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Lengthened temporal integration in schizophrenia

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ABSTRACT

Research in schizophrenia has tended to emphasize deficits in higher cognitive abilities, such as attention, memory, and executive function. Here we provide evidence for dysfunction at a more fundamental level of perceptual processing, temporal integration. On a measure of flicker fusion, patients with schizophrenia exhibited significantly lower thresholds than age and education matched healthy controls. We reasoned that this finding could result from a longer window of temporal integration or could reflect diminished repetition suppression: if every frame of the repeating stimulus were represented as novel, its perceived duration would be accordingly longer. To tease apart these non-exclusive hypotheses, we asked patients to report the number of stimuli perceived on the screen at once (numerosity) as they watched rapidly flashing stimuli that were either repeated or novel. Patients reported significantly higher numerosity than controls in all conditions, again indicating a longer window of temporal integration in schizophrenia. Further, patients showed the largest difference from controls in the repeated condition, suggesting a possible effect of weaker repetition suppression. Finally, we establish that our findings generalize to several different classes of stimuli (letters, pictures, faces, words, and pseudo-words), demonstrating a non-specific effect of a lengthened window of integration. We conclude that the visual system in schizophrenics integrates input over longer periods of time, and that repetition suppression may also be deficient. We suggest that these abnormalities in the processing of temporal information may underlie higher-level deficits in schizophrenia and account for the disturbed sense of continuity and fragmentation of events in time reported by patients.

1. Introduction

Although schizophrenia research has traditionally concentrated on high-level cognitive deficits, recent approaches have begun to emphasize dysfunction in the early stages of perceptual processing and explore the foundational role these may play in subsequent higher-level operations (Butler, Silverstein, & Dakin, 2008). A recurring theme among such studies is the inability of schizophrenics to properly coordinate events in time. Patients exhibit lengthened windows of simultaneity (Foucher, Lacambre, Pham, Giersch, & Elliott, 2007), shifted integration windows (Norton et al., 2008), higher levels of visual backward masking (Green, Nuechterlein, & Mintz, 1994; Butler, Harkavy-Friedman, Amador, & Gorman, 1996), impaired two-pulse resolution (Schwartz & Winstead, 1982), reduced sensitivity in temporal contrast detection (Slaghuis & Curran, 1999) and lowered thresholds in flicker-fusion detection (Black, Franklin, de Silva, & Wijewickrama, 1975; Slaghuis & Bishop, 2001). Downstream operations utilizing temporal information also appear to be affected. Patients show impaired motion perception (Chen et al., 1999b), deficient velocity discrimination (Chen et al., 1999c), and difficulty with smooth-pursuit eye movements (Chen et al., 1999a). The breadth and range of these results suggest that the basic temporal registration of sensory input in schizophrenia may be impaired.

To investigate basic duration perception in schizophrenia, we designed two experiments to measure temporal integration over very short time scales. The first experiment is a form of flicker fusion, requiring subjects to identify a series of digits rapidly alternated with their corresponding negative images (Stetson, Fiesta & Eagleman, 2007; Fiesta & Eagleman, 2008). If the integration window in schizophrenics is extended, as suggested by previous studies, then patients should fuse the two images at a significantly slower alternation rate than healthy control subjects. Such a result may reflect a failure to efficiently predict and compare forthcoming sensory events with present sensory input.

Because the perceived durations of repeated stimuli are briefer than those of novel stimuli (Pariyadath & Eagleman, 2008), a lower threshold in flicker fusion could reflect longer rates of

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visual persistence or an impairment in repetition suppression. To tease apart these two possibilities, we have designed a second experiment to test the repetition suppression hypothesis and to build off previous results that have shown a relationship between subjective duration and the neural phenomenon of repetition suppression (Pariyadath & Eagleman, 2008; Eagleman, 2008). Evidence for diminished repetition suppression in schizophrenia comes from studies showing impaired pre-pulse inhibition of the startle response (Hong et al., 2007; Swerdlow et al., 2006), decreased mismatch negativity amplitude (Javitt, Grochowski, Shelley, & Ritter, 1998; Light & Braff, 2005), and abnormal processing of oddball stimuli (Kiehl & Liddle, 2001). Patients appear to have difficulty with sensory gating, the initial screening and selection of relevant stimuli and the inhibition of irrelevant stimuli. We hypothesize that a lack of repetition suppression in schizophrenics could contribute to their expanded duration perception (Eagleman, 2008).

2. Method

2.1. Participants

Twenty-five patients with schizophrenia (mean age = 35 ± 9.6 years; mean education = 14 ± 1.8 years) and twenty-five age- and education-matched controls (mean age = 32 ± 9.7 years; mean education = 15 ± 3.1 years) participated in each study (Table 1). Patients were recruited from Harris Country Psychiatric Center and met DSM-IV criteria for schizophrenia. All participants had the purpose of the tests explained to them, and gave informed consent under the approval of the institutional review board of Baylor College of Medicine and the University of Texas. We excluded patients and controls with a history of traumatic brain injury, loss of consciousness, epilepsy, or any other neurological disorder. Tests with patients were undertaken as early as possible after admittance to the Psychiatric Center. All patients were receiving either Haldol or a combination of Haldol and Depakote.

2.2. Psychophysical testing

Participants were seated in a quiet room 60 cm in front of a CRT monitor (refresh rate 100 Hz). Responses were recorded using the numeric pad on a keyboard. Stimuli were generated using Matlab and the Psychophysics Toolbox (Brainard, 1997).

2.3. Measuring flicker fusion

To test for critical flicker fusion threshold (CFFT), an array of dots forming four numbers were presented horizontally in the center of the screen and rapidly alternated with the corresponding negative image (Fig. 1A and B; Stetson, Fiesta & Eagleman, 2007). When the stimuli alternate at a slow rate, the four numbers are easily reportable; however, when the rate is increased past a threshold, reporting drops to chance. The four numbers were presented for 1.5 s and were preceded by and followed by a noise mask. Participants were required to correctly identify all four of the numbers in order to pass a trial.

An adaptive staircase method was used to find the participants CFFT. The task started with an easy trial (low frequency), followed by a very challenging trial (high frequency). This was repeated until three correct answers were logged at a certain frequency. To achieve high temporal resolution using a CRT monitor, the refresh rate of the monitor was dynamically changed before each trial (Fiesta & Eagleman, 2008).

Table 1
Twenty five subjects participated from each group. WRAT = Wide Range Achievement Test, an test which quantifies ability to read words, comprehend sentences, spell, and solve math problems. PANSS = Positive and Negative Syndrome Scale, a medical scale used for measuring symptom severity in patients with schizophrenia.

Group demographics		
	Schizophrenia	Control
Sex (M/F)	19/6	13/12
Age (years)	35 ± 9.6	32 ± 9.7
Education (years)	14 ± 1.8	15 ± 3.1
WRAT	87 ± 15	81 ± 26
PANSS	83 ± 17	N/A
PANSS(positive)	17 ± 4	N/A
PANSS(negative)	25 ± 7	N/A
PANSS(global)	41 ± 9	N/A

2.4. Measuring the temporal integration window and repetition suppression with the proliferation task

On each trial, stimuli were flashed one at a time in a randomized location within 6.6° of fixation. Participants were exposed to four blocks of 30 trials each. In the 30 randomly-interleaved trials within each block, stimulus durations were 10, 20 or 30 ms (fixed within a trial), and the inter-stimulus interval was always equal to the stimulus duration; this yielded presentation frequency rates of 50, 25, and 17 Hz. To ensure that stimuli were not presented in close proximity on successive frames, each stimulus was presented in a different quadrant from the previous presentation. Perceptually, this rapidly presented stimulus does not map onto the physical reality because of visual persistence, the phenomenon that a briefly presented stimulus appears to last longer than the time it was physically presented: in general, stimuli < 100 ms in physical duration seem to last for ~100 ms (Efron, 1970; Di Lollo, 1977; Bowen, Pola, & Matin, 1973). Beyond this threshold, stimuli are perceived approximately accurately, i.e., close to their true physical duration. Because of visual persistence, each stimulus in the presentation is perceived to last longer than presented—in other words, the physically-present stimulus is accompanied by the 'ghosts' of stimuli that were presented recently. Thus more than one stimulus appears to temporally overlap on screen. We refer to the perceived multiplicity of stimuli as the proliferation effect.

We employed two conditions: in the first, the same stimulus was presented (Repeat condition); in the second, different stimuli were presented (Random condition). Trials lasted 1320 ms and ended with a mask of white noise. Participants then used a number-pad to report the number of stimuli subjectively present on screen at any one moment of time, that is, how many stimuli appeared to share screen time. This measure is their numerosity. A previous study of healthy participants showed that numerosity is significantly higher in the random condition than the repeat, indicating that novelty increases visual persistence. We collected numerosity for each trial and averaged within each block and condition (e.g., letters, Random condition) for each subject; this produced their Repeat numerosity and Random numerosity.

All participants were tested using single letter stimuli. A subset of the participants, 10 schizophrenia patients and 10 healthy controls, underwent further testing designed to measure whether the results generalized beyond letters. This subset was tested on stimuli consisting of faces, pictures, three letter words, and three letter non-words.

3. Results

3.1. Temporal eye chart

The results from the temporal eye chart task are presented in Fig. 1. Healthy controls had a mean temporal threshold of 25.8 Hz (SEM = 0.9). Schizophrenia patients had significantly lower thresholds than controls, $t_{48} = 3.33$, $p < 0.01$, and had a mean threshold of 20.6 Hz (SEM = 1.3).

3.2. Proliferation

In the proliferation task both controls, $t_{48} = 2.81$, $p < 0.01$, and subjects with schizophrenia, $t_{48} = 2.89$, $p < 0.01$ reported higher perceived numerosity in the Random than in the Repeat condition (Fig. 2). This confirms previous studies showing that because of longer rates of visual persistence, random stimuli tend to proliferate more (Pariyadath and Eagleman, 2008). The two groups differed, however, in the average number of stimuli reported. In both the Repeat and Random conditions, patients with schizophrenia perceived more stimuli to be simultaneously present on the screen than controls ($F_{1,1} = 9.9$, $p < 0.01$), consistent with the hypothesis that visual persistence is longer in schizophrenia. This effect held across all frequencies tested, Repeat ($F_{1,2} = 14.93$, $p < 0.001$), Random ($F_{1,2} = 10.36$, $p < 0.01$).

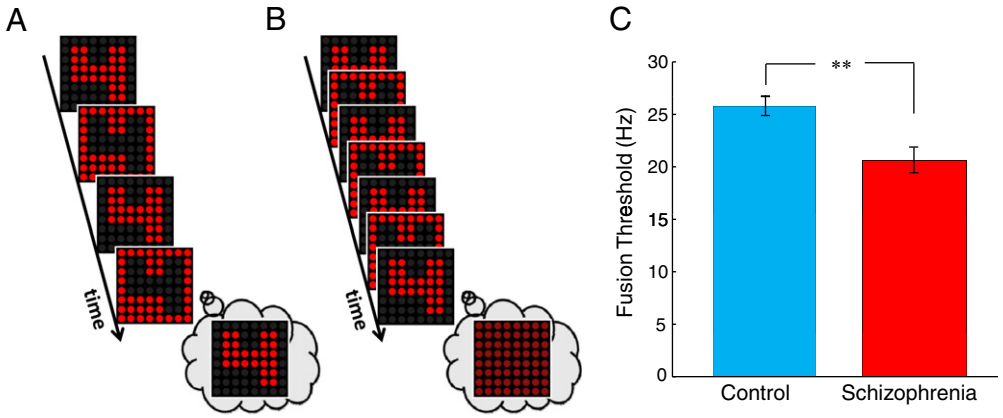

Fig. 1. Schizophrenic patients have lower critical flicker fusion thresholds (CFFT) than controls. (A) CFFT can be measured by flickering the negative image and the positive image of pixilated numbers at different frequencies (Stetson et al., 2007). At a slower flicker frequency, the number is easy to see; (B) at a faster flicker frequency, the positive and negative images appear to be fused and the number cannot be accurately reported. (C) Schizophrenia patients exhibit significantly lower thresholds than controls in the TEC task, $t_{48}=3.33$, $p<0.01$, paired t-tests. $n=25$. Error bars *SEM*.

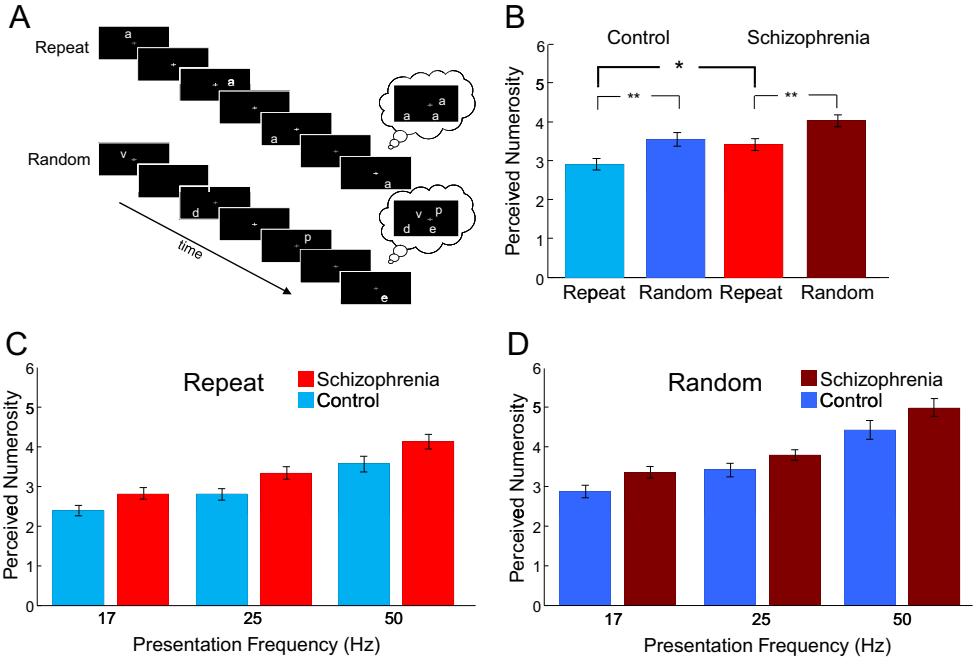

Fig. 2. Schizophrenic patients perceive decreased numerosity for repeated stimuli compared to random stimuli, higher overall numerosity, and a selective impairment in the processing of repeated stimuli. (a) Repeated stimuli have been shown to proliferate less than random stimuli (Pariyadath & Eagleman, 2008). (b) Controls ($t_{48}=2.81$, $p<0.01$) and schizophrenics ($t_{48}=2.89$, $p<0.01$) display lower perceived numerosity for repeated stimuli than random stimuli. Compared to controls, schizophrenic patients generally judge more stimuli to be simultaneously present on the screen ($F_{1,1}=9.9$, $p<0.01$). Significant group differences emerged only in the Repeat condition, $t_{48}=2.42$, $p=0.019$, implying a selective impairment in schizophrenics for the processing of repeated stimuli. (c) Overall, higher numerosity was perceived by schizophrenics across all frequencies tested, Repeat ($F_{1,2}=14.93$, $p<0.001$), Random ($F_{1,2}=10.36$, $p<0.01$). $n=25$. Error bars *SEM*.

To assess whether this group difference was driven by either the Repeat or Random condition, we compared numerosity between groups for each condition using paired t-tests with a Bonferroni correction for multiple comparisons. We found group differences only in the Repeat condition, $t_{48}=2.42$, $p=0.019$, Random $t_{48}=2.04$, $p=0.045$ suggesting that processing of *repeated* stimuli may be selectively disturbed in schizophrenia. This supports the proposal that the lengthened visual persistence is at least in part caused by problems with repetition suppression, which would lead to an exacerbated problem in the repeated case. Further studies, more sensitive to the effects of repetition suppression, are needed to confirm or disprove this hypothesis.

To ensure that our results were not specific to letters, we repeated these tests using four other classes of stimuli: faces, pictures, words, and non-words (i.e., length-matched pseudo-words). For all stimulus types, patients with schizophrenia showed significantly higher numerosity than controls in both the Repeat, $F_{1,3}=60.01$, $p<0.01$, and Random, $F_{1,3}=43.21$, $p<0.01$, conditions (Fig. 3), indicating that our findings represent a general lengthening of temporal integration in schizophrenia as opposed to a letter-specific effect.

4. Discussion

Using two measures of temporal processing, we have shown that the duration and integration of short intervals is lengthened in patients with schizophrenia. Fusion of temporally discrete events occurs at a lower threshold for alternating stimuli (Experiment 1), and this deficit extends to the visual persistence of both repeated and

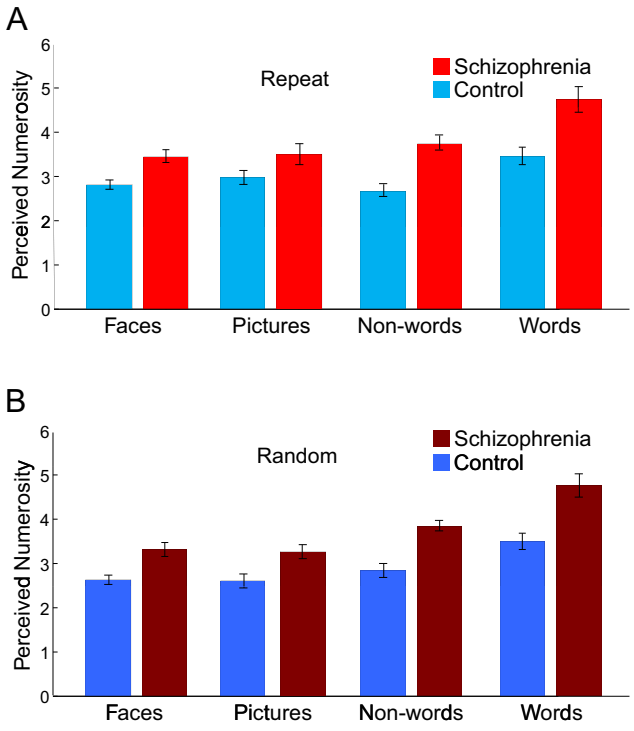

Fig. 3. Schizophrenic patients report increased numerosity under a variety of stimulus conditions. When presented with faces, pictures, scrambled words, and words patients judge more stimuli to be on the screen in both the (A) Repeat $F_{1,3}=60.01$, $p<0.01$, and (B) Random presentations, $F_{1,3}=43.21$, $p<0.01$. $n=10$. Error bars *SEM*.

random stimuli (Experiment 2). The difference between patients and controls was greatest in the Repeat condition, indicating that schizophrenics may have difficulty in the efficient encoding of predictable stimuli (i.e., repetition suppression). Although an effect of treatment cannot be ruled out, no correlation was found between participant thresholds and either the type of medication (Haldol or Depakote) or dosage administered.

We have previously proposed that the amount of neural energy required to represent a stimulus influences the subjective duration assigned to that stimulus (Eagleman, 2008; Eagleman & Pariyadath, 2009). A failure to efficiently encode sensory information would thus map directly onto a longer subjective experience of duration. To explain the present findings of longer visual persistence, we offer the following hypothesis. Diffusion tensor imaging studies in schizophrenia have repeatedly shown deficits in white matter integrity (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003), particularly in the pathways of the early visual system (Butler et al., 2006). Because the magnocellular neurons in the early visual system (those responsible for signaling transient on–off responses), are more heavily myelinated than parvocellular neurons, demyelination would preferentially affect the magnocellular pathway (Butler et al., 2007). Support for such a theory comes from studies of schizophrenia showing reduced amplitudes of event-related potentials and reduced fMRI activation for stimuli biased towards magnocellular processing (Butler et al., 2007, Martinez et al., 2008). In our study, a reduced or delayed magnocellular off-signal would lead to less inhibition of the sustained parvocellular response (Schwartz, Evans, Pena, & Winstead, 1994), and hence excessive energy expenditure. Longer visual persistence in this framework serves as an index of deficient information processing.

This inefficiency in the encoding of information within the first several hundred milliseconds of a stimulus presumably imposes a temporal bottleneck on downstream processes, and therefore would have a direct impact on temporal inferences. We suggest that several established markers of dysfunction in schizophrenia – including working memory capacity (Lee and Park, 2005) and compromised attentional control (Luck & Gold, 2008) – may derive from this basic inability to properly register temporal sensory information. Later stages of processing would be unable to construct an appropriate representation of the input stimuli leading to deficits in selecting, integrating, and interpreting information from the environment. This framework, emphasizing a difficulty in encoding event time structure, also corresponds well with phenomenological reports of schizophrenia which stress an impaired sense of temporal continuity (Uhlhaas & Mishara, 2007; Freedman, 1974).

The encoding efficiency hypothesis (Eagleman & Pariyadath, 2009) accounts for the results presented here, as well as with a wide range of studies examining temporal processing dysfunction in schizophrenia. For instance, patients overestimate time intervals not only for the short durations investigated in the present study, but also for intervals ranging from several seconds to one minute (Densen, 1977; Tysk, 1983, 1990; Wahl & Sieg, 1980; Davalos, Kisley, Polk, & Ross, 2003). Such duration overestimation has traditionally been explained in terms of a high-level cognitive process involving an internal clock which tracks the informational content of the stimulus (Treisman, 1963; Gibbon et al. 1984). Increases in perceived duration in such high-level models are often attributed to increases in attention (Zakay & Block, 1997; Tse, Intriligator, Rivest, & Cavanagh, 2004). Our hypothesis instead stresses a deficit in cortical inhibition, early in sensory processing that leads to excessive energy expenditure. Future studies might profitably compare distorted duration judgments in schizophrenic patients with their simultaneously recorded neural responses to determine precisely where and how these temporal impairments arise.

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