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Decreased Default Mode Neural Network Modulation with Age in Schizophrenia

Christopher Abbott¹, Dae Il Kim², Scott Sponheim^{4,5}, Juan Bustillo¹, and Vince D. Calhoun^{2,3}

¹ Department of Psychiatry, University of New Mexico 87131

² The Mind Research Network, Albuquerque, NM 87131

³ Departments of Electrical and Computer Engineering, Neurosciences, and Computer Science, University of New Mexico, Albuquerque, NM 87131

⁴ Veterans Affairs Medical Center (116B), One Veterans Drive, Minneapolis, MN 55417

⁵ Department of Psychiatry, University of Minnesota, Minneapolis, MN 55454

Abstract

Objective—Previous studies have shown that patients with schizophrenia have less modulation of the task-positive and default mode networks of the brain during novelty detection. To date, the relationship between network modulation and age has not been assessed in patients with a long duration of illness.

Method—Seventeen patients with schizophrenia with a minimum disorder duration of 15 years and 28 age-matched healthy controls from the Mind Clinical Imaging Consortium database completed the auditory oddball discrimination task. Independent component analysis identified temporally cohesive but spatially distributed neural networks. This study examined whether age was associated with modulation of executive control and default mode networks during novelty detection in the patient and control groups. Analyses also tested whether duration of illness, chlorpromazine equivalents and symptoms were predictive of network modulation in the patient group.

Results—The modulation for the anterior default mode network had a main effect by group ($F_{1,41} = 7.17, p = 0.011$) and an interaction of group and age ($F_{1,41} = 6.92, p = 0.012$). Older patients with schizophrenia tended to have less negative modulation of the anterior default mode network with age. Exploratory analyses revealed patients with schizophrenia had less positive modulation of the task-positive network than healthy controls ($F_{1,43} = 4.01, p = 0.052$).

Conclusions—Decreased negative modulation of the anterior default mode network occurs late in the disease course of schizophrenia. This may be related to inability of older patients to allocate attentional resources away from task-irrelevant stimuli in the environment.

Keywords

schizophrenia; duration of illness; fMRI; independent component analysis

Introduction

Previous investigators have suggested that older patients with schizophrenia have “static encephalopathy” (1) or “illness stabilization” (2) in late-life. A recent review challenged this conceptualization by focusing on longitudinal, structural brain changes in patients with schizophrenia who have been ill for an average of 10 years prior to their initial scan (3). Patients with schizophrenia had cortical gray matter volume reduction in frontal and temporal areas at -0.5% per year compared to healthy controls at -0.2% per year. Event related potentials examining the neural basis for detecting behaviorally salient stimuli (the “oddball” paradigm) have also shown a relationship with disease duration in patients with schizophrenia. Specifically, the latency of the P300 potential reflects cognitive processing speed and stimulus evaluation time (4). Increased latencies of the P300 have been associated with poor cognitive performance, aging and neurodegenerative diseases (5). Duration of illness in schizophrenia has been found to correlate with increased P300 latencies beyond normal aging (6–8). Although these studies have been cross-sectional, investigators have interpreted the increased latency as evidence of neurodegeneration in schizophrenia (6). Thus, the effects of age and duration of illness on neural structure and function in schizophrenia remain unclear.

The behavioral response to salient stimuli in the auditory oddball discrimination task temporally modulates two anticorrelated functional networks of the brain, the task-positive, frontal-parietal attentional networks and the task-negative, default mode networks. Task-positive networks consist of the dorsolateral prefrontal cortex, inferior parietal cortex, and the supplementary motor areas (9–11). Functions of the task-positive network include exteroceptive attentional orienting during unexpected or novel events (11). The default mode networks are interconnected, midline cortical structures, which include the medial prefrontal cortex, posterior cingulate/retrosplenial cortex, precuneus, and the inferior parietal lobule (12,13). Functions attributed to the default mode network include stimulus-independent thought (“mind-wandering”) and stimulus-oriented thought (14,15). The latter refers to the unfocused, broad monitoring of one’s external environment (14,16) and contrasts with the focused attention elicited by the task-positive networks during the behavioral response to novel stimuli. Patients with schizophrenia have diminished modulation of task-positive (17–19) and default mode networks during the behavioral response to salient stimuli (17,20). The diminished anticorrelation of these networks suggests that patients with schizophrenia have difficulty disengaging from task-irrelevant stimuli to activate competing, task-positive networks.

To date, no fMRI studies have investigated differences in task modulation during an oddball paradigm in patients with schizophrenia late in the disease course. The primary objective of this study was to assess the effect of age on diminished positive and negative modulation of neural networks in a patient sample with greater than 15 years of disease duration and age-matched controls from a large, multi-site fMRI database. Based on previous studies of brain structure and function of patients after the first episode, we predicted that patients with schizophrenia would have significantly less positive modulation of the task-positive networks and less negative modulation of the default mode networks with age relative to healthy controls during the behavioral response to salient stimuli.

Methods

Participants

Data for patients with schizophrenia and healthy non-psychiatric control subjects were taken from the Mind Clinical Imaging Consortium database. The database included over 300 patients with schizophrenia and demographically matched control subjects from geographically distributed sites within the United States of America: University of Iowa (IOWA), Harvard/

Massachusetts General Hospital (MGH), University of Minnesota (MINN), and the University of New Mexico (UNM). In the present analyses, we included all of the patients with schizophrenia with disease duration of at least 15 years and demographically age-matched healthy controls who had performed the auditory oddball task. The selection of patients with extended duration of illness was to test for long-term effects of illness on brain function. To ensure all subjects were performing the task and were adequately motivated, we included subjects with a minimum average target tone detection of 60% for each run.

The demographic characteristics of the patients with schizophrenia ($n = 17$) and healthy controls ($n = 28$) are presented in Table 1. The two groups did not differ in age, maternal or paternal education, or parental socioeconomic status. The patient group scored lower than controls on Wide Range Achievement Test Third Edition (Reading subtest) (WRAT3) ($t_{43} = 4.47, p < 0.001$), which is purported to assess premorbid intelligence. The patient group also had fewer mean years of education than the control group ($t_{41} = -3.38, p < 0.001$). The subjects were from all four sites (patients/controls): IOWA (2, 0), MGH (2, 10), MINN (8, 9), and UNM (5, 9). The patients were all treated with antipsychotics at the time of data acquisition. Positive and negative symptoms for the patient group were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (21, 22). These scores are summarized in Table 2.

Auditory Oddball Paradigm

The auditory oddball task was a randomized, event-related design that consisted of frequently occurring standard tones (1000 Hz, frequency rate 82%), infrequently occurring target or “oddball” tones (1200 Hz, frequency rate 9%), and the equally infrequent complex computer generated tones. Subjects were instructed to press a button every time they heard a target tone, and the percentage of correct hits and reaction times were recorded as behavioral measures. Stimuli were sequentially presented in four runs, each consisting of 90 stimuli in a fixed, pseudorandom order. Each auditory stimulus was 200 milliseconds (ms) in duration and interstimulus interval varied between 550 to 2050 ms with a mean interval of 1200 ms. The sequence allowed separate examination of evoked BOLD responses for each stimulus type (targets, novels, and standards).

Imaging Parameters

IOWA, MINN, and MGH used a Siemens 3 Tesla Trio Scanner. UNM used a Siemens 1.5 Tesla Sonata. The fMRI pulse sequences were the same for all four sites and consisted of the following: repetition time = 2 s, echo time = 30 ms (40 ms for UNM secondary to lower field strength), field of view = 22 cm, acquisition matrix 64×64 , flip angle = 90° , voxel size = $3.44 \times 3.44 \times 4 \text{ mm}^3$, slice thickness = 4 mm, slice-gap = 1 mm, and number of slices = 27.

fMRI Preprocessing

We used SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) to preprocess the fMRI data. Images were realigned using INRIalign, a motion correction algorithm unbiased by local signal changes (23). Images were spatially normalized into the standard Montreal Neurological Institute space (24) and slightly sub sampled to $3 \times 3 \times 3.4 \text{ mm}^3$, resulting in $53 \times 53 \times 46$ voxels. The images were spatially smoothed with a $9 \times 9 \times 9 \text{ mm}$ full width at half-maximum Gaussian kernel.

Independent Component Analysis

Independent component analysis (ICA) is a useful and reliable fMRI data analysis method for extracting the default mode and executive control networks (25). Based on the assumption that fMRI data represents a linear mixture of source signals, spatial independent component

analysis extracts these source signals and their respective time course from the fMRI data (26). We used the Group ICA fMRI Toolbox (GIFT), version 2.0b (<http://icatb.sourceforge.net>) to analyze the fMRI data with spatial ICA. We first used a minimum description length algorithm to find the optimal number of spatially independent components (27). The data were then further compressed with principal component analysis. Spatial ICA was applied to this reduced data-set and performed on all of the subjects at once with the Infomax algorithm (28). The ICA output consisted of series of spatial maps and their respective time courses.

Component Selection

We were interested in identifying the task-positive and default mode networks. After discarding the components that were related to artifact, we used the methods from Stevens *et al.* to select the components of interest (29). We compared each component spatial map with *a priori* maps of white matter and cerebral spinal fluid. Components that had a higher correlation with these maps were not considered to be meaningful activations and were discarded. We then compared the remaining components with spatial maps of the task-positive and default mode networks that have been previously identified by Damoiseaux (30). We qualitatively selected the components that best matched these spatial maps for additional analysis.

Statistical Analysis of Component Time courses

We used SPM5 to generate a general linear model design matrix for the four experimental runs of the auditory oddball task. We regressed the ICA time course with this design matrix to generate a series of beta weights for every experimental parameter (targets, novels, and standards). The beta weights from the regression represented the degree of modulation of the task relative to baseline and were used for group level analysis with each component of interest (17). We performed an analysis of covariance (ANCOVA) for the default mode network and the task-positive network beta weights for target detection that included the following factors: group (age-matched controls and patients with schizophrenia), age, and the interaction (group $\times$ age). IQ has been shown to be a potential factor for modulation of the brain activity during cognitive tasks (31). We performed a second ANCOVA for the default mode and executive control target beta weights with the following factors: group, IQ as measured by the WRAT-3, and the interaction (group $\times$ IQ). We then performed pairwise correlations with task modulation of the executive control and default mode networks and the duration of illness, chlorpromazine equivalents (32), and symptoms (positive, negative, disorganized) for the patients with schizophrenia.

Results

Behavioral Findings

We identified 20 patients with greater than 15 years of duration of illness and 34 age-matched controls who had completed the functional scans from the Mind Clinical Imaging Consortium database. After applying the behavioral criterion of $> 60\%$ correct for each run, these groups were further reduced to 17 patients and 28 controls. Healthy controls and the patients with schizophrenia had significant differences in reaction times (patients = 566.56 ms, SD = 148.52; controls = 472.69 ms, SD = 96.01; $t_{44} = 2.93$, $p < 0.001$).

Components

The minimum description length algorithm determined that the optimal number of components for our data set was 18. For the 45 subjects, the ICA output consisted of 3,240 spatial maps and respective time courses (45 subjects $\times$ 4 runs $\times$ 18 components = 3,240). Three components were related to artifact (drift) and another five components were excluded because of white

matter and cerebral spinal fluid correlations. From the remaining ten components, we identified one task-positive network and two components of the default mode network for additional analysis. Independent component analysis divided the default mode networks into an anterior and posterior component. The task-positive network and the default mode networks are shown in Figure 1 and Table 3.

Task Modulation, Group Differences and Age

The ANCOVA revealed a significant main effect for group ($F_{1,41} = 7.17, p = 0.011$) and a group $\times$ age interaction ($F_{1,41} = 6.92, p = 0.012$) for the anterior default mode network. Patients with schizophrenia had less negative modulation of the anterior default mode network during target detection with age. In contrast, healthy controls had more negative modulation of the anterior default mode network during target detection with age. These results are presented in Figure 2. To further evaluate the effect of group, a comparison of adjusted means between patients and controls revealed significant group differences at 40 years ($t = 2.09, p = 0.043$) and 60 years ($t = 2.17, p = 0.036$). The patients had more negative modulation of the anterior default mode networks at 40 years of age and less negative modulation at the 60 years of age relative to the healthy controls. Post-estimation analysis excluded the possibility of undue influence from leverage (Cook's distance < 0.4) and outliers. The posterior default mode network had no main effects for group or interactions (for group, $F_{1,41} = 0.03, p = 0.45$).

For the task-positive network, the ANCOVA did not reveal a main effect for group or for the interaction term (for group, $F_{1,41} = 1.68, p = 0.20$). In an exploratory analysis, an ANOVA with target betas for the task-positive control network and group revealed trend level significant difference ($F_{1,43} = 4.01, p = 0.052$). The patients with schizophrenia had less positive modulation of their executive control networks during target detection relative to healthy controls. These results are shown in Figure 3. Using a similar exploratory analysis, the posterior default mode network did not reveal any significant group differences ($F_{1,43} = 0.45, p = 0.51$).

Task Modulation, Group Differences and IQ

We did not find any main effects for group, IQ (as measured by the WRAT-3) or the interaction term (group $\times$ IQ) for the executive control or default mode networks.

Pairwise Correlations with Duration of Illness, Chlorpromazine Equivalents, and Symptoms

We did not find any significant correlations for the task modulation of the task-positive or default mode networks with duration of illness or chlorpromazine equivalents. We did not find significant correlations with the positive, negative, or disorganized symptoms from the SAPS and the SANS. As expected, age strongly correlated with disease duration in the patients with schizophrenia ($r = 0.71, p < 0.001$).

Discussion

We used independent component analysis to identify spatially independent networks that included the default mode and task-positive networks. For the anterior default mode network we found a group effect indicating that schizophrenia patients' modulation of the anterior default mode network differed from that of healthy controls. The anterior default mode network also exhibited an interaction of group and age. The interaction revealed that older healthy control subjects had *more* negative modulation of the anterior default mode network, while older patients had *less* negative modulation of this network. In an exploratory analysis, the task-positive network showed a trend towards less positive modulation in the patient group relative to the controls.

Diminished positive modulation of the task-positive network in this sample of patients is consistent with previous investigations with the auditory oddball discrimination task in schizophrenia. Earlier studies using the general linear model have shown that patients with schizophrenia have less hemodynamic response in frontal, parietal and other cortical and subcortical structures (18,19). A recent study using ICA has shown that patients with schizophrenia have the most striking group differences in a component that included the superior and middle frontal gyri and anterior cingulate similar to the task-positive network in our study (17). Our results suggest that the often-replicated “hypofrontality” with task-positive networks during novelty detection may be independent of age and duration of illness in patients with schizophrenia.

Our findings are also consistent with previous studies showing that patients with schizophrenia have anomalous modulation of the default mode network during the behavioral response to novelty detection (17,20). The first study to use ICA to evaluate default mode functioning in schizophrenia found that patients had higher frequency fluctuations and spatial differences relative to controls (20). These results suggest altered connectivity and less temporal synchrony [it wasn't really less temporal synchrony unless you mean the lower frequency synchrony....perhaps remove the word 'less'? or could say suggests 'less efficient synchrony'] of the default mode network in the patient group. [you could also refer to the Jafri FNC paper which showed more inter-network connectivity to default mode in the patients] A subsequent study revealed that the default mode network in patients has a longer period of negative modulation during novelty detection (17). The sluggish return of default mode activation may be consistent with patients' difficulty shifting from task-related activities back to stimulus-independent thought. Both of these studies used heterogeneous patient samples with broad age ranges (20 to 60 years, 18 to 70 years, respectively). We have extended these findings by showing that the loss of negative modulation of the anterior default mode network may be most robust with the older patient group.

The diminution of negative modulation of the default mode network with age in the patient group mirrors a resting state connectivity study on aging (33). Similar to our study, independent component analysis split the default mode network into an anterior and posterior component. The older, non-psychiatric sample used in this study had decreased resting state connectivity in the both anterior and posterior default mode networks relative to a younger control group. In the older sample, the integrity of the anterior default mode network signal change was inversely correlated with age. The older sample in this study had cognitive deficits in attention, concentration, processing speed, memory, and executive functioning correlating with decreased activity in the anterior default mode network. The patients in our study were significantly younger (average age 44.9 years) than the sample included in this study (average age 70.7 years), but the affected area of the anterior default mode network was similar. The results suggest that patients with schizophrenia may be susceptible to the early neural correlates of aging.

Patients late in the disease course of schizophrenia often have persisting cognitive and negative symptoms (34–36). The pathophysiology of these signs and symptoms may be related to the loss of negative modulation of the anterior default mode network. The anterior default mode network includes the dorsal medial prefrontal cortex (Brodmann's areas 8/9/10). This region is associated with introspection, self-referential thought, and social cognition (37). The default mode interference hypothesis states that the failed attenuation of default mode network during goal-directed tasks may interfere with task specific neural processing such as the behavioral response to salient stimuli (9,15). Granger causality analysis has determined that the anterior default mode network activity influences activity within the task-positive networks further supporting the importance of default mode activity (38). This hypothesis stresses the importance of the transition from rest to goal-directed activities involving motivation and

degree of cognitive difficulty. Persisting default mode activity during a task-related activity may result in attentional lapses decreasing performance and leading to cognitive impairment (9). Persisting default mode activity also diminishes the anticorrelation between task-positive networks and may be relevant to the pathophysiology of schizophrenia (39). The degree of anticorrelation between these networks does not appear to be static and may change with age and duration of illness.

This study does have several limitations. First, all patients were taking antipsychotics at the time of the scan, and the older patient population had a long history of antipsychotic exposure. We did not find a significant correlation between chlorpromazine equivalents and task modulation. Second, the patient sample had increased prevalence of substance abuse and dependence in their histories, which may have affected task modulation. We excluded patients that met current criteria for substance abuse or dependence within the month prior to study participation. Third, our small sample size of patients may have limited our within group comparison of symptoms and duration of illness. Finally, this was a multi-site study with four different research groups and scanners. However, we did not find any significant differences in component modulation between the four sites.

In conclusion, these findings show evidence of changes in the temporal modulation of the anterior default mode network with age in patients with schizophrenia. The loss of negative modulation of the anterior default mode network may have adverse effects on other, anticorrelated networks and suggests that neural functions in late-life schizophrenia may not be “static” or “stable”. Further research is needed in older patients with schizophrenia to better understand the effects of age and duration of illness on anticorrelated networks. A study comparing early-onset and late-onset patients would be an important step towards disentangling the effects of age and duration of illness on network modulation.

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Figure 1.

This figure is an overlay of the components of interest. The hot colors represent the task-positive network. The cool colors represent the default mode networks (anterior and posterior). These networks are negatively modulated during target detection.

Regression Lines for Patients and Healthy Controls

Figure 2.

The beta weights for the the anterior default mode network had a main effect for group ($F_{1, 41} = 7.17, p = 0.011$) and interaction of group and age ($F_{1, 41} = 6.92, p = 0.012$). The patients with schizophrenia had less negative modulation of the anterior DMN with age. The control subjects had more negative modulation of the anterior DMN during target detection with age.

Group Means for Patients and Controls

Figure 3.

An exploratory ANOVA, the beta weights for the task-positive network had trend level significance for group ($F_{1,43} = 4.01, p = 0.052$). The patients with schizophrenia had less positive modulation of the executive control network relative to healthy controls.

Table 1

This table displays demographic information for patients with schizophrenia and healthy controls.

Demographics	Schizophrenia (Mean/SD)	Controls (Mean/SD)	Statistics (<i>t</i> / <i>p</i>)
Sex (M/F)	12/5	20/8	
Age (yrs)	45.4 (7.51)	45.8 (6.0)	$t_{43} = 0.21/0.83$
Education (yrs)	13.82 (2.00)	15.92 (1.98)	$t_{41} = 3.55/0.002$
Maternal education (yrs)	13.07 (3.22)	13.11 (2.86)	$t_{40} = 0.05/0.96$
Paternal education (yrs)	13.94 (3.70)	13.88 (4.22)	$t_{40} = 0.04/0.97$
WRAT-3 Reading	46.35 (6.04)	52.64 (3.43)	$t_{43} = 4.47/0.0001$
SES	2.78 (1.01)	2.57 (0.74)	$t_{42} = 2.78/.008$
Parent SES	2.88 (0.96)	2.68 (0.86)	$t_{42} = 0.70/0.49$

Note: WRAT-3 = Wide Range Achievement Test, Third addition; SES = socioeconomic status. SES ranges from 1 (higher executives, major professionals) to 7 (unskilled employees).

Table 2

This table displays global rating symptom scores for the patients with schizophrenia using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). Global ratings range from 1 (absent) to 5 (severe).

	Mean (SD)
Scale for the Assessment of Positive Symptoms (total)	7.12 (3.20)
Hallucinations: Global Rating	2.35 (1.87)
Delusions: Global Rating	2.76 (1.35)
Bizarre Behavior: Global Rating	0.94 (1.08)
Thought Disorder: Global Rating	1.06(1.34)
Scale for the Assessment of Negative Symptoms (total)	8.88 (3.01)
Affect: Global Rating	1.76 (1.14)
Alogia: Global Rating	0.71 (0.92)
Avolition: Global Rating	2.53 (1.28)
Anhedonia: Global Rating	2.29 (1.16)
Attention: Global Rating	1.59 (1.33)

Table 3

This table shows the top five regions within each component of interest. The anatomic regions are based off a one-sample t test using SPM5. A Talairach labeling system was used to determine regions of significance at a threshold of $p < 1.0 \times 10^{-9}$, FDR corrected.

<u>Default Mode Network (Ant.)</u>	Brodmann Areas	R/L (cm³)	Maximum t Values (R/L)
Medial Frontal Gyrus	10, 32, 11, 9, 6, 8	11.2/13.7	24.5 (-3, 43, -7)/25.4 (3, 49, -5)
Anterior Cingulate	32, 10, 24, 25	6.7/7.3	23.5 (-3, 40, -7)/25.3 (3, 46, -5)
Superior Frontal Gyrus	9, 10, 8, 6	6.9/12.0	18.6 (-3, 54, 22)/17.7 (3, 56, 22)
Superior Temporal Gyrus	38, 39	0.1/0.9	9.1 (-42, 19, -26)/15.5 (42, 19, -19)
Inferior Frontal Gyrus	47, 11	0.1/3.1	8.9 (-39, 28, -17)/14.3 (39, 22, -16)
<u>Default Mode Network (Post.)</u>			
Precuneus	7, 31, 23, 19, 39	19.0/16.6	21.2 (-6, -59, 50)/14.3 (39, 22, -16)
Posterior Cingulate	23, 30, 31, 29	5.6/5.9	20.3 (-6, 57, 19)/20.9 (3, -55, 17)
Cingulate Gyrus	31, 23, 24	6.6/4.3	20.7 (-3, -45, 35)/17.6 (3, -33, 35)
Superior Parietal Lobule	7	0.8/0.5	17.3 (-9, -61, 53)/13.9 (6, -64, 53)
Cuneus	7, 30, 19, 18	0.8/1.1	15.2 (0, -65, 31)/17.1 (6, -68, 31)
<u>Task-Positive Network</u>			
Medial Frontal Gyrus	8, 6, 9	4.1/2.2	23.0 (-3, 26, 46)/20.1 (3, 28, 43)
Superior Frontal Gyrus	8, 10, 6, 9	6.0/1.3	20.1 (-3, 26, 48)/20.4 (3, 29, 46)
Cingulate Gyrus	32, 9, 23, 24, 31	1.9/0.5	18.1 (-6, 22, 40)/13.6 (3, 22, 40)
Middle Frontal Gyrus	10, 8, 46, 9, 6, 11	17.9/4.1	16.9 (-36, 52, -8)/12.4 (45, 10, 30)
Inferior Parietal Lobule	40, 7, 39	8.9/5.5	15.1 (-45, -59, 47)/16.3 (48, -38, 46)