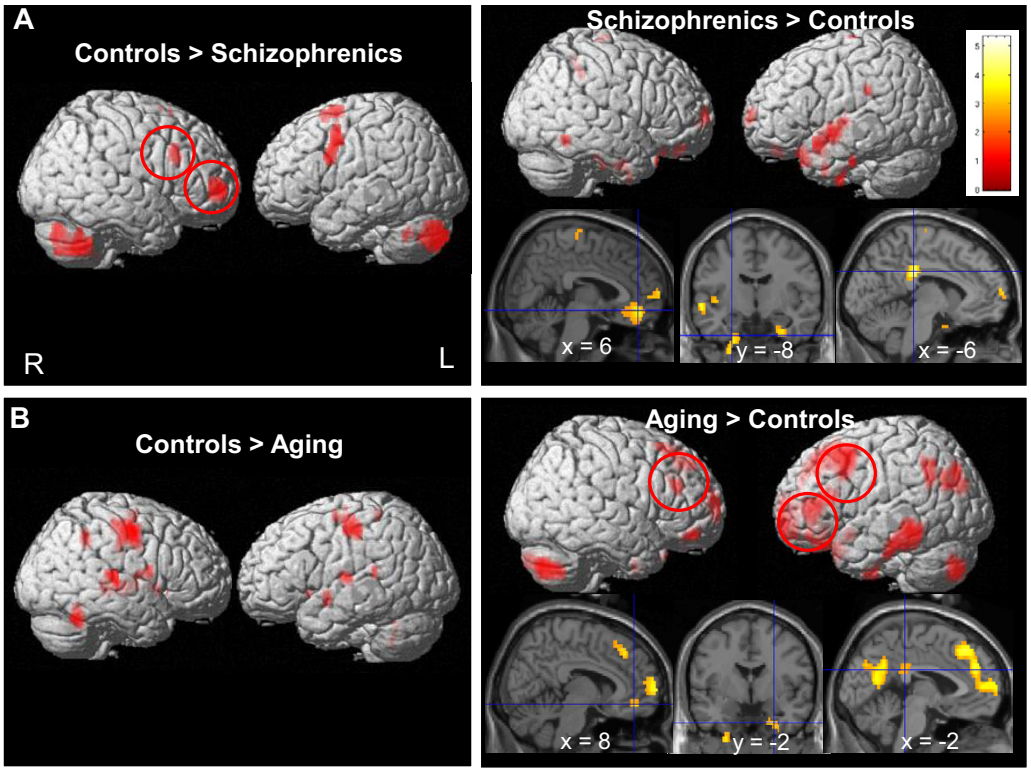

Figure 2. Comparisons of index groups with control subjects. Brain regions significantly activated by 2-back relative to the 0-back conditions overlaid onto a three-dimensionally rendered brain for: **(A)** patients with schizophrenia < control subjects (top left), patients with schizophrenia > control subjects (top right); and **(B)** healthy aging < control subjects (left) and healthy aging > control subjects (right). Patients with schizophrenia showed less activation in the right dorsolateral prefrontal cortex (DLPFC) than control subjects, whereas healthy aging subjects overactivated the left DLPFC (normally less-recruited than the right DLPFC in control subjects). Results are displayed at $p < .005$ for visualization. L, left; R, right.

Higher activity in patients was observed only in the SMA/motor part of the anterior cingulate cortex, bilateral post-central gyri, posterior insula bilaterally, right intra-parietal region, inferior and superior temporal gyri, and fusiform region (Figure 3A, right).

Pathophysiology Common to Patients with Schizophrenia and Healthy Aging Subjects. The formal conjunction analysis revealed that, in comparison with the control group, the two index groups shared decreased deactivation of the anterior mPFC (x,y,z = 4,42,−12, $Z = 4.2$), the parahippocampal gyrus region bilaterally (x,y,z = −24,−12,−40, $Z = 4.1$; x,y,z = 28,−4,−36, $Z = 3.8$), and the posterior cingulate cortex (x,y,z = −4,−32,32, $Z = 4.7$) (Figure 3B and Figure S3 in Supplement 1). Moreover, patients with schizophrenia and aging subjects shared hyperactivation in the left superior temporal cortex (x,y,z = −38,10,−16, $Z = 4.8$).

Discussion

The results of this study demonstrate that working memory impairments that are similar at the behavioral level in patients with schizophrenia and healthy aging subjects are reflected in both common and distinct neurophysiological features. Specifically, these two index groups share decreased deactivation of the parahippocampal gyrus region and the anterior mPFC but differ in the observed patterns of PFC dysfunction. Compared with young, healthy control subjects, patients with schizophrenia were hypofrontal (Figure 2A, left), whereas performance-matched older subjects over-activated the lateral PFC, particularly in the left hemisphere (Figure 2B). These differences in patterns of brain activation were further emphasized by direct comparison between the index groups (Figure 3A) and, importantly, cannot be explained on the basis of differences in cognitive performance. These observations suggest an intrinsic distinction between the neurobiological substrates of the working memory impairment in schizophrenia and normal aging. They further support the notion that DLPFC hypoactivation in schizophrenia is not due to poor task performance per se but, rather, reflects a fundamental neurophysiological characteristic of the disease as observed by PET. Our findings of both reduced DLPFC activation and reduced deactivation of the default mode network (including the anterior mPFC, posterior cingulate cortex, and temporal region) in schizophrenia could reflect a relative inefficiency of resource allocation between functionally competitive large-scale neurocognitive systems (22–24).

Differential Findings in Patients with Schizophrenia and Healthy Aging

Patients with schizophrenia showed underactivation of the right DLPFC and bilateral frontopolar cortices relative to both young control subjects and performance-matched older adults (Figure 2A, left; Figure 3A, right). This result showing PFC dysfunction in medication-free patients with schizophrenia extends numerous previous neuroimaging studies on working memory and executive functions in this patient group (2,5–8,12–14,19). The failure to activate the frontopolar cortex in patients might reflect an impairment in retrieving information from working memory or inappropriate use of strategies involving switching processes, because this brain region is frequently implicated in working memory (25) and memory retrieval (26) and when combining working memory with task switching processes (27,28). As noted previously, although the majority of neuroimaging studies of working memory in schizophre-

Table 2. Regions of Activation Observed in the 2-Back > 0-Back Contrast Compared Between Groups

Anatomical Structure (BA)	Patients > Control Subjects				Aging > Control Subjects				Aging > Patients				Patients > Aging			
	MNI Coordinates			*Z* Value	MNI Coordinates			*Z* Value	MNI Coordinates			*Z* Value	MNI Coordinates			*Z* Value
	x	y	z		x	y	z		x	y	z		x	y	z	
Frontal																
Anterior mPFC	6	44	−12	3.6	0	54	8	4.0								
L sFG (BA 8)					−18	28	44	4.7	−46	6	44	5.3				
R sFG (BA 8)					30	22	56	3.4								
R mFG (BA 9)					52	34	28	3.1	52	34	28	3.7				
L mFG (BA 46)					−32	16	48	4.4								
L fronto-polar cx (BA 10)					−20	64	0	3.5	−26	56	−16	3.1				
R fronto-polar cx (BA 10)					48	46	−20	3.8	32	52	0	3.8				
Anterior cingulate cx/SMA					−8	44	32	4.4	−4	26	44	4.9	−6	−16	68	3.9
Posterior cingulate cx	−6	−30	32	4.7	−4	−58	32	3.7								
R GPoC (BA 4)													44	−14	48	4.5
L GPoC (BA 4)													−54	−28	48	3.7
Cerebellum																
L cerebellar hemisphere									−18	−88	−44	4.6				
R cerebellar hemisphere									30	−76	−36	5.1				
Temporal Gyrus																
R insula													40	−10	4	5.1
L insula													−40	−12	4	3.9
R sTG (BA 22)													66	−28	12	4.2
L sTG (BA 22)	−38	8	−16	4.7	−60	−56	28	3.3					−66	−28	−20	3.6
L mTG (BA 21)					−60	−40	−12	4.1	−60	−38	−8	5.1				
Intra-Parietal Cortex													38	−44	44	4.9
Fusiform Gyrus													−48	−72	4	3.8
													48	−60	−8	4
Parahippocampal Region	−24	−12	−44	3.8	−24	−10	−48	3.6								
	26	−6	−32	3.3												

BA, Brodmann area; cx, cortex; GPoC, post-central gyrus; L, left; mFG, middle frontal gyrus; mPFC, medial prefrontal cortex; MNI, Montreal Neurological Institute; mTG, middle temporal gyrus; R, right; sFG, superior frontal gyrus; SMA, supplementary motor area; sTG, superior temporal gyrus.

nia, particularly those using PET, have reported reduced DLPFC activity compared with healthy young control subjects (2,5,6,29), there are also a number of reports of hyperfrontality (8,9). Differences in the directionality of the findings (i.e., too much or too little prefrontal recruitment) (7) might be due to a number of discrepancies across studies, such as different clinical symptoms, stage of illness, and medication status in the patients; interindividual differences in strategy or behavioral performance (30), methodological

Table 3. Regions of Activation Observed in the 2 Back > 0 Back Contrast Comparing Control Subjects > Aging and Control Subjects > Patients

Anatomical Structure (BA)	Control Subjects > Aging				Control Subjects > Patients			
	MNI Coordinates			*Z* Value	MNI Coordinates			*Z* Value
	x	y	z		x	y	z	
Frontal								
R fronto-polar cx (BA 10)					28		4	4.1
R mFG (BA 9/46)					34		32	3.1
SMA/motor ACC	−12	−6	52	3.9				
L premotor cx					−48	8	28	3.5
Pre-SMA					−4	4	64	3.9
R GPrC (BA 4)	40	−10	44	4.1				
L GPrC (BA 4)	−52	−26	52	3.6				
Thalamus					14	−10	4	3.6
Cerebellum								
L lat. cerebellar hemisphere					−22	−76	−36	5.1
R lat. cerebellar hemisphere	44	−54	−24	4.5	42	−58	−48	3.4

ACC, anterior cingulate cortex; lat., lateral; GPrC, precentral gyrus (motor cortex); other abbreviations as in Table 2.

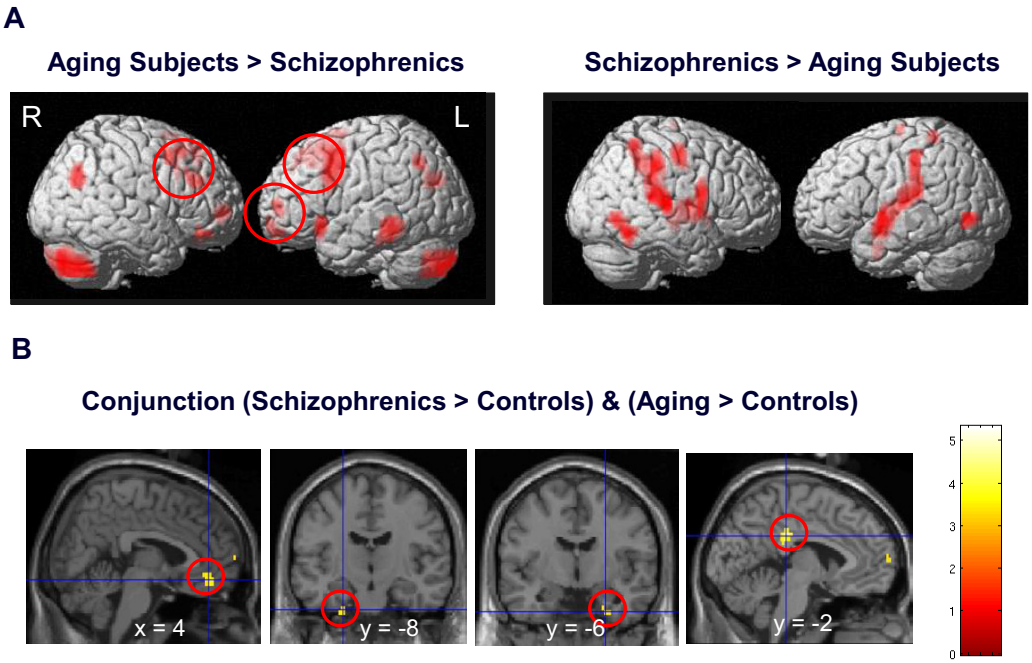

Figure 3. (A) Direct comparison of patients with schizophrenia and healthy aging subjects. Data for brain regions significantly activated by 2-back relative to the 0-back conditions overlaid onto a three-dimensionally rendered brain for aging subjects > patients with schizophrenia and patients with schizophrenia > aging. Healthy aging subjects overactivated the left lateral prefrontal cortex (PFC) compared with patients with schizophrenia, whereas patients with schizophrenia did not activate any PFC region more than aging subjects. **(B)** Common findings in aging and schizophrenia. Conjunction analysis of patients with schizophrenia and healthy aging subjects overlaid on sagittal and coronal slices. Decreased deactivation of the anterior medial PFC, parahippocampal region, and posterior cingulate cortex were observed in both patients with schizophrenia and healthy aging subjects. L, left; R, right.

differences in imaging modality, or task demands; capacity constraints of task load (8,11,12,15); and possibly the engagement of dysfunctional and compensatory macro-circuits (14). It cannot be excluded that use of different cognitive strategies might also influence the pattern of brain differences observed between patients and aging subjects. One hypothesis is that even when schizophrenic patients are able to keep up with processing demands, they do so less efficiently than control subjects, and this "working harder to keep up" necessitates the recruitment of greater and/or less-focused cortical activity (31). It has been proposed that there is an inverted U-shaped function between working memory load and DLPFC activation, such that increasing task demands are associated with increasing activation, which falls off after the working memory capacity of the subject is exceeded (12,14). This curve would be shifted to the left in schizophrenia, causing patients to show more activation than control subjects at low task demands and to reach their maximum capacity earlier, consequently, showing less activation.

Supporting this view, intact or even relatively increased prefrontal cortical activation has been found in patients whose working memory performance is near normal (4,8,11,12,14,15). Although this approach has the advantage of ruling out confounds such as lack of effort or poor performance per se, such studies do not address the important question of the neurobiological mechanism by which patients cognitively fail. Instead, those results suggest that when patients are able to keep up with working memory processing demands, they tend to do so less efficiently by engaging greater cerebral metabolic activity or a less focused cortical response (4,8,9,12,14,15). In contrast, our study examined two groups in whom working memory performance is impaired, and we matched schizophrenic patients with healthy aging subjects on the basis of poor working memory performance in a pairwise fashion. Our analyses demonstrated hypoactivation of the DLPFC in the group with schizophrenia and not in the aging group. Because all subjects in this study were unmedicated, the observed impairment in DLPFC function in schizophrenia cannot be attributed to concurrent neuroleptic treatment. Our findings not only demonstrate that DLPFC circuits are implicated in the pathophysiology of schizophrenia; they also extend to the comparison with older healthy subjects previous findings comparing patients with schizophrenia and affective disorders, where the former were found to perform worse in executive function tasks and to have more DLPFC activation deficits (4,17,29,32).

In addition to the differential pattern of PFC recruitment compared with aging subjects, patients with schizophrenia, as compared with control subjects, showed relatively greater activity in the SMA, bilateral insula, temporal cortices, and the intra-parietal region, complementing similar previous overactivation reported in a meta-analysis of executive functions in schizophrenia (7). These regions might be associated with a compensatory response and/or might be recruited for implementing alternate strategies to support task performance.

Conversely and in contrast to patients with schizophrenia, when compared with young subjects, healthy aging subjects showed greater activity in the lateral PFC, particularly in the left hemisphere. This over-recruitment in healthy aging subjects is consistent with previous functional neuroimaging studies reporting that older adults activate other frontal regions more than younger adults during demanding cognitive control tasks, including verbal and spatial working memory tasks and verbal encoding and retrieval from episodic memory (21,33,34).

Commonalities Between Patients and Healthy Aging

Patients with schizophrenia and healthy aging subjects shared decreased deactivation of the anterior mPFC, the parahippocampal

gyrus region, and the posterior cingulate cortex (Figure 3B and Figure S3 in Supplement 1). These results are consistent with previous reports that the parahippocampal region—which comprises the entorhinal, perirhinal, and parahippocampal cortices—is sensitive to the effect of aging (35). This brain region reciprocally connects the hippocampus and the neocortex and is critical for normal learning and memory (36). The pattern of reduced deactivation observed in the parahippocampal region in patients and healthy aging subjects might be due to inappropriate use of long-term memory encoding during our working memory paradigm. Moreover, the similar pattern of reduced deactivation observed in the anterior mPFC and posterior cingulate cortex in the two index groups is consistent with previous reports showing that these brain regions are part of the "default mode network," less deactivated in healthy aging than in young control subjects (37–39), and are also less deactivated in patients as compared with healthy young control subjects during a working memory paradigm (23,24,40). These functional changes in the parahippocampal region and the anterior mPFC shared by the two index groups might either reflect a compensatory process or a deficit in cognitive control with deficient resource allocation to the task at hand.

The reduced activation of the DLPFC and reduced deactivation of the parahippocampal gyrus we observed in patients with schizophrenia might reflect the disturbed functional connectivity between the PFC and the medial-temporal lobe region during working memory performance (23). Such inappropriate interaction between the DLPFC and medial-temporal lobe is also present in healthy aging subjects performing working memory paradigms (41,42).

Another common physiological feature that could act in parallel to the observed distributed cerebral changes in schizophrenia and aging compared with young control subjects is related to the dopaminergic system, which undergoes age-related degeneration (43) and is also known to be dysregulated in schizophrenia (44). Dopamine is critical not only for modulating PFC and working memory function but also for regulating episodic memory (45), dependent upon the parahippocampal formation. A recent multimodal neuroimaging study combining functional magnetic resonance imaging and measures of midbrain dopamine synthesis with 6-[18F]fluoro-L-dopa PET reported an age-related change in the direction of the relationship (from a positive to a negative correlation) between midbrain dopamine synthesis and prefrontal activity, suggesting an age-dependent dopaminergic tuning mechanism for prefrontal reward processing (46). Together, these findings support the idea that dysfunctional dopaminergic modulation in aging and schizophrenia might impact the working memory system that depends on the functional interplay between prefrontal and parahippocampal regions.

Conclusions

Our results clarify mechanisms of brain dysfunction by identifying common and distinct pathophysiological features in schizophrenia and healthy aging. Patients with schizophrenia and healthy aging subjects matched for performance were studied with the exact same experimental methods and research design. Our results demonstrate that, in these two very different populations, the same impairments at the behavioral level are reflected in both common and differential neurophysiological features. The most prominent commonality was that these two groups both failed to suppress activation of the parahippocampal gyrus and anterior mPFC during working memory. The main difference between the two similarly performing groups was found in the DLPFC: patients with schizophrenia hypoactivated the right DLPFC, whereas normally aging individuals overactivated this region, thereby differentiating the neural mechanisms underlying the working memory deficits that characterize these two groups of subjects. These findings demonstrate that poor working memory performance per se in schizophrenia is not the cause but rather the result of dysfunctional prefrontal cortices of patients. Our results also offer new insights into the various mechanisms by which cognitive failure in the working memory domain can arise.

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Supplementary material cited in this article is available online.

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