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Evidence for Intact Local Connectivity but Disrupted Regional Function in the Occipital Lobe in Children and Adolescents with Schizophrenia

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Abstract: It has long been known that specific visual frequencies result in greater blood flow to the striate cortex. These peaks are thought to reflect synchrony of local neuronal firing that is reflective of local cortical networks. Since disrupted neural connectivity is a possible etiology for schizophrenia, our goal was to investigate whether localized connectivity, as measured by aberrant synchrony, is abnormal in children and adolescents with schizophrenia. Subjects included 25 children and adolescents with schizophrenia and 39 controls matched for age and gender. Subjects were scanned on a Siemens 3 Tesla Trio scanner while observing flashing checkerboard presented at either 1, 4, 8, or 12 Hz. Image processing included both a standard GLM model and a Fourier transform analysis. Patients had significantly smaller volume of activation in the occipital lobe compared to controls. There were no differences in the integral or percent signal change of the hemodynamic response function for each of the four frequencies. Occipital activation was stable during development between childhood and late adolescence. Finally, both patients and controls demonstrated an increased response between 4 and 8 Hz consistent with synchrony or entrainment in the neuronal response. Children and adolescents with schizophrenia had a significantly lower volume of activation in the occipital lobe in response to the flashing checkerboard task. However, features of intact local connectivity in patients, such as the hemodynamic response function and maximal response at 8 Hz, were normal. These results are consistent with abnormalities in regional connectivity with preserved local connectivity in early-onset schizophrenia. *Hum Brain Mapp 33:1803–1811, 2012.*

Key words: early-onset schizophrenia; functional magnetic resonance imaging; fMRI; flashing checkerboard; hemodynamic response function

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INTRODUCTION

Schizophrenia is a debilitating illness associated with an array of clinical symptoms and cognitive deficits [Andreasen et al., 1998]. The neurobiological findings in schizophrenia have been reported in multiple cortical and subcortical brain regions, including all four lobes of the brain, the limbic system, thalamus, striatum, and the cerebellum [Andreasen et al., 1998; MacDonald et al., 2009; Pearlson and Marsh, 1999; White et al., 2008a,b]. One of the principal theories that integrates the global nature of the illness with the clinical phenotype postulates a disruption in brain connectivity [Andreasen, 1997; Friston, 1998; Weinberger et al., 1992]. Multiple studies using a variety of techniques, including postmortem brain samples [Dean et al., 2009; Lewis and Akil, 1997; Perlman et al., 2004], diffusion tensor imaging [White et al., 2008b], and functional magnetic resonance imaging [MacDonald et al., 2009] have provided support for the theory of disrupted connectivity in the pathogenesis of schizophrenia.

Connectivity can be parsed into connections residing within local networks (i.e., those that involve communication either within the same or neighboring cortical regions) [Douglas and Martin, 2007], or long range connections between remote brain regions. The vast majority of neuroimaging studies to date have focused on long-range connections between different brain regions using techniques that measure functional and effective connectivity. These include techniques such as independent components analyses [Calhoun et al., 2001] and seed pixel correlation analyses [Stephan et al., 2001], that identify brain regions which show similar covariance patterns. Measurements of local connectivity have been difficult to achieve without invasive techniques and relate to networks within localized cortical layers.

One potential technique to measure local connectivity is by tapping into the frequency response of the visual cortex during oscillating visual input. There are now multiple studies that demonstrate that flashing stimuli at 8 Hz evokes the greatest neural response in the striate cortex. This 8-Hz peak has been found using PET [Fox and Raichle, 1984, 1985], fMRI [Kwong et al., 1992; Ozus et al., 2001; Parkes et al., 2004; Singh et al., 2003; Thomas and Menon, 1998; Zhu et al., 1998], and ERP studies [Herrmann, 2001; Singh et al., 2003]. The evidence from ERP studies demonstrates that the differences are reflective of underlying neuronal activity, rather than a result of differences in blood flow.

The reason for the 8-Hz peak in activation is unknown, although there is emerging evidence that alpha and theta wave activity (8–14 Hz) play an important role as an internal clock for cognitive processes [Buzsaki, 2005; Lakatos et al., 2008; Palva and Palva, 2007]. In fact, studies in macaque monkeys have found that the lower theta frequencies modulate the higher gamma frequencies, which serve as an internal clock [Lakatos et al., 2005]. Thus, external sources that correspond with the frequency of the internal clock may create a damped resonance frequency. This 8-Hz peak is thought to be a result of synchrony involving local neuronal firing, which has been defined as neuronal entrainment. Since this synchrony is thought to reflect localized connectivity, it was our goal to study whether entrainment, or local connectivity, is disrupted in children and adolescents with schizophrenia. Disruption of entrainment could reflect either a primary impairment in local connectivity, or alternatively, top-down abnormalities related to higher-order connectivity.

TABLE I. Demographic characteristics for the patient and control groups and clinical characteristics for the patient group

	Patients ($n = 25$) Mean/SD	Controls ($n = 39$) Mean/SD	P
Demographic measures			
Age (years/SD)	14.8/3.0	14.6/3.3	ns
Sex (M/F)	18/7	23/16	ns
Parental SES	39.2 (13.7)	52.9 (9.3)	<0.001
Clinical measures			
Age of onset (years/SD)	12.0 (3.3)		
Psychotic symptoms (mean/SD)	2.5/1.0		
Negative symptoms (mean/SD)	2.8/0.7		
Disorganized symptoms (mean/SD)	2.0/1.0		
Diagnoses			
Schizophrenia	$n = 19$		
Schizoaffective disorder	$n = 3$		
Schizophreniform disorder	$n = 3$		

MATERIALS AND METHODS

Subjects

A total of 70 subjects participated in the study, however, four patients and two controls were excluded secondary to excessive head motion during the fMRI session. Thus, the study sample consisted of 64 children; 25 children and adolescents with schizophrenia (18 males and 7 females) and 39 controls (23 males and 16 females). The demographic and clinical information for the two groups is provided in Table I. All participants underwent a diagnostic evaluation using the Kiddie-SADS-PL [Kaufman et al., 1997]. Of the children and adolescents with schizophrenia, also known as early-onset schizophrenia (EOS), additional clinical measures included the Scale for the Assessment of Negative Symptoms (SANS) [Andreasen, 1983], and the scale for the Assessment of Positive Symptoms (SAPS) [Andreasen, 1984]. The mean age of the patient and control groups were 14.8 (S.D. 3.0) and 14.6 (S.D. 3.3) years, respectively. The age range for both groups was between 8 and 19 years. All but four patients were on medication at the time of testing. The medications included aripiprazole ($n = 6$), risperidone ($n = 4$), quetiapine ($n = 4$), olanzapine ($n = 1$), clozaril ($n = 4$), and ziprasidone ($n = 2$).

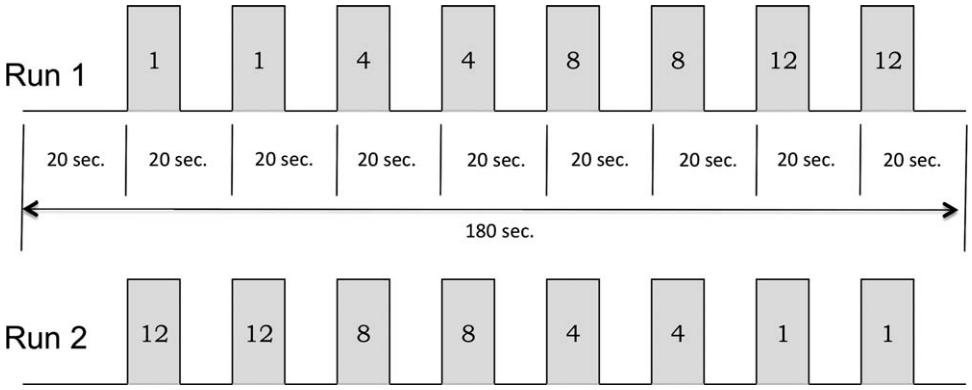

Figure 1.
Timing for the flashing checkerboard functional magnetic resonance imaging paradigm. The numbers placed between the blocks reflect the frequency of the flashing checkerboard in Hz.

The control group had no evidence of a past or present psychiatric disorder and no history of schizophrenia or psychosis in a first degree relative. Patients and controls were excluded if they had a history of substance dependence, ongoing substance abuse (within the past month), or a neurological disorder, head injury, or medical illness involving the brain. The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Institutional Review Board at the University of Minnesota. The nature of the experiment was explained to the participants and their parents and informed consent from the parents and informed assent from the child was obtained prior to participation.

Functional Imaging Paradigm

The fMRI paradigm consisted of a flashing checkerboard that was back-projected onto a screen located within the bore. The flashing checkerboard was presented using a block design with four different frequencies (1, 4, 8, and 12 Hz). The timing for the two fMRI runs are shown in Figure 1. After a 20-s rest period, the stimuli (Fig. 2A and it's negative image) were presented sequentially with a frequency of 20 s (10 s on followed by a 10 s off). Each 20-s block was presented twice within each run, and there were two runs, each lasting 180 s.

MRI Sequence

All MR images were acquired with a 3T Siemens MR System (Erlangen, Germany) at the Center for Magnetic resonance Research in University of Minnesota. Head immobilization was performed using a vacuum bag. Following an initial localizer, a series of high-resolution slices were obtained to find the coronal midline. This was performed to correct for any rotation along the y-axis. Next a series of high-resolution sagittal images were acquired along the midline of the brain. These were used to orient the slice with the midpoint of the posterior slice at the calcarine fissure and oriented along the anterior/posterior commissure (ACPC) plane.

Functional images were acquired using a gradient echo sequence in 16 contiguous axial slices with an in plane resolution of 3.5×3.5 mm^2 and a 2-mm slice thickness. The region covered is shown in Figure 2D. The fMRI sequence parameters were: TE = 30 ms, TR = 1,000 ms, flip angle = 60°, FoV = 224 mm, FoV phase 100%. A total of 180 measurements were obtained in each of the two runs.

Image Processing

The functional images were preprocessed using a combination of Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) [Cox, 1996] and FSL's FMRIB's Software Library (http://www.fmrib.ox.ac.uk/fsl/) [Smith et al., 2004]. Following the conversion from DICOM to Nifti format, correction for slice timing and motion was performed using AFNI [Cox, 1996]. Subjects who had greater than 2.5-mm head motion in either the x, y, or z directions were excluded from the analyses. From a total of 29 patients and 41 controls scanned, 4 patients and 2 controls were excluded secondary to excessive motion. Following preprocessing, two different algorithms were then utilized to assess the hemodynamic response function and extent of the activations between the patients and controls.

Region of Interest Analysis

The preprocessed images were oriented to standard MNI space utilizing FSL in a three-stage process. First, a mean EPI image was generated from the fMRI time series for each individual. This mean EPI image was registered to Montreal Neurological Institute space through a 12-parameter transformation [Jenkinson and Smith, 2001; Jenkinson et al., 2002]. Finally, the 12-parameter transform was applied to the entire fMRI time series for each individual and each run. Single-subject analyses were performed

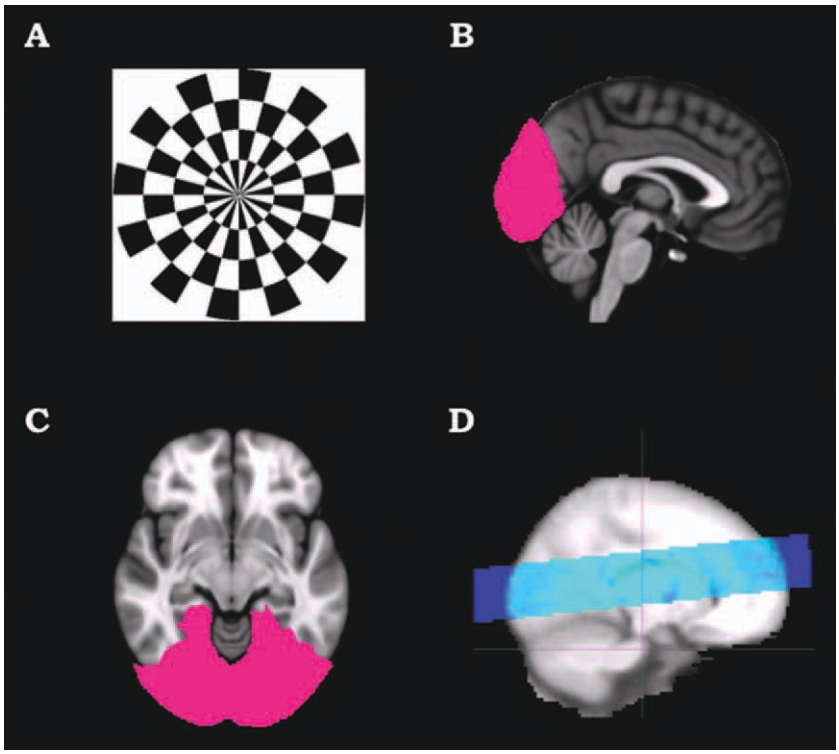

Figure 2.
(**A**) Flashing checkerboard image that was alternated with it's negative image and presented at four different frequencies; (**B**) sagittal and (**C**) axial sections that show the occipital lobe mask; (**D**) slice prescription for the fMRI acquisition. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

using FMRIB's fMRI Expert Analysis Tool FEAT (www.fmrib.ox.ac.uk/fsl/feat5/index). The flashing checkerboard was modeled as a square wave with a 0.05-Hz frequency. This time series was convolved with the hemodynamic response function (HRF) that was modeled from a linear combination of gamma functions. Next, a general linear model (GLM) was implemented using FMRIB's Improved Linear Model (FILM). A singular value decomposition (SVD) was utilized to assess the fit of each voxel to the design matrix using local autocorrelation [Woolrich et al., 2001]. The two within-subject runs were combined using a fixed effects model.

A mask of the occipital lobe in MNI space was obtained from the Harvard-Oxford Atlas within FSL (Fig. 2C,D). The volume of activation was obtained using an in-house MATLAB program which calculated the number of voxels within the occipital mask that that exceeded a set threshold, determined as $P < 0.05$ corrected at the cluster level.

Fourier Analysis

To assess the hemodynamic waveform without a priori assumptions of its shape, a voxel-wide Fourier transform was performed on time series data within each run. The first 10 TRs were excluded to allow for a symmetric time series. Voxels which had a peak frequency corresponding to 0.05 Hz (corresponding to the block design with 20-s periods) were identified in the dataset. Next, the largest contiguous set of voxels responding to this frequency was extracted, yielding a set of voxels which had a frequency response identical to the stimulus presentation. The anatomic location of these voxels was evaluated to ensure that they were in the occipital lobe. The time series for each voxel within the Fourier identified region of interest in the occipital lobe were averaged and parsed to correspond with either the 1, 4, 8, or 12 Hz stimuli.

Statistical Analyses

The demographic data was assessed using chi-square for categorical and *t*-tests for continuous data. Assessment of the volume of activation in the occipital lobe was performed using *t*-tests and ANCOVA with age and sex as covariates. Developmental trends were evaluated using a 2 (group) by 3 (age group) ANOVA. The maximum signal change and integral of the HRF for each of the frequencies were evaluated using a (2) diagnosis by (4) frequency repeated-measures, mixed model ANOVA, with diagnosis

and frequency as the fixed effects, and subject as the random variable. Paired *t* tests were used post hoc to evaluate differences between the individual frequencies.

RESULTS

There were no differences in either the mean age or sex distributions between the patient and control groups. There was a significant difference in the parental SES between groups ($t = 4.6$, df = 59, $P < 0.001$). Of the EOS patients, 19 patients had schizophrenia, 3 had schizoaffective disorder, and 3 had schizophreniform disorder. The age of onset of psychotic symptoms was 12.0 years (SD 3.3). The positive and negative symptoms had a mean within the mild to moderate level, and the disorganized symptoms tended to be more mild (Table I).

Region of Interest Analysis

The volume of activation within the occipital lobe was significantly greater in controls compared to patients ($t = 2.0$, df 62, $P = 0.05$). The mean volume of activation within the occipital lobe was 35.8 cm^3 in patients compared to 45.0 cm^3 in controls. Importantly, the difference was not a result of an arbitrary threshold, since the patient/control difference was present across multiple thresholds (see Fig. 3). In addition, the difference remained significant when controlling for age ($F_{1,61} = 4.4$, $P = 0.04$), age and gender ($F_{1,60} = 5.2$, $P = 0.02$), but not when controlling for SES. The findings also remained significant when controlling for age, sex, and the volume of the occipital lobe slice ($F_{1,58} = 5.1$, $P = 0.03$). There were no differences between patients and controls in the mean *z*-score of activated voxels. In addition, there were no differences between patients and controls in the extent of activation when evaluating at each specific frequency.

Developmental effects of occipital lobe activation were evaluated by dividing the subjects into three different age groups (8- to 12-, 13- to 16-, and 17- to 19-year-olds). This resulted in 13 controls in each of the three age groups, and 7, 9, and 9 patients in each of the three age groups, respectively. A 2 (diagnosis) by 3 (age group) ANOVA was performed with an effect of diagnosis ($F_{1,60} = 4.4$, $P = 0.04$), but without an effect of age group or an age group by diagnosis interaction. In addition, there were no age-related differences in the HRF within the patient and control group when evaluated individually. In addition, the HRF also demonstrated no age-related differences. Each age group had the same frequency–response pattern of a lower integral of the HRF at 1 Hz and a peak at 8 Hz. Thus, occipital lobe activation and HRF appears to be relatively stable from childhood through older adolescence.

Fourier Analysis

A (2) group by (4) frequency repeated measures mixed model ANOVA was performed to evaluate for differences between patients and controls in the integral of the HRF at the different frequencies. There was a significant effect of frequency ($F_{3,111} = 7.1$, $P = 0.0002$), without a significant effect of group or a group by frequency interaction. Since there was not a significant group effect, the patients and controls were pooled for the post hoc analyses of frequency. Paired *t* tests found that the 1-Hz flashing checkerboard evoked a significantly less HRF integral than either 4 Hz ($t = 3.7$, df 38, $P = 0.0006$) and 8 Hz ($t = 4.5$, df 38, $P < 0.0001$). In addition, 8 Hz had a significantly greater HRF integral compared to 12 Hz ($t = 2.2$, df 38, $P = 0.03$). These analyses were repeated for the peak percent signal change of the HRF for each frequency and the results were unchanged. The HRF and values for the integral of the HRF for each frequency and group are shown in Figure 4.

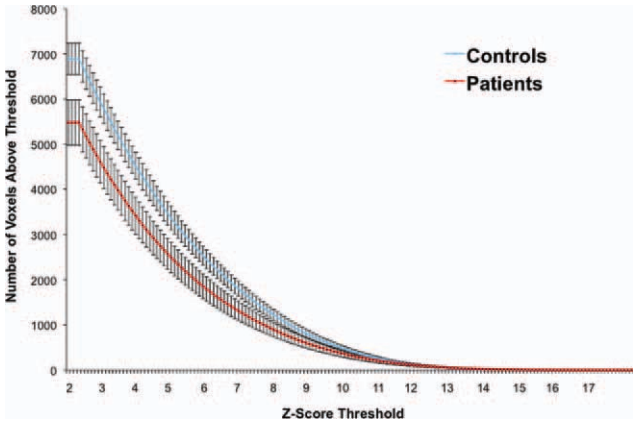

Figure 3.
Volume of activation between patients and controls at different thresholds of significance. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

Several important findings emerge from this work. The first finding is that there are no differences between the different HRFs at the different flashing checkerboard frequencies. This could reflect that local connectivity, measured through entrainment, appears to remain intact in patients with EOS. Entrainment involves a local cooperation of neural networks that when stimulated, becomes time locked with the driving frequency of the visual stimuli [Parkes et al., 2004; Rager and Singer, 1998]. Studies performed with PET [Fox and Raichle, 1984, 1985], fMRI [Kwong et al., 1992; Ozus et al., 2001; Parkes et al., 2004; Thomas and Menon, 1998; Zhu et al., 1998] and EEG [Herrmann, 2001] have shown that the driving frequency that produces the maximum synchrony is between 8 and 10 Hz and its associated harmonics. We found no differences in the EOS patients and controls in the peak percent signal change or the integral of the HRF at any of the four frequencies tested. In addition, both groups had peak

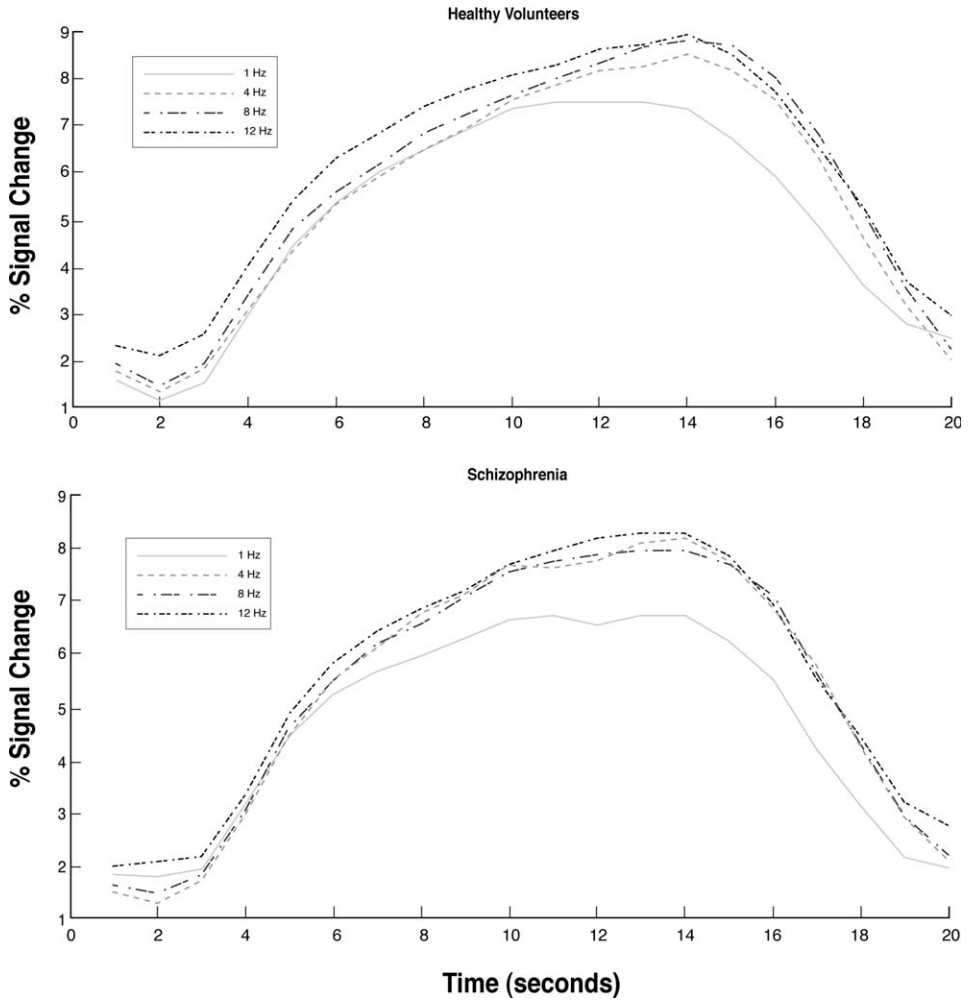

Figure 4.

Hemodynamic response curves at different frequencies for the healthy volunteers (Top) and the patients with schizophrenia (Bottom).

activations at around 8 Hz, paralleling studies performed in healthy adult populations.

There were significant differences in the HRF between 1 and 4 Hz, and between 1 and 8 Hz in both the patient and control groups. There was also a significant difference between 8 and 12 Hz, but no significant difference between 4 and 8 Hz. These findings are very similar to the work of Ozus et al. (Ozus et al. 2001), who found a significant increase in the maximum percent signal change from 1 to 4 Hz, with a plateau between 4 and 8 Hz and a slight decrease, although not significant, at 12 Hz. Finally, there were no age related differences in the HRF for each of the four frequencies. However, since the occipital lobe is one of the earlier brain regions to develop [Huttenlocher and de Courten, 1987; Thompson and Nelson, 2001; White et al., 2010a], it is not surprising that there are no age-related differences in the HRF in the occipital lobe.

The second important finding is that although the peak response occurred in both groups at 8 Hz, children and adolescents with schizophrenia had a significantly smaller volume of activation in the occipital lobe compared to controls. The difference in volume of activation was present irrespective of the applied *z*-threshold (see Fig. 3), although there were no significant differences in the mean value of the activation between the patients and controls. This implies that it is the volume of activation across voxels that is different, rather than the magnitude of activation within voxels. These findings, taken together, suggest intact local connectivity but disrupted regional connectivity. Thus, the information from V1 extends into other regions of the occipital lobe patients, but not to the same extent as is found in the controls. Further research focusing specifically on connectivity of neuronal activity spreading from V1 to other occipital lobe regions is necessary to

confirm whether these differences reflect true aberrant connectivity. There have now been several studies of children and adolescents with schizophrenia that show aberrant connectivity between distant brain regions on higher order cognitive tasks [Haenschel et al., 2007; Pauly et al., 2008; White et al., 2011a, 2011b]. Reports of decreased cortical thickness in the occipital lobe [Narr et al., 2005] may also correspond to decreased activation in these regions.

Adult patients with chronic schizophrenia have been shown to have a greater volume of activation, without a greater peak activation, compared to matched controls in the lateral occipital lobe during an object processing task [Wynn et al., 2008]. Subjects in this study also viewed an 8-Hz frequency contrast reversing flashing checkerboard wedge paradigm, in which the wedges made five complete rotations over 30 s. This task was to evaluate early visual processing between patients and controls and this task resulted in no significant differences between patients and controls [Wynn et al., 2008]. The differences between the lack of early visual differences seen in early visual processes between the study by Wynn et al. [2008] and our study could be due to differences in age (mean age of 38.8 years in the Wynn study versus 14.8 years in our study), duration of illness, medication effects, differences in the paradigm, and/or differences in the analysis approaches. Finally, the inclusion of several different tasks, each which tap different components of early to middle level visual processing, is important to more fully evaluate the connectivity of the visual system.

There has been a growing literature supporting abnormalities in early-stage visual processes in schizophrenia [Butler and Javitt, 2005]. For example, early visual deficits, identified as decreased occipital lobe activation has been shown in EOS patients performing a visuospatial working memory (WkM) task [Haenschel et al., 2007]. While there is a considerable body of work focusing on higher-level cognitive abnormalities in schizophrenia, there is evidence that more fundamental processes involving simple sensory networks are disrupted in schizophrenia [Butler et al., 2001, 2005; Haenschel et al., 2007; Wynn et al., 2008]. This disruption could be due to either direct abnormalities in primary sensory networks, or alternatively, these could represent disruptions in the top-down modulation of these neural circuits. It is thought that even lower level perceptual information is processed and modulated through distributed cortical networks [McIntosh, 1999; Mesulam, 1990]. However, the nature of how these networks are disrupted in schizophrenia is unclear.

The primary visual cortex (V1) involves a complex local network where 90% of the cells are subject to suppression by neighboring cells [Jones et al., 2001]. Interestingly, postmortem studies in schizophrenia have identified reductions in cortical-cortical connections [Rajkowska et al., 1998] and abnormalities in non-pyramidal cells in Layer IV of the cortex [Benes et al., 2001]. This cortical layer tends to be more involved in the input layer involving longer-range communication between brain regions. Thus, one explanation of these findings is that connectivity within the superficial layers of the cortex are intact in schizophrenia, whereas abnormalities are present in the deeper layers of the cortex, or those that are more involved in long distance transmission of signals.

There are several limitations to the current study. First, we did not parse the stimuli in such a manner in which we could investigate the HRF related to the parvocellular and magnocellular pathways. Given recent findings of abnormalities related to the magnocellular pathways, designing stimuli that would parse out these different pathways might provide greater detail of the aberrant neural pathways. Second, as is true with most fMRI studies, we are assuming a relationship between the BOLD effect and neuronal activity. Not only is there now considerable evidence supporting such a relationship [Kim et al., 2004], ERP studies of the visual response to flashing objects also support greater neuronal activity at 8-Hz. Third, the use of a complementary event-related paradigm may have allowed us to better model the hemodynamic waveform for each of the different frequencies, as well as evaluating additive effects. However, the block paradigm also allowed for the additional Fourier analysis, which does not rely on assumptions related to modeling the HRF. Fourth, a block design of with a frequency of 0.05 Hz (20 s) does not allow for a full return of the HRF to baseline [Leniger-Follert and Hossmann, 1979], however, having two sequential blocks at the same frequency does allow for accurate modeling of the HRF. The second block of visual activation is only influenced by the frequency of the former block, which is at the same frequency. This design allowed for a 30-s gap between different frequencies and these were used to evaluate the HRF. Fifth, all but four of the patients were on medication at the time of testing. While medication has been shown to alter functional connectivity in patients with schizophrenia, it tends to alter it in a manner in which it is more normalized [Stephan et al., 2001]. However, it is possible that medication status could affect the extent of activation in the occipital lobe. Finally, the age group analysis did not have a large number of subjects, and thus the findings of the age-related stability of the HRF are preliminary. Either studies with larger number of subjects, or preferably longitudinal studies will be important to confirm the stability of the HRF in the occipital lobe over development.

CONCLUSIONS

In summary, we found that children and adolescents with schizophrenia show similar patterns of entrainment during visual stimulation of the occipital cortex compared to a matched control group. This may reflect intact local neural connectivity. Children and adolescents with schizophrenia, however, had significantly less overall volume of activation in the occipital lobe compared to controls. This may reflect aberrant connectivity as the neuronal signals

travel from V1 to other regions in the occipital lobe. Alternatively, these differences may reflect aberrant top-down control of neuronal signals. Future work in evaluating entrainment coupling EEG with finer, high-resolution imaging (i.e., spin-echo techniques at higher field strengths) may help to better parse the occipital lobe and identify aberrant functional connectivity.

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REFERENCES

Andreasen NC (1983): The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA: The University of Iowa.

Andreasen NC (1984): The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA: The University of Iowa.

Andreasen NC (1997): Linking mind and brain in the study of mental illnesses: A project for a scientific psychopathology. Science 275:1586–1593.

Andreasen NC, Paradiso S, O'Leary DS (1998): "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 24:203–218.

Benes FM, Vincent SL, Todtenkopf M (2001): The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. Biol Psychiatry 50:395–406.

Butler PD, Javitt DC (2005): Early-stage visual processing deficits in schizophrenia. Curr Opin Psychiatry 18:151–157.

Butler PD, Schechter I, Zemon V, Schwartz SG, Greenstein VC, Gordon J, Schroeder CE, Javitt DC (2001): Dysfunction of early-stage visual processing in schizophrenia. Am J Psychiatry 158:1126–1133.

Butler PD, Zemon V, Schechter I, Saperstein AM, Hoptman MJ, Lim KO, Revheim N, Silipo G, Javitt DC (2005): Early-stage visual processing and cortical amplification deficits in schizophrenia. Arch Gen Psychiatry 62:495–504.

Buzsaki G (2005): Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory. Hippocampus 15:827–840.

Calhoun VD, Adali T, Pearlson GD, Pekar JJ (2001): A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 14:140–151.

Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.

Dean B, Boer S, Gibbons A, Money T, Scarr E (2009): Recent advances in postmortem pathology and neurochemistry in schizophrenia. Curr Opin Psychiatry 22:154–160.

Douglas RJ, Martin KA (2007): Mapping the matrix: the ways of neocortex. Neuron 56:226–238.

Fox PT, Raichle ME (1984): Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. J Neurophysiol 51:1109–1120.

Fox PT, Raichle ME (1985): Stimulus rate determines regional brain blood flow in striate cortex. Ann Neurol 17:303–305.

Friston KJ (1998): The disconnection hypothesis. Schizophr Res 30:115–125.

Haenschel C, Bittner RA, Haertling F, Rotarska-Jagiela A, Maurer K, Singer W, Linden DE (2007): Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: A study with event-related potentials and functional magnetic resonance imaging. Arch Gen Psychiatry 64:1229–1240.

Herrmann CS (2001): Human EEG responses to 1–100 Hz flicker: Resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. Exp Brain Res 137:346–353.

Huttenlocher PR, de Courten C (1987): The development of synapses in striate cortex of man. Hum Neurobiol 6:1–9.

Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Jenkinson M, Smith S (2001): A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143–156.

Jones HE, Grieve KL, Wang W, Sillito AM (2001): Surround suppression in primate V1. J Neurophysiol 86:2011–2028.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997): Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988.

Kim DS, Ronen I, Olman C, Kim SG, Ugurbil K, Toth LJ (2004): Spatial relationship between neuronal activity and BOLD functional MRI. Neuroimage 21:876–885.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, et al. (1992): Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 89:5675–5679.

Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE (2008): Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 320:110–113.

Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G, Schroeder CE (2005): An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J Neurophysiol 94:1904–1911.

Leniger-Follert E, Hossmann KA (1979): Simultaneous measurements of microflow and evoked potentials in the somatomotor cortex of the cat brain during specific sensory activation. Pflugers Arch 380:85–89.

Lewis DA, Akil M (1997): Cortical dopamine in schizophrenia: Strategies for postmortem studies. J Psychiatr Res 31:175–195.

MacDonald AW III, Thermenos HW, Barch DM, Seidman LJ (2009): Imaging genetic liability to schizophrenia: Systematic review of FMRI studies of patients' nonpsychotic relatives. Schizophr Bull 35:1142–1162.

McIntosh AR (1999): Mapping cognition to the brain through neural interactions. Memory 7:523–548.

Mesulam MM (1990): Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28:597–613.

Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, Sevy S, Wang Y, Schrock K, Bilder RM (2005): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 58:32–40.

Ozus B, Liu HL, Chen L, Iyer MB, Fox PT, Gao JH (2001): Rate dependence of human visual cortical response due to brief

stimulation: An event-related fMRI study. Magn Reson Imaging 19:21–25.

Palva S, Palva JM (2007): New vistas for alpha-frequency band oscillations. Trends Neurosci 30:150–158.

Parkes LM, Fries P, Kerskens CM, Norris DG (2004): Reduced BOLD response to periodic visual stimulation. Neuroimage 21:236–243.

Pauly K, Seiferth NY, Kellermann T, Backes V, Vloet TD, Shah NJ, Schneider F, Habel U, Kircher TT (2008): Cerebral dysfunctions of emotion-cognition interactions in adolescent-onset schizophrenia. J Am Acad Child Adolesc Psychiatry 47:1299–1310.

Pearlson GD, Marsh L (1999): Structural brain imaging in schizophrenia: A selective review. Biol Psychiatry 46:627–649.

Perlman WR, Weickert CS, Akil M, Kleinman JE (2004): Postmortem investigations of the pathophysiology of schizophrenia: The role of susceptibility genes. J Psychiatry Neurosci 29:287–293.

Rager G, Singer W (1998): The response of cat visual cortex to flicker stimuli of variable frequency. Eur J Neurosci 10:1856–1877.

Rajkowska G, Selemon LD, Goldman-Rakic PS (1998): Neuronal and glial somal size in the prefrontal cortex: A postmortem morphometric study of schizophrenia and Huntington disease. Arch Gen Psychiatry 55:215–224.

Singh M, Kim S, Kim TS (2003): Correlation between BOLD-fMRI and EEG signal changes in response to visual stimulus frequency in humans. Magn Reson Med 49:108–114.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, et al. (2004): Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl 1):S208–S219.

Stephan KE, Magnotta VA, White T, Arndt S, Flaum M, O'Leary DS, Andreasen NC (2001): Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. Psychol Med 31:1065–1078.

Thomas CG, Menon RS (1998): Amplitude response and stimulus presentation frequency response of human primary visual cortex using BOLD EPI at 4 T. Magn Reson Med 40:203–209.

Thompson RA, Nelson CA (2001): Developmental science and the media. Early brain development. Am Psychol 56:5–15.

Weinberger DR, Berman KF, Suddath R, Torrey F (1992): Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 149:890–897.

White T, Cullen K, Rohrer LM, Karatekin C, Luciana M, Schmidt M, Hongwanishkul D, Kumra S, Charles Schulz S, Lim KO (2008a): Limbic structures and networks in children and adolescents with schizophrenia. Schizophr Bull 34:18–29.

White T, Nelson M, Lim KO (2008b): Diffusion tensor imaging in psychiatric disorders. Top Magn Reson Imaging 19:97–109.

White T, Su S, Schmidt M, Kao CY, Sapiro G (2010a): The development of gyrification in childhood and adolescence. Brain Cogn 72:36–45.

White T, Hongwanishkul D, Schmidt M (2011a): Increased anterior cingulate and temporal lobe activity during visuospatial working memory in children and adolescents with schizophrenia. Schizophr Res 125:118–128.

White T, Schmidt M, Kim DI, Calhoun VD (2011b): Disrupted functional brain connectivity during verbal working memory in children and adolescents with schizophrenia. Cereb Cortex 21:510–518.

Woolrich MW, Ripley BD, Brady M, Smith SM (2001): Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14:1370–1386.

Wynn JK, Green MF, Engel S, Korb A, Lee J, Glahn D, Nuechterlein KH, Cohen MS (2008): Increased extent of object-selective cortex in schizophrenia. Psychiatry Res 164:97–105.

Zhu XH, Kim SG, Andersen P, Ogawa S, Ugurbil K, Chen W (1998): Simultaneous oxygenation and perfusion imaging study of functional activity in primary visual cortex at different visual stimulation frequency: Quantitative correlation between BOLD and CBF changes. Magn Reson Med 40:703–711.