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Temporal Processing in Schizophrenia: Effects of Task-Difficulty on Behavioral Discrimination and Neuronal Responses

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Introduction

Temporal processing deficits in schizophrenia have been reported since the early twentieth century and continue to interest investigators (Carroll et al., 2008; Davalos et al., 2003; Fisher, 1929; Rammsayer, 1990). Motivating this interest is the fact that temporal processing is central to many aspects of human cognition. The ability to form a time perspective helps us adapt to environmental events while also allowing us to plan for the future. Accurately judging elapsed time has been associated with relatively basic tasks such as planning and sequencing to higher order processes that are involved in driving, sports, music, or understanding cues that predict later events (Ferrandez et al. 2003; Macar, 2006; Mangels et al. 1998; Tracy et al. 1998). Navon (1978) argued that our perception of the world consists of a hierarchy of dimensions and that time occupies the highest level of that hierarchy.

The primacy of timing in human cognition has led investigators to suggest that its dysfunction may be at the root of deficits in planning and aspects of decision making that have long been observed in schizophrenia (Macar & Vidal, 2009; Volz, et al., 2001). Carroll and colleagues (2008) have suggested that timing deficits also can be conceptualized in the context of the temporal coordination of information processing. A disturbance in this process, referred to as cognitive dysmetria, may underlie many symptoms of schizophrenia, including hallucinations, delusions, and disorganized speech and behavior (Andreasen et al. 1998). As such, understanding the etiology of timing deficits in schizophrenia may provide important insights into disease pathology.

Previous studies suggest that temporal processing deficits in schizophrenia occur at multiple levels. A study evaluating pre-attentive event-related potentials (ERPs) demonstrated that timing-related responses at an “easy” level of difficulty in patients with schizophrenia did

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not differ from those in healthy comparison subjects (Davalos et al., 2005). These same evoked responses did differ, however, under more “difficult” conditions. Despite a task-difficulty-related difference in early evoked responses, behavioral judgments were impaired under both difficulty levels. The results suggest that the fidelity of timing information can be preserved at some level, possibly during initial processing, but is not appropriately processed at later stages.

Functional magnetic resonance imaging (fMRI), which provides information about the task-related responses of large populations of neurons across the brain, is well-suited to further investigate the nature of timing deficits in schizophrenia. To date, however, only one prior fMRI study has examined timing in the disorder (Volz et al. 2001). With performance level matched between groups, Volz and colleagues observed decreased prefrontal cortex and striatum timing-related responses in patients with schizophrenia, relative to comparison subjects. This finding was interpreted as evidence for deficits in both central timing mechanisms (striatum) and working memory and attention (prefrontal cortex).

The present study builds on the work of Volz and colleagues in three ways. First, we employ a task with varying levels of difficulty. Fletcher and colleagues (1999) have asserted that studies focusing on clinical populations may benefit from inclusion of a wide range of difficulty-levels to detect whether dysfunctional performance reflects a gross inability to perform a specific type of task or whether deficits are only observed on more difficult conditions (Fletcher et al. 1999). The inclusion of multiple levels of difficulty also improves our ability to interpret task-related responses. Second, the present study includes a larger cohort of patients and healthy comparison subjects. Third, greater sensitivity is afforded in the present study by the use of a 3 Tesla scanner, compared to 1.5T scanner used previously. The present study was designed to test the hypothesis that individuals with schizophrenia will exhibit impaired neuronal responses during temporal processing independently of whether there are significant differences in behavior between groups.

Experimental Materials and Methods

Subjects

Participants consisted of twenty individuals who met DSM-IV criteria for schizophrenia and twenty healthy comparison subjects matched for age (18–55 years), gender, and right-handedness. Patient diagnoses were made by two raters following interviews with the Diagnostic Instrument for Genetic Studies (DIGS). The DIGS includes the Structured Clinical Interview for DSM-IV in addition to other qualitative and quantitative assessment. Two patients were neuroleptic naive, five were treated with first-generation neuroleptics (haloperidol, prolixin, thiothixene, and fluphenazine), and thirteen with a variety of second-generation neuroleptics including olanzapine, risperidone, and ziprasidone. All patients were clinically stable with a minimum illness duration of three years. Healthy comparison subjects were recruited from the community. Subjects in the comparison group participated in a previous fMRI study of temporal processing (Tregellas et al., 2006). Exclusion criteria included a current diagnosis of major depression, substance abuse, neurological disorders, head trauma, or any personal or first-degree family history of psychosis. Four schizophrenia participants and two control participants were excluded due to excess head motion (>1 mm)

during scanning. The final group mean age was 48.4 (SD=6.8) for the schizophrenia subjects and 41.2 (SD= 9.7) for the comparison subjects. There was no significant difference in age between groups. There were seven women in the final control group and eight in the final schizophrenia group.

Subjects who smoked refrained from smoking for at least 30 min prior to the study. All volunteers provided written, informed consent approved by the University of Colorado IRB.

Task Design

The methods used in this study were similar to those described previously (Tregellas, et al., 2006). Clustered volume fMR images were obtained while subjects performed an auditory time discrimination task. The task consisted of two discrimination conditions, “easy” and “difficult”, and a baseline condition (Fig. I). Categorizations of “easy” or “difficult” were based on behavioral accuracies in a previous study (Davalos et al., 2005). In the “easy” condition, participants were presented with two tones, the first 200 ms, the second either shorter (70 ms, 100 ms) or longer (300 ms, 330 ms) than the first, separated by 500 ms. Half of the comparison tones were shorter and half were longer and all were presented in a pseudo randomized order. Participants were asked to press one of two buttons on a handheld response pad to indicate whether the second tone was longer or shorter than the first tone. In the “difficult” condition, the duration of the second tone was more similar to the standard tone, either shorter (160 ms, 170 ms) or longer (230 ms, 240 ms). Finally, in the baseline condition, both tones were 200 ms. Participants were told the tones were identical and were instructed to simply press either button after they heard the pair of tones. Use of the clustered volume approach allowed stimuli to be presented and judgments made in the absence of scanner noise. Because of the hemodynamic response delay, neuronal activity can be measured by acquiring volumes several seconds following timing processes of interest. This technique substantially improves signal detection in auditory fMRI experiments (Edmister et al., 1999). Instructions to make a judgment or simply press a button (in the baseline condition) were presented via MR-compatible goggles (Resonance Technology, Inc.). The same screen was maintained throughout the run, with a change in text color indicating when subjects were to engage in each condition. MR-compatible headphones (Resonance Technology, Inc.) were used to present tones 500 ms after each echo-planar volume was acquired. Stimuli were complex tones (75 dB SPL) composed from 5 frequencies (0.125, 0.25, 0.50, 0.75 and 1 kHz), each with a 50 ms attack and 25 ms decay. The paradigm was written and presented in E-prime (Psychology Tools, Inc.). Timing for each discrimination/baseline event included 2-s scanning, 500 ms silence, 1-s stimulus presentation and 2.5 s to judge and/or respond, totaling 6 s (Fig. I). Each of two runs contained 10 blocks (40 presentations) of each condition, “easy”, “difficult” or baseline, presented in pseudo-randomized order across the run. There was a brief (approximately 30 seconds) pause between the runs. Subjects were not informed of the “easy” versus “difficult” block distinction during the run, but were told ahead of time that task difficulty varied throughout the experiment.

MR Parameters

Studies were performed with on 3T GE MR system using a standard quadrature head coil. At the beginning of each scan, a high-resolution, T1-weighted anatomical scan was acquired. Functional images were acquired with a gradient-echo T2* Blood Oxygenation Level Dependant (BOLD) contrast technique, with TR=6000ms (as a clustered volume acquisition of 2000 ms, plus an additional 4000 ms silent interval), TE=30ms, FOV=220mm², 64² matrix, 31 slices, 4mm thick, no gap, angled parallel to the planum sphenoidale. Additionally, one IR-EPI (TI=505ms) volume was acquired from each subject to improve coregistration between the functional and anatomical images.

Data analysis

Data were analyzed using SPM2 (Wellcome Dept. of Imaging Neuroscience, London). The first four image volumes were excluded for saturation effects. Data from each subject were realigned to the first volume, normalized to the Montreal Neurological Institute template, using a gray-matter-segmented IR-EPI as an intermediate to improve registration between the functional and anatomical images, and smoothed with an 8 mm FWHM Gaussian kernel. Data were modeled with a hemodynamic response function, using the general linear model in SPM2.

A whole-brain, random effects analysis was implemented by entering parameter estimates for each individual's first level analysis (SPM contrast images) into second-level t-tests for each contrast of interest, "easy" – baseline, "difficult" – baseline, and "difficult" – "easy". Group differences were assessed for the three contrasts. To improve statistical power, results were masked with a gray-matter mask.

Based on previous temporal processing research, a priori hypotheses about specific regions of interest (ROIs) were evaluated. ROIs included the supplementary motor area (Pastor, et al., 2004), insula/opercula (Bamiou, et al., 2006), striatum (Malapani, et al., 1998), thalamus (Stevens, et al., 2007), dorsolateral prefrontal cortex (DLPFC) (Rao, et al., 2001) and cerebellar vermis (Ivry, et al., 2002). Regions were defined anatomically based on the Wake Forest University Pickatlas (Maldjian, et al., 2003). The DLPFC ROI consisted of Brodmann Areas 9 and 46 combined, excluding the superior frontal gyrus. The thalamic ROIs included the entire anatomical structure. The mean response averaged across all voxels in each ROI was determined using the Marsbar toolbox (Brett, et al., 2002). Functional results are overlaid onto the group average T1-weighted anatomical images.

Results

Behavioral Results

Behavioral data collected during scanning were evaluated to assess accuracy and reaction times. No significant differences between groups were observed in terms of mean reaction times in the easy condition (controls = 589ms, SD= 163; schizophrenia group = 673ms, SD= 195) or the difficult condition (controls = 835ms, SD= 237; schizophrenia group = 841ms, SD= 210). In terms of the baseline condition, during which participants were simply asked to press either of the two buttons following presentation of identical stimuli, mean reaction

time for the controls was 417ms (SD=204ms) compared to 524ms (SD=234ms) for the schizophrenia group ($p=.09$). The control group made significantly fewer errors than the schizophrenia group in both conditions. On the “easy” task, (based on 80 trials per participant), the control group’s mean percentage correct during easy trials was 98.89% (SD=1.48), versus 90.70% (SD=11.02) for the schizophrenia group ($t=3.13$, $df=32$, $p<.005$). For the “difficult” condition (based on 80 trials per participant), the control group (88.61%, SD=7.60) continued to perform significantly better than the schizophrenia group (75.31%, SD=13.40), $t=3.61$, $df=32$, $p<.001$.

fMRI Results

Hemodynamic responses during the temporal discrimination task in the healthy subjects were reported previously (Tregellas et al., 2006). In the current study, group differences in hemodynamic response (control >schizophrenia) were assessed for three contrasts. In the easy discrimination condition, individuals with schizophrenia showed reduced activation in the supplementary motor area (SMA), insular/opercular cortex, and dorsolateral prefrontal cortex (DLPFC) (Table I, Fig. II).

In the difficult discrimination condition, the schizophrenia group exhibited a more robust reduction in response in the SMA, insular/opercular cortex and DLPFC. In addition, reduced activation was observed in the striatum and thalamus (Fig. III). Results from the difficult–easy contrast indicate that the schizophrenia group exhibited reduced activation in the insular/opercular cortex and striatum (Fig. IV). Figure IV also shows the average percent signal change, relative the global mean, for the mean of all voxels in the insular/opercular cortex and striatum ROIs. Lastly, task related activation during the “difficult” condition compared to “easy” temporal processing condition in both healthy controls and patients with schizophrenia is presented (supplementary figure).

Two additional exploratory analyses of the difficult–easy contrast were performed to examine the possible effects of neuroleptics on results. Within the schizophrenia group, no differences were observed between the 14 neuroleptic-treated patients and the two neuroleptic-free patients, either in an ROA analysis, or a more liberal whole-brain analysis thresholded at a statistical threshold of $p < 0.01$, uncorrected. In addition, a comparison of the two unmedicated patients to healthy comparison subjects revealed insular/opercular and striatum deficits in the patients. This deficit was significant at $p < 0.01$, uncorrected, in an exploratory whole-brain analysis, and nearly significant (right insula/operculum $t=1.61$, $p=0.062$; left striatum $t=1.42$, $p=0.086$) in the more conservative ROI analysis.

To examine the possibility that activation differences between conditions were due to differences in processing time or accuracy, reaction times and response accuracies were evaluated as regressors in additional second level regression analyses. No significant results were observed, suggesting that activation differences were not related simply to differences in behavioral performance.

Discussion

The present study replicated previous findings of temporal processing deficits in schizophrenia (Carroll et al. 2008; Davalos, et al., 2002; Davalos, et al., 2003; Davalos, et al., 2005; Rammsayer, 1990; Tysk, 1990), and identified a network of brain regions that showed reduced temporal processing-related responses in patients with schizophrenia including the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), striatum, thalamus and insula/operculum. A comparison of task-related responses at different difficulty levels suggests that deficits in striatum and insula/operculum function were especially pronounced in schizophrenia under conditions of high task difficulty.

Behaviorally, patients with schizophrenia performed less accurately during both conditions. This finding is consistent with results from a previous timing study that measured both ERPs and behavioral responses (Davalos, et al., 2005). In that study, pre-attentive ERPs were found to be sensitive to task-difficulty, but temporal judgments were impaired during all difficulty levels. These data are consistent with the notion that while early temporal processing in schizophrenia can be unimpaired at low difficulty levels, later stages of temporal processing, including temporal judgment, may be impaired more broadly in the disease. Some insight into the specificity of impaired temporal judgments in schizophrenia can be informed by the fMRI results described below.

The following sections focus on specific regions of the brain implicated in temporal processing deficits in schizophrenia, and the roles that each region is thought to play in timing. The (pre)SMA was found to be underactive in schizophrenia in both conditions. The SMA has repeatedly been shown to be a key structure involved; during temporal processing (Ferrandez et al. 2003; Macar et al., 2002; Rao et al., 2001; Tregellas et al., 2006), in the 'pulse accumulation' process (Macar et al., 2004), and in attending to an internal time-line against which timing comparisons can be made (Coull et al., 2004). Although our prior study in controls found recruitment of the SMA in temporal processing to be load-dependent (Tregellas et al., 2006), a group x difficulty interaction was not observed in the present study.

Decreased timing-related responses in patients with schizophrenia also were observed in the insular/opercular cortices across conditions, with more pronounced deficits in the difficult compared to the easy condition. The insular/opercular cortex is involved in many aspects of timing, including attention to time components (Coull et al. 2000; Coull et al. 2004), encoding interval sequence information (Schubotz et al. 2000), and duration perception (Maquet et al. 1996; Ferrandez et al. 2003; Lewis and Miall 2003; Hinton et al. 2004).

The dorsolateral prefrontal cortex (DLPFC) also showed reduced activity in patients with schizophrenia in both conditions. Involvement of the DLPFC in timing has been observed across a wide range of timing tasks, from duration perception (Rao et al. 2001; Lewis and Miall 2003; Smith et al. 2003) to interval time estimation (Macar et al. 2002; Basso et al. 2003) and motor timing (Rubia et al. 1998; Jancke et al. 2000). The specific role of the DLPFC in timing, however, is not clearly understood. In timing studies which involve longer-term durations, the DLPFC may be primarily involved in working memory, i.e.

maintaining temporal information online for later comparisons. However, given that the DLPFC also is involved in paradigms which minimize working memory components (i.e. ISIs less than 500 ms used in the current study), we and others argue that reduced response in the region in schizophrenia is thought to reflect a timing-specific deficit (Smith et al. 2003; Tregellas et al., 2006).

Unlike in the DLPFC and SMA, timing-related responses in the thalamus were significantly diminished in schizophrenia only in the difficult condition, suggesting a load-dependent group difference. The thalamus previously has been identified as a key node of the fronto-striatal network that is involved in complex temporal processing tasks (e.g. motor sequencing and perceptual timing (in the range of hundreds of milliseconds) (Menon et al, 2000; Rubia & Smith, 2004). Rao and colleagues (2001) observed thalamic response during timing, but not pitch perception, and suggested a thalamic role in forming representations of time.

Finally, the striatum, specifically the putamen, was the region most impaired in schizophrenia, in terms of spatial extent of response differences. The striatum is thought to play a central role in temporal processing which has been demonstrated in studies using animal models, controls and populations with disorders affecting the striatum, such as Parkinson's disease (Maricq et al., 1981; Meck, 1996; Schubotz et al. 2000; Harrington et al., 1998; Ferrandez et al., 2003; Coull et al., 2004). Striatum involvement in temporal processing dysfunction in schizophrenia previously was observed in the one prior fMRI study of temporal processing deficits in schizophrenia (Volz et al., 2001).

As with the thalamus, timing-related responses in the striatum were reduced in the schizophrenia group only in the difficult condition, even at a substantially more liberal statistical threshold (whole brain $p < 0.05$, uncorrected). This finding suggests that relatively easy temporal judgment deficits in schizophrenia may result from dysfunction of components of the temporal processing network other than the striatum.

Inferences about striatum dysfunction observed in the present study potentially are limited by neuroleptic use in patients with schizophrenia. Because animal studies have shown that dopamine agonists and antagonists can affect temporal processing, it is possible that neuroleptics, nearly all of which act on dopaminergic systems, may alter dopamine-dependent striatum function (Meck 1986. Maricq et al., 1981). Exploratory analyses evaluating two neuroleptic-free patients in the current study argue against this possibility, however. Striatum responses in the unmediated patients were not significantly different from mediated patients, and, like the neuroleptic-treated patients, were reduced when compared to healthy controls.

Another limitation of the current study is that because behavioral differences between the two groups were observed, we cannot rule out the possibility that some aspects of the differences in neuronal responses may have been affected by poor behavioral task performance. Past studies have suggested that when clinical populations (e.g. schizophrenia) are unable to behaviorally execute tasks, patterns of brain activation may represent

compensatory mechanisms when they fail to successfully recruit brain regions necessary for cognitive tasks (Hugdahl et al., 2004).

Three conclusions can be drawn from this study. First, we conclude that individuals with schizophrenia exhibit timing deficits across easy and difficult conditions, a finding generally consistent with prior studies. Given previous work showing unimpaired early temporal processing in schizophrenia during relatively easy task difficulty, it is likely that the neuronal and behavioral deficits observed in this study involve later stages of temporal processing or duration judgment. Second, temporal processing deficits in schizophrenia involve a wide-spread network of brain regions, including the SMA, DLPFC, striatum, thalamus and insula/operculum. Lastly, response deficits in specific parts of this network, the striatum and insula/operculum, are highly load-dependent. This suggests that generalized timing deficits in schizophrenia may involve a broad network dysfunction, but that specific regions contribute to more demanding temporal judgment deficits. Future work is needed to determine the effect of neuroleptics on temporal processing deficits in schizophrenia, and whether timing deficits may be a type of cognitive dysfunction that can be ameliorated with rehabilitation and/or pharmacological therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure I.

Schematic representation of experimental design. During the “easy” condition, the 200ms standard tone was followed by a comparison tone of 70, 100 300 or 330ms (+/- 50 or 65%). During the “difficult” condition, the comparison tone was 160,170, 230 or 240ms (+/- 15, 20%). During “baseline”, subjects pressed a button, but did not judge, following presentation of two 200ms tones.

Figure II.

Temporal processing during “easy” temporal processing. Reduced activation in the schizophrenia group relative to controls was observed in the supplementary motor area (SMA), insula/opercular cortex, and the dorsolateral prefrontal cortex (DLPFC). Statistical parametric maps thresholded at $p < 0.01$, overlaid onto the average T1-weighted anatomy of all subjects.

Figure III.

Temporal processing during “difficult” temporal processing. Reduced activation in the schizophrenia group relative to controls was observed in the SMA, insula/opercular cortex, and the DLPFC, as well as the striatum and thalamus. Statistical parametric maps thresholded at $p < 0.01$, overlaid onto the average T1-weighted anatomy of all subjects.

Figure IV. “Difficult” compared to “easy” temporal processing. Reduced activation in the schizophrenia group relative to controls was observed in the insula/opercular cortex and the striatum. Statistical parametric maps thresholded at $p < 0.01$, overlaid onto the average T1-weighted anatomy of all subjects.

Table 1

MINI coordinates and statistics for brain regions with greater activation in controls compared to individuals with schizophrenia

	x	y	z	t value	P value
Easy					
Operculum/Insula (L)	-36	24	-3	1.79	0.042
Pre-SMA (R)	12	21	51	1.69	0.051
DLPFC (L)	-48	9	36	1.88	0.035
Difficult					
Operculum/Insula (R)	51	24	0	2.06	0.03
	30	24	-6	2.25	0.016
Operculum/Insula (L)	36	27	-9	2.69	0.006
Pre-SMA (R)	12	24	51	2.8	0.004
Putamen (R)	18	12	6	1.85	0.37
Putamen (L)	-24	-3	3	2.24	0.016
DLPFC (R)	45	12	18	1.95	0.03
DLPFC (L)	-45	12	36	1.77	0.043
Thalamus (R)	9	-6	6	1.93	.031
Difficult-Easy					
Operculum/Insula (R)	48	27	3	2.07	0.023
Putamen (R)	21	18	3	2.46	>0.001
Putamen (L)	-24	18	-6	1.67	0.052