ORIGINAL ARTICLE

Regionally Specific Disturbance of Dorsolateral Prefrontal–Hippocampal Functional Connectivity in Schizophrenia

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Background: Two brain regions often implicated in schizophrenia are the dorsolateral prefrontal cortex (DLPFC) and the hippocampal formation (HF). It has been hypothesized that the pathophysiology of the disorder might involve an alteration of functional interactions between medial temporal and prefrontal areas.

Methods: We used neuroimaging data acquired during a working memory challenge and a sensorimotor control task in 22 medication-free schizophrenic patients and 22 performance-, age-, and sex-matched healthy subjects to investigate "functional connectivity" between HF and DLPFC in schizophrenia. The HF blood flow, measured with positron emission tomography, was assessed within a probabilistic template. Brain areas whose activity was positively or negatively coupled to HF were identified using voxelwise analysis of covariance throughout the entire brain and analyzed using a random effects model.

Results: During working memory, patients showed reduced activation of the right DLPFC and left cerebellum. In both groups, inverse correlations were observed between the HF and the contralateral DLPFC and inferior parietal lobule. While these did not differ between diagnostic groups during the control task, the working memory challenge revealed a specific abnormality in DLPFC-HF functional connectivity—while the right DLPFC was significantly coupled to the left HF in both groups during the control task, this correlation was not seen in healthy subjects during working memory but persisted undiminished in patients, resulting in a significant task-by-group interaction.

Conclusions: Our results suggest a regionally specific alteration of HF-DLPFC functional connectivity in schizophrenia that manifests as an unmodulated persistence of an HF-DLPFC linkage during working memory activation. Thus, a mechanism by which HF dysfunction may manifest in schizophrenia is by inappropriate reciprocal modulatory interaction with the DLPFC.

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MUCH INTEREST IN schizophrenia research has centered on the dorsolateral prefrontal cortex (DLPFC)[1] and the hippocampal formation (HF),[2] brain regions where multiple abnormalities are demonstrated by converging evidence from neuropathologic findings[3,4] and structural[5] and functional[6,7] neuroimaging. Since the HF provides important input to the DLPFC[8] and because neonatal HF lesions in animals induce postpubertally manifested changes in prefrontal cortex[9] mimicking aspects of schizophrenic pathophysiology, it has been hypothesized that the interaction between these two regions might be particularly disturbed in the disorder.[10,11] This so-called "disconnection" hypothesis[12] is also attractive since the HF is selectively vulnerable to some obstetrical insults,[13] and a disturbed interaction with the DLPFC would thus offer an explanation of epidemiological data linking schizophrenia to early neurodevelopmental disturbances.[14] Previous neuroimaging studies of schizophrenia have observed patterns of abnormal activity prominently involving temporal lobe areas and the DLPFC.[15,16] However, no neuroimaging data exist that specifically target the HF to examine its functional connections in schizophrenia.

To identify interactions of the HF with other brain areas, we used the "functional connectivity" approach popular in neuroimaging. It is based on linear covariation; as an operational definition, two brain regions are said to be functionally

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Table 1. Demographics, Performance, and Symptoms*

	Male/ Female, No.	Age, y	Education, y	Right-Handed, No. (%)	Accuracy, %†		PANSS		
					0-Back Task	2-Back Task	Positive Rating	Negative Rating	Total
Controls (n = 22)	16/6	31.8 ± 7.8	16.5 ± 2.5	21 (95)	98.3 ± 3.9	68.8 ± 10.9	. . .	. . .	. . .
Patients (n = 22)	16/6	30.6 ± 6.5	13.5 ± 2.7	21 (95)	95.3 ± 12.3	67.8 ± 15.8	16.35 ± 6.3	17.3 ± 6.3	65.2 ± 15.8
t Test	. . .	$P = .60$	$P < .001$	$P > .99$	$P = .30$	$P = .85$	. . .	. . .	. . .

Abbreviation: PANSS, Positive and Negative Syndrome Scale.
*Unless otherwise indicated, values are mean ± SD.
†Chance = 25%.

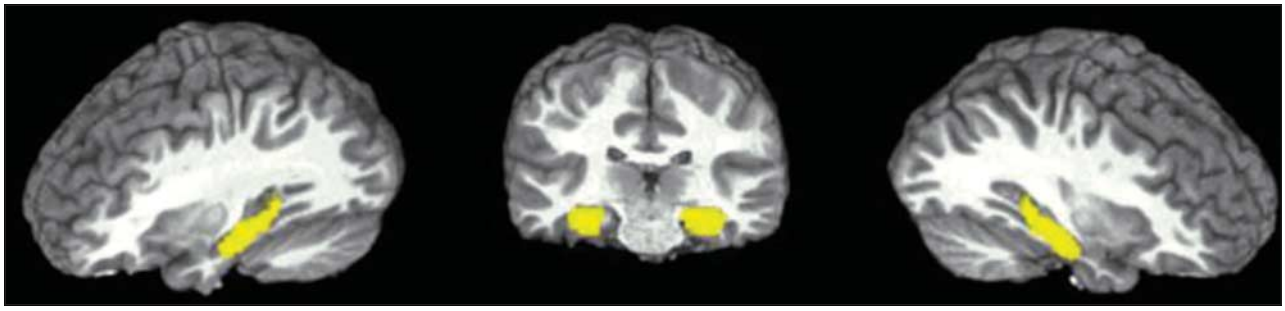

Figure 1. The left and right hippocampal volumes of interest, as derived from the International Consortium for Brain Mapping probabilistic brain atlas, rendered on 3-dimensional reconstructions of a representative brain.

connected if their activities covary from scan to scan,[17] the temporal resolution depending on the imaging modality used.[18] This measure therefore describes a functional linkage and should not be assumed to imply anatomical or causal connections. We measured cerebral blood flow using positron emission tomography (PET) in 22 patients with schizophrenia and 22 matched healthy subjects and canvassed the entire brain voxel by voxel using analysis of covariance to identify areas whose blood flow was significantly (positively or negatively) linked to that of the HF. Our a priori hypothesis, based on the data cited, was that the most prominent disturbance of HF connectivity in schizophrenia would involve the link to the DLPFC. Since prefrontal cortex dysfunction is a well-replicated feature of the disorder, we employed a working memory paradigm to investigate whether DLPFC-related cognitive dysfunction could be linked to abnormalities of HF-DLPFC interaction.

METHODS

SUBJECTS

Twenty-two patients with *DSM-IV*–diagnosed schizophrenia participated in this study. All had been previously treated with neuroleptics. Two weeks prior to the experiment, all medication was withdrawn. Twenty-two subjects matched for performance on the task, age, sex, and handedness without any history or signs of neuropsychiatric or other illness and not taking medication were studied as a control group. Matching was achieved from a larger group of controls scanned as part of an ongoing protocol. Demographic data are summarized in **Table 1**. All subjects participated after giving informed consent as approved by the National Institute of Mental Health Institutional Review Board and the National Institutes of Health Radiation Safety Committee. Subjects abstained from caffeine and nicotine for 4 hours prior to the scanning session.

NEUROIMAGING EXPERIMENT

The behavioral paradigm and imaging procedures have been detailed elsewhere.[15] Subjects performed a version of the *n*-back working memory task. During the 0-back sensorimotor control condition, subjects were instructed to press one of 4 buttons corresponding to a single digit (1, 2, 3, or 4 presented randomly). During the working memory 2-back condition, subjects were to press the button corresponding to the numeral that had been displayed two screens previously. Performance was assessed by the percentage of correct responses. Multiple PET regional cerebral blood flow (rCBF) measurements were made for each subject (7 each of the 0-back and 2-back tasks in alternation, with injection of 10 mCi of radioactive water [$H_2{}^{15}O$] per scan) on an Advance 3-dimensional scanner (General Electric, Milwaukee, Wis). Images were attenuation-corrected and reconstructed (32 planes, 6.5 mm full width half maximum). After subtraction of background activity and registration,[19] images were normalized to an average template, scaled proportionally to remove global flow variations, and smoothed (10 mm^3 full width half maximum Gaussian kernel) using Statistical Parametric Mapping version 99 software (Wellcome Department of Cognitive Neurology, London, England).

ANALYSIS OF IMAGING DATA

The HF was defined in normalized space using a publicly available probabilistic brain atlas (International Consortium for Brain Mapping[20]). Probability volumes for the HF were thresholded at 50% a priori, resulting in a volume-of-interest that included the hippocampus proper and the entorhinal cortex (**Figure 1**). Average activity within these templates was extracted for each scan. For each subject, mean-centered within-condition average hippocampal activity was used as a covariate of interest in analysis of covariance to identify voxels whose activity showed significant covariation, positive or negative, with HF rCBF. This procedure ensured that this comparison was independent of the task (activation) effect. Using this analysis, 2

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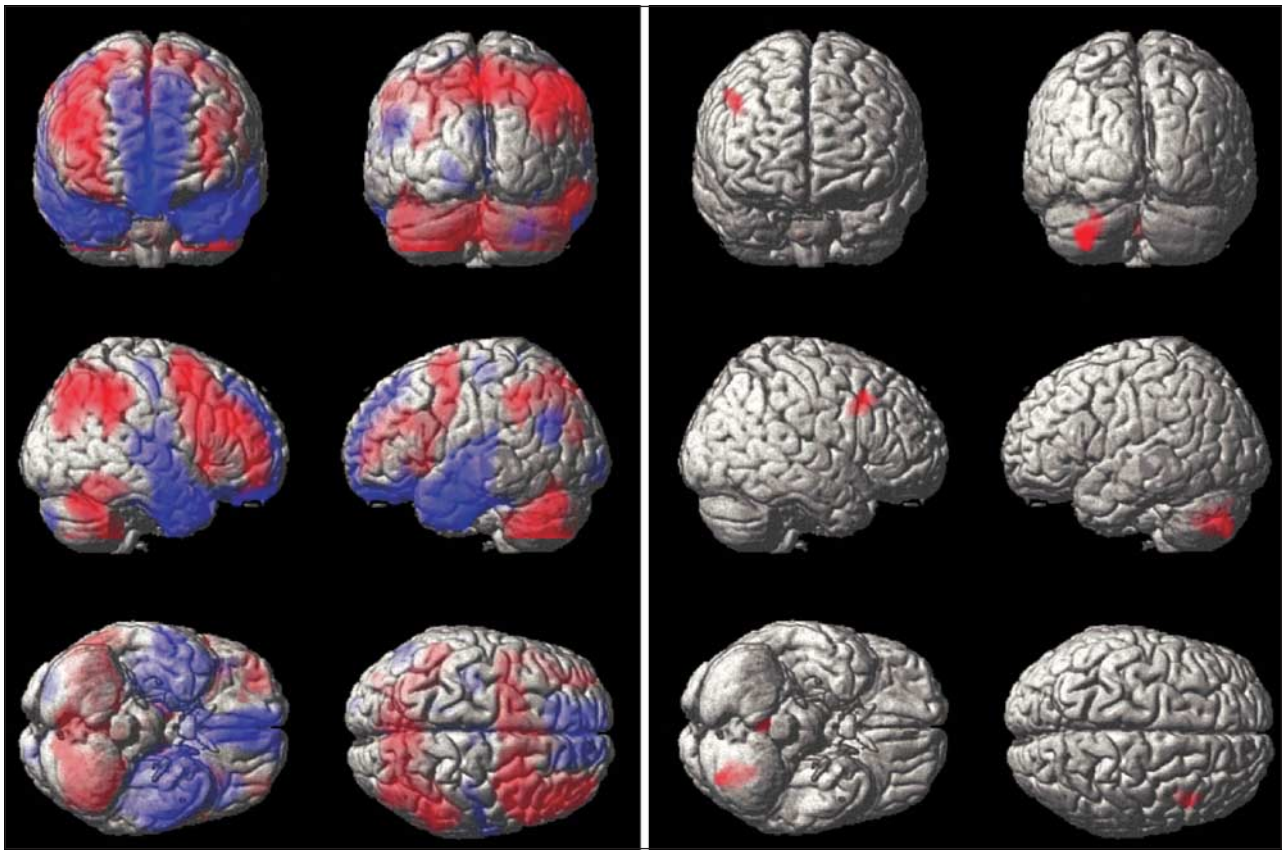

Figure 2. Left, Main effect of task-significant activations (red) and deactivations (blue), comparing the working memory condition (2-back) with its sensorimotor control (0-back). Right, Task × group interaction analysis of regional cerebral blood flow data, showing regions where healthy subjects activate significantly more (red) or less (blue) than patients. Highlighted voxels are significant at $P \leq .01$ ($P \leq .05$ corrected for multiple comparisons).

brain areas are called functionally connected if their rCBF covaries over time (in this case, from scan to scan, acquired 6 minutes apart).[17]

Using Statistical Parametric Mapping version 99 software, effects at each voxel were estimated according to the general linear model, and regionally specific effects were computed by analysis of covariance using linear contrasts identifying brain regions activated or deactivated by the working memory task, differences in the activation-deactivation patterns between the diagnostic groups, and HF functional connectivity. In this context, *activation* refers to greater activity during the 2-back task than during the 0-back task, while *deactivation* denotes greater activity during the 0-back task than during the 2-back task.

Finally, comparison between groups to identify regions showing a significant across-task change in functional connectivity or a change in activation was performed using a random effects approach. For this we estimated the appropriate statistic image for each subject separately (first level) and entered the subject-specific maps into a second-level analysis.[21] Maps were thresholded at $P < .01$ ($z = 3.09$), and correction for multiple comparisons was effected by controlling for cluster size (resulting in a cluster-level correction threshold of $P < .05$, corrected).

Localization of maxima is reported in the coordinate space of Talairach and Tournoux[22] as millimeters relative to the anterior commissure. Brodmann areas, if given, are approximate and were identified by adjusting for differences between the Brain Mapping Consortium template and the Talairach and Tournoux atlas by affine transformation.

RESULTS

BEHAVIOR

The performance of patients and controls was matched for both the 0-back and 2-back tasks (Table 1). Subjects performed significantly above the 25% chance level ($P < .001$ by t test, both groups).

ACTIVATIONS

Statistical maps of the main effect of task condition as well as the group × task interaction are shown in **Figure 2**. Detailed coordinates and z scores of these contrasts are available on request from the authors. They were similar to results previously reported for 13 of these patients and controls.[15] The working memory (2-back) condition led to significant activations of the DLPFC and inferior parietal lobule (iPL) bilaterally, left anterior cingulate, right thalamus, and cerebellar hemispheres. Deactivations were seen in the left parahippocampal gyrus and bilaterally in inferotemporal areas, medial frontal cortex, medial parietal lobule, lateral temporal cortex, and angular gyri. Analysis of the group × task interaction (Figure 2, right) in this performance-matched sample showed significant differ-

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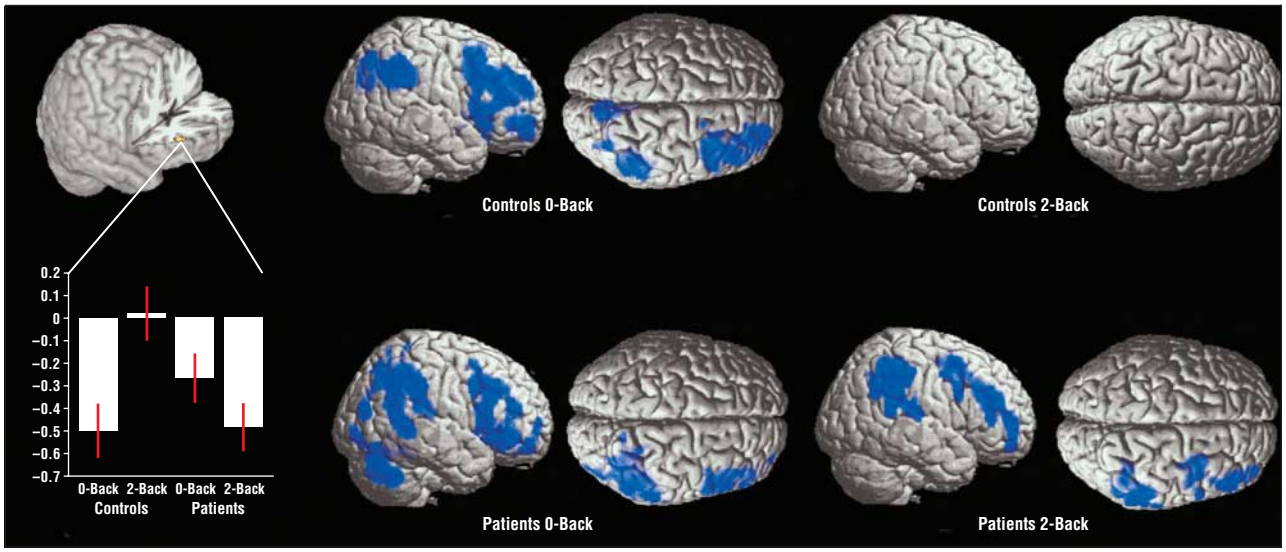

Figure 3. Top left, Cutout showing area of significant group × task interaction of left hippocampal formation connectivity in the right dorsolateral prefrontal cortex. Bottom left, Mean values for covariation with left hippocampal formation in the region of interaction, showing significant coupling during both the 2-back and 0-back tasks in patients but only during the 0-back task in controls. Error bars indicate standard errors. Center and right, Analysis of covariance maps showing areas that were significantly negatively correlated with left hippocampal formation regional cerebral blood flow. Highlighted voxels are significant at $P \leq .01$ ($P \leq .05$ corrected for multiple comparisons).

ences in 2 regions: right DLPFC (x, y, z=44, 14, 36; z=4.26; $P < .001$) and left cerebellar hemisphere (x, y, z=–34, –76, –40; $z=4.22$; $P < .001$).

FUNCTIONAL CONNECTIVITY ANALYSIS

Results of the connectivity analyses are summarized in **Figure 3** and **Table 2**. For both groups, regions showing positive covariation with the hippocampal formation included the ipsilateral temporal lobe, anterior cingulate, and medial frontal cortex, but these findings were not significant after within-group correction using the random effects model. Patterns were similar for the 0-back and 2-back tasks, and no within-group differences emerged on testing. Statistics showing positive functional connectivity using a fixed effects model are available from the authors as supplementary material (http://cbdb.nimh.nih.gov/arch05), while we focus here on results for negative covariation.

LEFT HF

Controls

In controls, the statistical map for negative correlations with left HF activity (Figure 3, blue voxels) showed the strongest inverse link with the contralateral DLPFC, followed by the iPL. Connectivity was significantly different between task conditions: the coupling of the HF to the DLPFC (and to a lesser degree the iPL) was significantly diminished during the 2-back task (x, y, z=34, 24, 36; $z=3.52$; $P < .01$).

Patients

In patients, the pattern of negative correlations with left HF activity (Figure 3, blue voxels) was similar to that of controls during the 0-back task. However, during the working memory condition, the left HF–right DLPFC connectivity persisted undiminished in the patients, in marked contrast to control subjects (Figure 3). Reflecting this persistent linkage during the 2-back task, patients, unlike controls, did not show a significant difference between task conditions.

GROUP DIFFERENCES IN LEFT HF FUNCTIONAL CONNECTIVITY

Formal testing for group × task interaction for HF functional connectivity identified a selective change of left HF connectivity to the middle frontal gyrus in the right DLPFC (x, y, z=36, 44, 4; z=4.73; $P < .001$), reflecting the fact that this area became relatively uncoupled during the 2-back task in control subjects but not in patients (Figure 3, right). There were no other significant group differences in the connectivity-by-task interaction.

To ascertain whether the observed Brodmann area 46–HF connectivity change occurred selectively in this circuit or was also present in other areas with which the DLPFC but not the HF was significantly linked, we extracted the average rCBF in the right DLPFC area that showed significant coupling with the left HF and investigated its positive and negative connectivity. Positive functional connectivity was seen with the surrounding DLPFC, iPL, and cingulate (especially retrosplenial) areas. Examination of negative DLPFC covariation confirmed the HF connectivity findings (significant at the chosen threshold [$P < .05$, corrected, cluster level] during the 0- and 2-back tasks in patients but only during the 0-back task in healthy subjects), and testing of the group × task interaction for functional connectivity did not reveal significant between-group differences in any additional regions.

Finally, to check whether differences in variance might have increased the power to detect correlations in the

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Table 2. Maxima of Areas Negatively Correlated With Left Hippocampal Regional Cerebral Blood Flow

	Maxima of Areas With Negative Left Hippocampal Correlation*			
	0-Back Task		2-Back Task	
Anatomical Description	Controls	Patients	Controls	Patients
BA 9	38, 26, 32 (z = 4.24)	. . .	. . .	50, 34, 28 (z = 3.41)
BA 46	44, 36, 20 (z = 3.86)	42, 50, 20 (z = 4.29)	. . .	40, 54, 0 (z = 3.39)
BA 10	26, 56, 24 (z = 3.90)	40, 54, 12 (z = 4.07)	. . .	. . .
Inferior parietal lobule (BA 40)	54, 54, 36 (z = 3.66); 48, 48, 44 (z = 3.56)†	66, –42, 36 (z = 4.63); 44, –66, 40 (z = 3.80)†	. . .	38, –48, 44 (z = 3.31)
Cerebellar hemisphere	. . .	38, –70, –20 (z = 4.18)	. . .	. . .
Middle temporal gyrus (BA 21)	. . .	56, –50, 5 (z = 4.36)	. . .	. . .
Frontal inferior gyrus (BA 47)	. . .	56, 36, –8 (z = 3.84)	. . .	. . .

Abbreviation: BA, Brodmann area.

*Maxima are reported as millimeters from the anterior commissure in the coordinate space (x, y, z) of the Talairach and Tournoux[22] atlas. All reported maxima were significant at $P < .001$, uncorrected, and survived a cluster-level correction for multiple comparisons at $P < .05$.

†There was more than 1 significant peak in this anatomical area.

schizophrenia groups, the variance of the hippocampal region of interest used for the covariate analysis was compared between groups using the Levene test. No significant difference in variance was found ($F_{1,610} = 2.28$, $P = .14$).

RIGHT HF

Connectivity of the right hippocampus was qualitatively similar to that of the left side but did not survive correction for multiple comparisons. Detailed coordinates from a fixed effects analysis are available from the authors as supplementary material (http://cbdb.nimh.nih.gov/arch05). Again, patterns of positive right HF connectivity were similar between tasks and did not differ between patients and controls. In patients, the pattern of areas covarying negatively with the right HF was similar to the left side and again did not change appreciably with task conditions. In controls, the right HF showed no negative connectivity during the 0-back or 2-back task.

COMMENT

FUNCTIONAL SUBSYSTEMS

In this study we used functional connectivity to delineate brain regions whose activity covaried with that of the HF. We identified a group of brain regions that were negatively functionally coupled to the HF during performance of a cognitive test paradigm, most prominently the iPL and DLPFC. This could reflect inverse functional connectivity of the HF with each of these structures. Alternatively, the HF may show strong negative covariation with only some of them if the remaining subregions are strongly (positively) interconnected among themselves. Neuroanatomical evidence exists for both of these explanations. Direct connections of the iPL to the HF have been described,[23,24] as have pathways connecting the DLPFC and HF.[8,25] In favor of the second explanation, the DLPFC and iPL are known to have strong reciprocal connections.[26-28] The fact that the correlation between these structures carries a negative sign does not imply that our observations indicate inhibitory interactions in the neurophysiological sense, since inhibition and excitation can result in similar effects on blood flow and correlations.[29]

The regions showing negative functional connectivity with the HF within condition are also important for working memory function.[30,31] Indeed, they were found to be activated during working memory by contrasting 2-back and 0-back rCBF. In contrast, the role of the HF itself in working memory is less clear. Hippocampectomized patients are able to perform working memory tasks of the kind presented here without impairments.[32] While the HF may be involved in binding of features[33] or recall of highly familiar items,[34] most neuropsychological and imaging data[35] suggest that white matter performance is dominated by DLPFC-iPL functionality. It may even be advantageous during the *n*-back task not to encode the presented items in long-term memory to avoid potential interference effects. In accordance with this, our data showed a relative deactivation of the HF and the regions to which it was positively correlated during the 2-back task. Moreover, healthy subjects also showed diminished functional coupling between the HF and DLPFC (Brodmann area 46) under working memory load. This suggests that, under normal circumstances, the HF is not only relatively deactivated but also less functionally coupled to this portion of the brain regions underlying executive function during working memory.

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DIFFERENCES BETWEEN PATIENTS AND HEALTHY SUBJECTS

Activations

Patients showed significantly decreased activation in the DLPFC and cerebellum relative to controls. The finding of hypofrontality is similar to our own previous results with this paradigm[15] and many others.[36] The fact that it was present even in this performance-matched sample demonstrates that hypofrontality is a signature of disease-related working memory–related prefrontal dysfunction in PET, while functional magnetic resonance imaging studies with the same paradigm show a similar localization of abnormalities but more complex directionality effects.[37] A trend for relatively higher rCBF during working memory in patients than in controls was found in the entorhinal cortex but did not survive correction for multiple comparisons (x, y, z = −24, −12, −28; z = 3.89; $P < .001$, uncorrected). Since this region is deactivated during working memory in controls, this represents attenuated deactivation in patients.

Functional Connectivity

The main goal of this study was to investigate differences in HF functional connectivity between patients and healthy subjects. The negative connectivity of the left HF showed a significant difference (Figure 3). Patients and controls exhibited the same pattern of connectivity to the iPL and contralateral DLPFC during the sensorimotor control task, but the imposition of a working memory load led to a group difference—while HF-DLPFC connectivity was attenuated in healthy subjects, the functional linkage between these regions persisted undiminished in patients (Figure 3), as reflected in a significant group-by-task interaction of HF connectivity. The middle frontal gyrus in the right DLPFC was the only brain region showing this effect.

Our analysis thus uncovered a disturbance of left HF–right DLPFC functional connectivity in patients that only became apparent during working memory load. Since an alteration was found only in the covariation with DLPFC and the entire brain was canvassed, this suggests regional specificity of the observed interaction effect. Indeed, the analysis of connectivity of the right DLPFC showed no additional loci of functional connectivity with a group-by-task interaction, making the observed effect attributable to the relationship between the DLPFC and HF alone. Since these analyses were conducted within task, it is unlikely that they were influenced by the activation differences between groups discussed above.

Since the left HF–right DLPFC linkage was diminished during working memory in healthy subjects, we interpret its persistence in patients as dysfunctional. This is supported by the data summarized above showing that HF functionality is not necessary for working memory performance. Our analyses suggest a twofold mechanism by which, in the normal case, DLPFC and HF function is compartmentalized during a working memory load: First, during working memory the DLPFC was activated while the HF was deactivated. Second, the analysis of within-condition connectivity showed that the two structures became relatively uncoupled under working memory load in healthy controls only. In patients, this was abnormal on both accounts: DLPFC activation and HF deactivation were significantly diminished, and the coupling of these structures persisted during working memory. It is important to note that our data do not imply that the observed persistent within-condition negative interaction between the HF and DLPFC is responsible for the deactivation deficit of the HF in patients during working memory compared with the control task—it is not the negative sign of the interaction but the fact that it persists during working memory that suggests that the task-related uncoupling of these structures in patients is deficient.

Together with the well-replicated finding of DLPFC activation deficits in schizophrenia, the importance of the DLPFC for working memory, and the status of working memory dysfunction as a core deficit in the neuropsychology of schizophrenia, our results are consistent with the possibility that the observed failure to modulate HF-DLPFC linkage and the lack of HF-DLPFC compartmentalization might to some degree contribute to the DLPFC dysfunction that is a signature of that disorder. This theory is supported by a previous finding that HF volume predicted DLPFC activation, but, importantly, only in patients, not in healthy subjects, underscoring the pathological nature of this correlation,[10] and the theory is consistent with animal data showing that early lesions in the HF lead to DLPFC dysfunction with a maturational delay.[38] Specifically, emergence of behavioral abnormalities akin to schizophrenia[39] and working memory dysfunction in animals has been documented.

Since the observed effect involves a covariation, no inferences about causality can be made. It is conceivable that impaired DLPFC function could be the cause of the observed pathological functional linkage during working memory. The findings of a neuroimaging study of working memory activation in monozygotic twins, one of whom sustained a traumatic frontal lobe injury, are consistent with this interpretation since the injured twin had increased HF activation and decreased DLPFC activity.[40] Seen from this angle, our findings could be a consequence of DLPFC inadequacy during working memory. The observed persistent linkage of the right DLPFC with the left HF could correspond to an alternative strategy involving declarative memory. In this context we note that abnormalities were only found for right DLPFC–left HF covariation. While we have not seen consistent laterality effects for prefrontal effects in normal controls[41] and schizophrenic patients,[15] the recent literature shows differential effects for left and right DLPFC in the generation vs execution of a cognitive plan[42] and in inductive vs deductive reasoning,[43] meriting further inquiries into the contribution of functional connectivity to laterality effects in DLPFC functional specialization.

Previous analyses of functional connectivity of the DLPFC using a seed voxel outside the area identified here as the locus of abnormal HF-DLPFC interaction during verbal fluency did not identify the HF as being differentially linked to this structure but rather the superior temporal gyrus.[44,45] This finding and other reports of dys-

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connectivity during verbal fluency[46] suggest that functional abnormalities in connectivity may be task dependent and that further insight into disturbed connectivity might be gathered by querying other regions of the DLPFC, in accordance with the animal-model observation that early HF lesions may lead to reorganization of intraprefrontal circuitry.[1] We also note that regions such as the cerebellum and superior temporal gyrus were functionally connected to the HF in schizophrenic patients but not in controls during the 0-back task. While there was no significant between-group difference in these areas, further research might demonstrate that they are part of a more distributed dysfunctional network associated with working memory impairment in schizophrenia.

LIMITATIONS OF THIS APPROACH

To operationalize the degree of linkage between brain regions, our study employed functional connectivity, which is based on covariance. The advantages and disadvantages of this approach have been discussed in detail elsewhere.[15,17] Limitations arise because observed functional connectivity does not imply anatomical connectivity (although, as seen here, neuroanatomical data were consistent with the results obtained by this method), neuronal interactions need not be linear, and linear correlation does not imply causality. However, much neuroimaging evidence suggests that linear correlations do capture an important aspect of neuronal interactions across different scales. It would be of interest to extend the present data using analysis methods that allow the investigation of directional interactions and models of causal relationships, such as effective connectivity.[47]

In using an anatomically defined region to quantify HF activity, the present analysis represents a potential advance over the use of seed voxels or spherical volumes of interest to query connectivity. Future work could extend this approach by regional parcellation of the HF into subregions to assess their individual connectivity profiles. The observation that the entorhinal portion of the parahippocampal gyrus was the part of the HF region of interest where a deactivation deficit in patients was identified suggests that this might be the subregion associated with the observed connectivity changes, since the entorhinal cortex forms the main port of entry and exit for interactions of the HF with the neocortex.[48,49]

Since we studied patients with chronic illness, it would be of interest to extend the findings to the early stages of the disease. This would also remove the confounding effect of previous neuroleptic treatment, which might have had an effect on the observed interactions even though treatment was withdrawn before the study. Finally, we required temporary abstinence from nicotine and caffeine because of the effects of these substances on rCBF.[50,51] Since more patients than controls consumed cigarettes and coffee, this might have contributed to group differences during abstinence as well; however, no data on such effects are available, and there is no suggestion that such effects, if present, would be regionally selective.

In summary, our analysis of connectivity in schizophrenia indicates a regionally specific alteration of HF-DLPFC functional linkage by demonstrating unmodulated persistence of coupling of these structures during a working memory load condition in patients but not in controls. Since animals with hippocampal lesions also show a dysregulation of striatal dopamine metabolism and because a tight correspondence between this dysregulation and prefrontal cortex dysfunction in schizophrenic patients has been demonstrated,[52] the present finding suggests a possible causal account of the emergence of these aspects of schizophrenic pathophysiology from HF dysfunction. Such a sequence of events would lead from a primary, early developmental insult to the HF via deficits in HF-DLPFC connectivity and induced maturational deficits in DLPFC circuitry to DLPFC dysfunction, which accounts for the core neuropsychology of the disorder and is linked to dopaminergic disinhibition. This theory is in agreement with a neurodevelopmental hypothesis of schizophrenia.[14] While it is highly implausible that this complex, frequent, and heterogeneous disorder can be reduced to a single causal chain, this formulation may help to guide further research in suggesting a study of persistent inhibitory HF-DLPFC interactions in humans with schizophrenia and animal models of the disorder.

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