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ABSTRACT
Timing disorders in schizophrenia are a well-known phenomenon. However, no studies have yet assessed the role of temporal distortions in early-onset schizophrenia (EOS), despite evidence that distorted time perception may share genetic risk factors with schizophrenia and may be a useful indicator in identifying individuals at risk for schizophrenia. In the present study, we investigated the ability of 10 patients with EOS (mean age = 21.5 years, *SD* = 6) matched with 20 healthy control participants (mean age = 25.3 years, *SD* = 4.6) in order to compare the durations of two visual events, presented either sequentially or overlapping in time, along with neuropsychological assessments of attention, working memory, and executive functions. Each participant had to judge a total of 336 stimuli. We found that temporal overlap had a greater negative effect on ability to judge the duration of a pair of stimuli in EOS patients than in healthy control participants. In addition, EOS patients showed impairments in attention and executive functions. Furthermore, in EOS patients, the scores for executive and attentional functions were significantly correlated with accuracy of temporal estimation in the overlap condition ($r = 0.31$, $p < 0.05$ and $r = 0.57$, $p < 0.05$, respectively). These preliminary results suggest that impairments in neuropsychological functions participate in the deficit in time estimation observed in patients with EOS. These conclusions highlight the importance of testing time perception in patients with EOS and could contribute to the development of cognitive remediation-based therapy for these patients.

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Early-onset schizophrenia; time perception; attention; executive functions; temporal overlap

Introduction

Schizophrenia is a severe, devastating, and common psychiatric disorder (approximately 1% of general population; Van Os, Driessen, Gunther, & Delespaul, 2000). Early-onset schizophrenia (EOS) is defined as schizophrenia with an onset before the age of 18 years. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) criteria for EOS are the same as for adult-onset schizophrenia (American Psychiatric Association [APA], 2000). Interestingly, compared to cases with adult onset, the process of EOS has a greater impact on cognition and brain-anatomical markers. Furthermore, previous studies with EOS patients have reported significant deficits in several specific cognitive functions, including mental flexibility and working memory (Jepsen et al., 2010). Due to their severe impairments, EOS patients may present a particular interest in relation to the developmental process of schizophrenia.

Although distorted time perception may share genetic risk factors with schizophrenia and be a useful indicator in identifying individuals at risk for schizophrenia, to our knowledge, no previous study has assessed the role of temporal distortions in EOS. However, recent reviews of the literature on the neural bases of timing reveal a remarkable overlap with the circuits and brain structures that are affected in schizophrenia (Gómez, Atakan, & Ortuño, 2014; Ortuño, Guillén-Grima, López-Garcia, Gómez, & Pla, 2011; Ward, Kellendonk, Kandel, & Balsam, 2012).

In recent years, the interest in research on time perception in schizophrenia, which was also previously studied in the early 20th century, has increased for two main reasons: (1) Various models of schizophrenia pathogenesis integrate time perception as a key process. Some authors suggest that schizophrenia is associated with an excessive temporal integration of events, possibly leading to delusion (Franck, Posoda, & Pichon, & Haggard, 2005). Early authors mentioned also a disturbance in time perception, somehow involved in the functioning of psychosis (Andreasen, 1999). The "cognitive dysmetria model" of Andreasen suggests that schizophrenia is associated with a major failure of a supra-chronometric system, reflected in timing tasks and in both psychiatric and cognitive symptoms; (2) dysfunctions of time perception may be involved in the daily living difficulties experienced by these patients. Some authors (Davalos, Kisley, & Ross, 2003) have argued that timing dysfunctions affecting motor sequencing or temporal event planning processes may account for daily life functioning impairment rather than executive dysfunction.

Human time perception processes are very complex and have long been the subject of diverse theories, from philosophy to cognitive sciences. The major breakthrough in recent years is the

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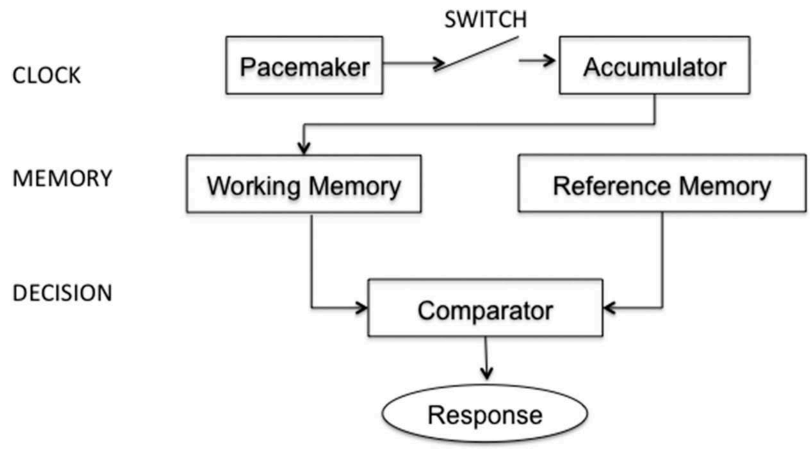

Figure 1. Model of time perception based on Church and Gibbon (1990).

availability of a relatively consensual model of time perception. In the present study, we have chosen to rely on Gibbon and Church's (1990) well-known scalar expectancy theory of time (see Figure 1), which is currently widely accepted (for a review, see Grondin, 2010). This theory postulates the existence of a cognitive temporal processor which stocks subjective time units, mainly depending on the allocation of attentional resources. According to this model, time perception involves two successive steps. The first step, the storage of the temporal pulse in an accumulator, is a time-specific process. The second step leads to a decision through a comparison between the pulse level estimated from working memory and samples of previous time durations from the reference memory.

Clinical and experimental data suggest strongly that time estimation of patients with schizophrenia is less accurate than that of healthy subjects. Memory impairments in schizophrenia are well known, in both working and episodic memory, and attention deficits are also well documented (Forbes & Lawrie, 2009; Ranganath, Minzenberg, & Ragland, 2008). Some authors (Elvevåg, Brown, Weinberger, & Goldberg, 2003) found that patients with schizophrenia were less accurate than healthy controls at recognizing a standard duration on a temporal generalization task. Furthermore, patients' performance differed significantly from that of controls on a temporal bisection task, in which participants categorized durations as either short or long. They concluded that patients with schizophrenia were less accurate at estimating brief time periods, and that this deficit may reflect the dysfunction of biopsychological timing processes.

Other researchers (Lee et al., 2009) investigated time perception dysfunction and its neuropsychological correlates in patients with schizophrenia. In their study, 38 patients and 38 age- and sex-matched healthy volunteers were compared in an auditory temporal bisection paradigm using two interval ranges (a 400/800 ms condition and a 1000/2000 ms condition). They found that in patients, short-term memory performance was negatively associated with duration judgment in both conditions, whereas executive dysfunction was correlated with a general performance deficit in the 400/800 ms condition. They concluded that time perception abnormalities in schizophrenia might be a part of neuropsychological dysfunction (in particular with short-term and working memory). Other recent studies have tried to address the question of whether time misperception is a single or a more generalized disorder using brief visual or auditory stimuli in the range of milliseconds (50–100 ms), which puts minimal demands on non-temporal processes. Researchers have used discrimination tasks and shown that the timing judgment of patients with schizophrenia was less accurate than those of healthy participants (Carroll, Boggs, & O'Donnell et al., 2008, 2009; Elvevag, Egan, & Goldberg, 2000).

However, whereas both clinical observations and experimental data show that time perception is impaired in patients with schizophrenia, the underlying mechanisms remain to be ascertained. Do deficits in cognitive processes, such as working memory and sustained attention, lead to the behavioral expression of impaired interval timing in schizophrenia? Or, conversely, does deficient temporal information processing contribute to a wide range of symptoms associated with schizophrenia? Distortions in the perception of temporal intervals could lead to failure to perceive correctly the temporal sequence of contiguous events. If timing dysfunction and schizophrenic symptoms are causally related, then a correlation might be expected between severity of cognitive symptoms and severity of timing impairment. These questions are of particular interest as time perception impairment might be a key deficit in schizophrenia, deteriorating the perception of environment and relationships in patients. There is a need for a better understanding of the relationship between cognitive deficits and impaired time perception in EOS.

The objective of the present study was to examine and understand better the relationships between time estimation and cognitive functioning in EOS patients. We hypothesized that when two events partially overlap in time, performance of patients with EOS should be impaired and that could be related to an incapacity to divide their attention on two stimuli. Regarding the literature on time perception, we could argue that if performance in the overlap condition is impaired, it would be consistent with the single-clock model to estimate the duration of two intervals (i.e., the estimation of one interval depend on the estimation of the other; Gibbon & Church, 1990). Furthermore, these results would be consistent with the idea of one single-clock model with a crucial role of attentional mechanisms. When two events partially overlap in time, we must divide our attention to preserve the time estimation of the first stimulus and to estimate the duration of the second event.

The aim of our study is also to highlight the fact that temporal processes are disturbed even at early stages of the disorder, suggesting that they might offer a useful cue to evaluate cognitive impairments in patients with EOS.

Methods

Study participants

The study was conducted on 10 stabilized outpatients with EOS (mean age = 21.5 years, *SD* = 6; age range = 9–24 years; 7 males, 3 females) recruited from French child and adolescent psychiatry day hospitals. They were diagnosed according to the DSM-IV-TR criteria and symptoms were assessed using the Positive and Negative Syndrome Scale (Kay, Opler, & Lindenmayer, 1989). At the time of testing, eight individuals with schizophrenia were taking atypical antipsychotic medications; information was not available on medication for the other two patients. The mean age at onset of schizophrenia was 15.3 ± 4 years and the mean age at the time of the study was 21.5 ± 6 years and the mean illness duration was 7.5 ± 3.3 years. Patients with schizophrenia were matched with 20 healthy control participants (mean age = 25.3 years, *SD* = 4.6) on sex and level of education (level of education was obtained by counting the number of years of school education; see Table 1). They were no difference between our two groups for age ($t(28) = -1.93$, $p = 0.06$, NS[not significant]) and for level of education ($t(28) = 1.13$, $p = 0.21$, NS). Exclusion criteria for control participants included history of psychiatric disorders, learning disability, intellectual disability, chronic somatic or head injuries, neurological disease, and abuse of psychoactive substances.

Table 1. Demographic, clinical, and neuropsychological data on the participants (patients with schizophrenia and control participants).

	Patients	Controls
Gender (M/F)	7/3	14/6
Age (mean/*SD*)	21.5 ± 6	25.3 ± 4.64
Level of education (mean/*SD*) in years	15 ± 8	18 ± 6
Medication (typical/atypical/unknown)	0/8/2	
PANSS positive symptoms* (mean ± *SD*)	21.43 ± 4.69	
PANSS negative symptoms* mean ± *SD*)	22.29 ± 5.22	
PANSS general symptoms* (mean ± *SD*)	39 ± 5.51	
Age at onset (mean ± *SD*)	15.3 ± 4.22	
Attention		
TEAch	<5	50–75
d2	25–50	50–75
Executive functions		
Trail Making Test A	10	75–90
Trail Making Test B	<5	50–75
Stroop	<5	50
Verbal Working Memory (span)		
Verbal span	6	7
Inverse span	4	4

At the time of testing, eight individuals with schizophrenia were taking atypical antipsychotic medications; information was not available on medication for the other two patients. The mean age at onset of schizophrenia was 15.3 ± 4 years and the mean age at the time of the study was 21.5 ± 6 years. Performance for attention and executive functions are expressed by a percentile that is a measure indicating the value below which a given percentage of observations in a normative group of observations fall. For example, the 20th percentile is the value (or score) below which 20% of observations are found in a normative sample. A percentile equal or below 5 is considered as pathological. For Verbal Working Memory, we used the span score; normal spans are considered equal to 7 ± 2.

*PANSS, Positive and Negative Syndrome Scale.

All patients and control participants had normal or corrected-to-normal visual acuity. The experimental protocol used in the present study conformed to standards and ethics of the Helsinki Declaration (World Medical Association, 2008). The protocol was approved by the ethics committee and written informed consent was obtained from parents for patients under age 18 and from patients over age 18.

Neuropsychological evaluation

The neuropsychological evaluation of each patient revealed no language disorders and no signs of apraxia or agnosia. The neuropsychological test battery included measures of different aspects of attention, executive functions, and verbal working memory (see Table 1). Attention was evaluated with the Test of Everyday Attention for Children (TEACh; Manly, Anderson, Nimmo-Smith Turner, Watson, & Robertson, 2001) for patients under 16 years and with the d2 Test of Attention (Bates & Lemay, 2004) for patients over 16 years. The Trail Making Test A and B was used to assess mental flexibility and the Stroop test to assess inhibitory processes (Lezak, 1995). In addition, verbal span and verbal working memory were assessed with the Verbal Working Memory subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 2000). In order to reduce the number of statistical comparisons and avoid redundancy, selected core test outcome measures were combined into composite cognitive domains according to their putative content, combining test scores reflecting the same functional domain (Kumra et al., 2000). We created three composite domains: attention, working memory, and executive functions (including flexibility and inhibitory processes).

Apparatus

All experiments were conducted on a 13-inch MacBook computer. The monitor was set at a resolution of 1024 × 768 pixels and ran at a refresh rate of 60 Hz. The experimental stimuli were created with Matlab R2007a (Mathworks, Sherborn, MA, USA) and displayed with the PsychToolbox (V1.05; Brainard, 1997; Pelli, 1997).

Stimuli and procedure

All stimuli consisted of two discs, one blue and one red (represented respectively by a filled disc and by an open disc in Figure 2), displayed on a uniform white background (luminance: 40 cd/m^2). Each disc had a diameter of 1.0°of visual angle. The first disc could appear anywhere on a virtual circle centered on the central fixation point (radius = 2.6°of visual angle), and the second disc was always presented at the diametrically opposite position. The presentation of the stimuli was parafoveal. One of the discs, called the standard, always lasted one second, whereas the other, called the test, was presented for one of the set of possible durations. The method of constant stimuli was used to manipulate the duration ratio

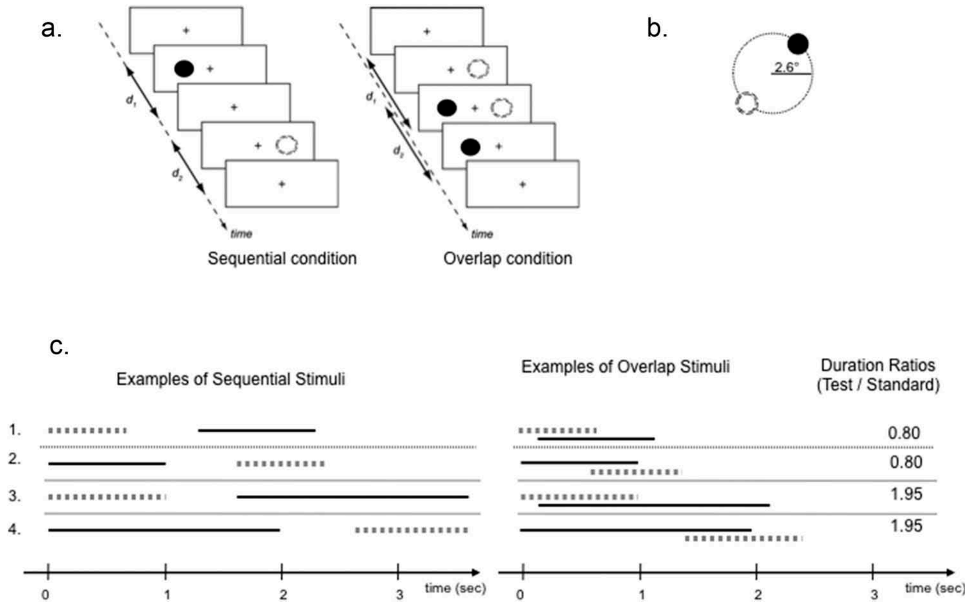

Figure 2. Experimental temporal conditions. (A) Illustration of the two conditions, on the left when stimuli are presented sequentially, and on the right when they overlap. In each condition, the two discs (represented here either by a filled disc or an open disc) were shown diametrically opposed (here left and right, although any other position was possible). (B) An example of the different positions of the two discs; the first disc could appear anywhere on a virtual circle centered on the central fixation (radius = 2.6° of visual angle), while the second disc was always diametrically opposed (here the first disc is randomly placed at 1 o'clock, thus imposing the placement of the second disc at 7 o'clock). (C) Examples of both temporal conditions, on the left when stimuli are presented sequentially, on the right when they overlap in time. One disc was always presented for one second (the standard) and the other (the test) was presented for a variable duration, a ratio of between 0.3 and 3.0, respectively in milliseconds: 0.3299, 0.5141, 0.8011, 1.2483, 1.9453, and 3.0314. The continuous line represents the duration of one disc and the two dashed lines represent the duration of the other disc. In the sequential condition, the second disc follows the first after half a second. In examples (2) and (3), the standard is presented before the test. In examples (1) and (2), the duration ratio is 0.80 and in examples (3) and (4) the duration ratio is 1.95.

between standard and test. Six duration ratios were chosen, equally spaced on a log scale between 0.3 and 3.0 (the ratio 1.0 was avoided because it is ambiguous). Two temporal conditions were contrasted: In the *sequential condition*, one stimulus was presented after the other one, whereas in the *overlap condition*, the two stimuli overlapped in time. In the sequential condition, the gap between the first and second discs was 500 ms. In the overlap condition, the first disc disappeared halfway through the duration of the second disc (see Figure 2).

The experiment took place in the experimenter's office and lasted for approximately 30 min. The same experimenter was present for all participants. The display was viewed from a distance of approximately 57 cm, although participants were free to move their head. A trial began with the presentation of a small fixation cross for 500 ms at the center of the display area. The stimulus (the two discs) was then presented binocularly (the fixation cross was always present), followed by a blank screen until the participant responded by pressing a key. The next trial followed immediately. Participants were asked to compare the duration of the two discs by answering the question: "Was the red disc presented for longer than the blue one?" To answer YES, they had to press the space bar, and to answer NO, they had to refrain from pressing the space bar (go/no-go task). A training set was presented before the session, and no feedback was provided. For each participant, we collected the proportion of times the red disc was reported to have lasted longer than the blue one, and then converted this into the proportion of times the first disc was reported to have lasted longer than the second one.

A session was composed of 48 stimuli presented in a random order (two colors: blue and red) × two order conditions (the standard before the test or the reverse) × two temporal conditions (sequential or overlap) × six duration ratios. Participants ran seven sessions, thereby judging 336 pairs of stimuli altogether. After each session, they could take a break for as long as they wished. Throughout the data collection process, the experimenter sat on the opposite side of the computer monitor, at a location where the experimenter could monitor the participant's gaze direction. Before initiating each block, the experimenter ensured that the participant's gaze was directed close to the center of the screen.

Statistical analysis

For each observer and each temporal condition, we computed the proportion of times the first disc was perceived to be longer than the second as a function of the duration ratio between the two discs. These proportions were fit with a psychometric function (cumulative Gaussian) after taking the logarithm of the duration ratios. The fits provided two parameters: the bias (corresponding to the duration ratio that led to chance performance) and the slope (the rate at which proportion of "longer" judgments increased with increasing duration ratio) which corresponds to the participant's sensitivity in discriminating the durations of the two stimuli: the steeper the slope, the better the discrimination. Similarly, and perhaps more intuitively, sensitivity can also be characterized by a threshold measure that represents how different the durations of the two stimuli had to be in order for the participant to discriminate them better than chance: the smaller the threshold, the greater the sensitivity. Here, we report thresholds to reach 75% discrimination performance, and compute this from the psychometric fit as the difference in duration ratio between the 75% and 50% points.

Finally, the relationships between neuropsychological scores and time estimation in the overlap condition were explored using Pearson correlations.

Results

The results presented in Figures 3(a,b) represent the psychometric functions for the two temporal conditions (for control participants in Figure 3(a) and for patients in Figure 3(b)).

All healthy participants overestimated systematically the duration of the second event in all temporal conditions, and therefore displayed a negative time-order error (TOE[1]). The overestimation bias reached 1.14 ± 0.16 in the sequential condition and 1.29 ± 0.25 in the overlap condition; these biases are both significantly different from 1.0 ($F(1,18) = 3.55$, $p < 0.01$). Furthermore, the TOEs for the two temporal conditions were significantly different from each other, with a larger bias in the overlap condition ($t(38) = 4.18$, $p < 0.05$). Early-onset patients with schizophrenia also overestimated systematically the duration of the second event in all temporal conditions. Their overestimation bias was 1.10 ± 0.12 in the sequential condition and 1.19 ± 0.31 in the overlap condition; these biases are both significantly different from 1.0 ($F(1,8) = 2.65$, $p < 0.05$).

A comparison of sequential and overlap conditions for each healthy participant (open circles) and patients with schizophrenia (filled circles) revealed that thresholds were systematically higher in the overlap condition than in the sequential condition, especially for EOS patients (see Figure 3(c)). In other words, the majority of participants were worse at discriminating the duration of two stimuli when these stimuli overlapped in time. The mean duration ratio threshold in the sequential condition was 1.32 for control participants and 1.55 for patients with schizophrenia ($t(18) = 2.18$, $p = 0.05$)); in the overlap condition, these thresholds rose to 1.53 and 1.78 for controls and patients with schizophrenia, respectively ($t(18) = 3.13$, $p = 0.01$)). One EOS patient has a notably high overlap threshold but when we remove his performance from our patients group, there is still a group effect for the overlap condition ($t(17) = 2.14$, $p = 0.05$)).

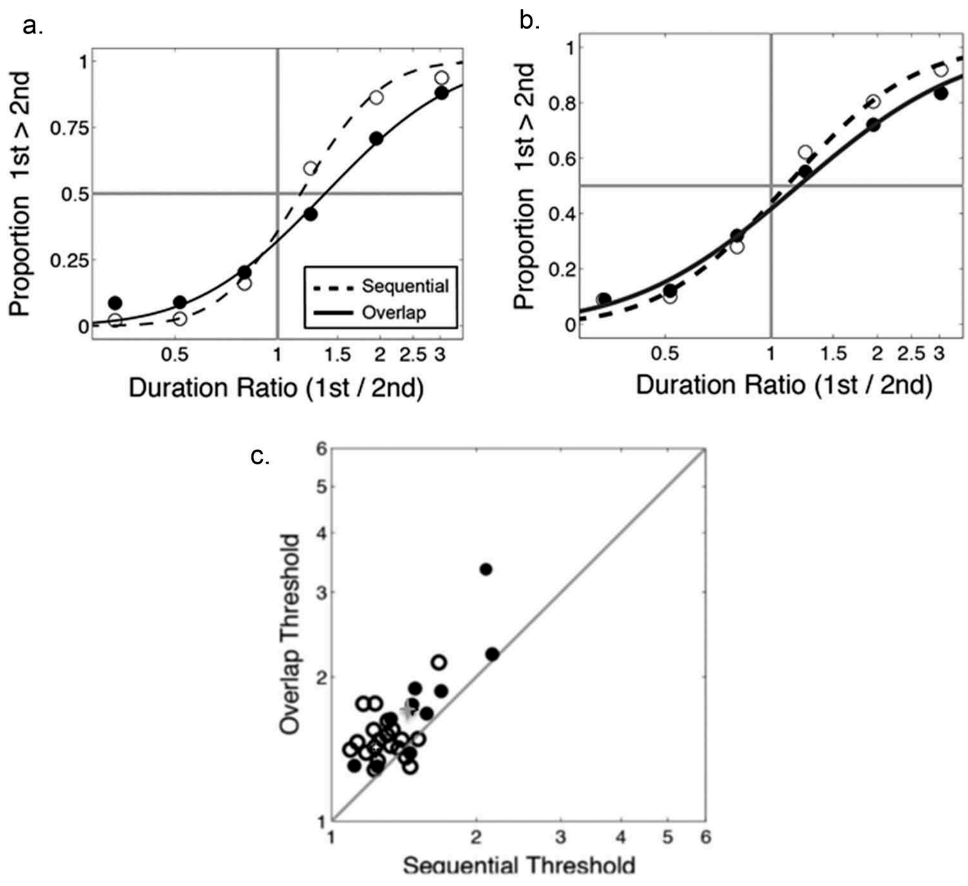

Figure 3. Results for healthy participants (A) and patients with schizophrenia (B). (A and B) The proportion of times the first disc was perceived to last longer than the second disc is shown as a function of the duration ratio (first disc duration divided by second). On the psychometric functions, the continuous line represents the overlap condition and the dashed line represents the sequential condition. Data were pooled across all healthy participants (N = 20) and across all patients with schizophrenia (N = 10). (C). Thresholds for the overlap condition are plotted against those for the sequential condition. Each circle represents one participant, healthy participants as open circles and patients with schizophrenia as filled circles. The white cross represents the threshold mean for the overlap/sequential conditions for healthy participants, and the gray cross for the patients with schizophrenia. The bias of each psychometric function is represented by the point of subjective equality (PSE). The PSE represents the duration ratio at which the duration of a test disc was perceived as equal to the duration of the standard disc (always 1s).

Table 2. Pearson correlations for patients with schizophrenia between neuropsychological scores (attention, executive functions, and verbal working memory) and temporal estimation in the overlap condition.

	Attention	Executive functions	Verbal working memory	Temporal estimates (overlap condition)
Attention	1	0.67*	0.51*	0.57*
Executive functions	–	1	0.23	0.31*
Verbal working memory	–	–	1	0.11
Temporal estimates (overlap condition)	–	–	–	1

*$p < 0.05$.

Finally, we investigated the relationship between time estimation and cognitive functioning of EOS patients (see Table 2). In EOS patients, the scores for executive and attentional functions were significantly correlated with temporal estimation in the overlap condition ($r = 0.31$, $p < 0.05$ and $r = 0.57$, $p < 0.05$, respectively). Thus, the more patients were impaired in executive and attentional tasks, the more difficulty they had estimating the relative duration of two stimuli that overlapped in time. Interestingly, no correlation was found between working memory performance and time estimation ($r = 0.11$, $p > 0.05$).

Discussion

Our preliminary main results are that EOS patients experienced significantly more difficulties than healthy controls when judging the duration of two visual events that overlapped in time, and this difficulty is significantly correlated with impairments in attentional and executive functions.

Furthermore, some differences between the first trials and the last ones for both groups (i.e., for the last items, participants - both controls and EOS patients - performed worse, being more variable in their response), but this difference between first trials and last trials was the same for both groups of participants. So we can consider that this does not explain the global difference in performance in the overlap condition between the two groups. These findings are consistent with the results of a previous study conducted by our team on non-schizophrenic brain-damaged patients (de Montalembert & Mamassian, 2010). Our results were fairly consistent with the idea of one single-clock model with a crucial role of attentional mechanisms. When two events partially overlap in time, we must divide our attention to preserve the time estimation of the first stimulus and to estimate the duration of the second event. For brain-damaged patients with hemineglect (i.e., a deficient response to stimuli presented to the side contra-lateral to the affected brain hemisphere; Heilman, Watson, & Valenstein, 2003), this capacity to divide attention is impaired when it is first oriented to the ipsilateral side. Attentional mechanisms are divided to feed the clock, not the reverse; when events overlap in time, attention can be divided rather than shifts from one event to the other, it is clearly not a fixed or rigid mechanism.

These results are of particular interest with regard to the mechanism underlying impaired time perception in patients with schizophrenia. Thus, our results raise the issue of involvement of attentional processes in time estimation. Concerning schizophrenia, the main point is to clarify whether temporal discrimination deficits reflect pure temporal perception dysfunction as opposed to reflecting schizophrenia-related neuropsychological dysfunctions. Some authors have suggested that impaired time perception in patients with schizophrenia is secondary to thought disorders and primary cognitive impairments (Carroll, O'Donnell, & Shekhar et al., 2009). The strong correlations observed in the present study between time estimation and attentional or executive cognitive resources are in line with previous studies conducted on healthy individuals exposed to a dual-task paradigm showing that increasing demands on attentional resources decrease the accuracy of time estimation. These previous studies suggested that the time processor requires attentional resources to perform accurately (Carrasco, 2011; Coull, Frith, & Büchel et al., 2000). Patients with schizophrenia seem to perform poorly on time estimation tasks partially because of non-time-related impairments. When two events partially overlap in time, we must divide our attention to continue with time estimation of the first stimulus while also estimating duration of the second event. In patients with schizophrenia, this capacity to divide attention appeared to be impaired. Our results on both healthy participants and EOS patients highlight the importance of attentional mechanisms for timing judgments and about the potential neural and cerebral substrates of these mechanisms. Convergent findings from brain imaging and neuropsychological studies have suggested that there is a partial overlap of cortical and subcortical regions engaged in time perception tasks with regions engaged in tasks requiring increased cognitive effort. Specifically, Alustiza et al. (2016) found a pattern of frontoparietal and basal ganglia activation common to timing and increased cognitive effort. In schizophrenia patients, they observed that the involvement of most of these overlapping cortical and subcortical areas, primarily in the right hemisphere, was reduced in comparison to that in healthy controls.

Our study also highlights the fact that temporal processes are disturbed even at early stages of the disorder, suggesting that they might offer a useful cue to evaluate cognitive impairments in patients with EOS. These results are in accordance with Rao findings of an early cortical failure (resulting from a dysfunction of the supplementary motor area) related to attention disturbances leading to temporal processing deficits in schizophrenia (Rao, Mayer, & Harrington, 2001). Considering the wide overlapping between neural networks involved in high-level cognitive functions (such as attentional processes) and temporal processing, timing performance could be a sensitive measure of cognitive functioning and a reliable indicator of impairment to the underlying neural substrate. Temporal processing could be thinking as a "cognitive primitive," a fundamental neuropsychological process that has a broad influence on cognition – and as a reflect of "something wrong" even if neuropsychological pencil tasks are preserved in EOS patients (Alustiza et al., 2016; Foster et al., 2013; Piras et al., 2014; Radua, del Pozo, Gómez, Guillen-Grima, & Ortuño, 2014).

We did not find any correlations between working memory processes and time estimation. This last result is not consistent with the results of previous studies (Roy, Grondin, & Roy, 2012), suggesting that time perception disturbances in schizophrenia may result from working memory impairments. One explanation for these discrepant results could be related to a difference in the severity of symptoms in the two samples of patients. Another possibility might be due to the task itself: in Roy's experiment, participants had to reproduce time intervals, whereas in our experiment, their task was to estimate the duration of temporal events.

Concerning study limitations, our study was hampered by the small sample size, which increases the risk of Type II errors. However, there was little variability in terms of cognitive deficits in our group and their medication profile was similar (i.e., atypical antipsychotic medication). To better account for the role of symptom severity and/or symptom type in temporal performance, it will be important for future studies to include more individuals at different phases of schizophrenia and with different symptom profiles.

Conclusions

A large literature, from clinical cases to experimental studies, has shown that patients diagnosed with schizophrenia display cognitive deficits and timing impairments (e.g., Alústiza et al., 2016). Interestingly, individuals at risk of developing schizophrenia (usually relatives) have also been reported to show interval timing deficits. A previous study (Penney, Meck, Roberts, Gibbon, & Erlenmeyer-Kimling, 2005) compared time perception in offspring of parents diagnosed with schizophrenia to offspring of parents diagnosed with major affective disorder and to healthy controls, and found greater variability in time estimation only in offspring of parents who had been diagnosed with schizophrenia. Thus, distorted time perception may share genetic risk factors with schizophrenia and could be a useful indicator in identifying individuals at risk for schizophrenia. Despite the increased research on time perception, there are still critical questions that need to be addressed, particularly in the field of psychiatric disorders. Understanding the processes underlying this neglected phenomenon could help to develop cognitive remediation-based therapy, which opens a promising field for patients with schizophrenia (Harvey & Bowie, 2012).

Note

1. A bias toward perceiving the first or the second object as temporally longer is referred to in the literature as "time-order error" (TOE; Hellström, 1985). The TOE is positive when it corresponds to an overestimation of the first stimulus relative to the second, and negative in the opposite case. In our experiment, the TOE would be negative if the bias is larger than 1; for instance, a bias of 1.3 means that the duration of the second stimulus is overestimated by 30%.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

Alústiza, I., Radua, J., Albajes-Eizagirre, A., Domínguez, M., Aubá, E., & Ortuño, F. (2016). Meta-analysis of functional neuroimaging and cognitive control studies in schizophrenia: Preliminary elucidation of a core dysfunctional timing network. *Frontiers in Psychology*, *7*. doi:10.3389/fpsyg.2016.00192

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author. *DSM-IV-TR*.

Andreasen, N. C. (1999). A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Archives of General Psychiatry*, *56*, 781–787. doi:10.1001/archpsyc.56.9.781

Bates, M. E., & Lemay, E. P. (2004). The d2 test of attention: Construct validity and extensions in scoring techniques. *Journal of the International Neuropsychological Society*, *10*, 392–400. doi:10.1017/S135561770410307X

Brainard, D. H. (1997). The psychophysics toolbox. *Spatial Vision*, *10*, 433–436. doi:10.1163/156856897X00357

Carrasco, M. (2011). Visual attention: The past 25 years. *Vision Research*, *51*, 1484–1525. doi:10.1016/j.visres.2011.04.012

Carroll, C. A., Shekhar, A., & Hetrick, W P. (2008). Temporal processing dysfunction in schizophrenia. *Brain and Cognition*, *67*, 150–161. doi:10.1016/j.bandc.2007.12.005

Carroll, C. A., O'Donnell, B.F., Shekhar, A., & Hetrick, W P. (2009). Timing dysfunctions in schizophrenia span from millisecond to several-second durations. *Brain and Cognition*, *70*, 181–190. doi:10.1016/j.bandc.2009.02.001

Coull, J. T., & Nobre, A.C. (2000). Orienting attention in time: Behavioral and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia*, *38*, 808–819. doi:10.1016/j.bandc.2009.02.001

Davalos, D. B., Kisley, M. A., & Ross, R. G. (2003). Effects of interval duration on temporal processing in schizophrenia. *Brain and Cognition*, *52*, 295–301. doi:10.1016/S0278-2626(03)00157-X

de Montalembert, M., & Mamassian, P. (2010). Processing temporal events simultaneously in healthy human adults and in hemi-neglect patients. *Neuropsychologia*, *50*, 791–799. doi:10.1016/j.neuropsychologia.2012.01.013

Elvevag B., Egan, M. F., & Goldberg, T. E. (2000). Memory for temporal order in patients with schizophrenia. *Schizophrenia Research*, *46*, 187–193. doi:10.1016/S0920-9964(00)00014-1

Elvevåg, B., Brown, G. D. A., Weinberger, D R., & Goldberg, T E. (2003). Duration judgments in patients with schizophrenia. *Psychological Medicine*, *33*, 1249–1261. doi:10.1017/S0033291703008122

Forbes, N. F., & Lawrie, S M. (2009). Working memory in schizophrenia: A meta-analysis. *Psychological Medicine*, *39*, 889–905. doi:10.1017/S0033291708004558

Foster, S. M., Kisley, M. A., Davis, H. P., Diede, N. T., Campbell, A. M., & Davalos, D. B. (2013). Cognitive function predicts neural activity associated with pre-attentive temporal processing. *Neuropsychologia*, *51*, 211–219. doi:10.1016/j.neuropsychologia.2012.09.017

Franck, N., Posada, A., Pichon, S., & Haggard, P. (2005). Altered subjective time of events in schizophrenia. *The Journal of Nervous and Mental Disease*, *193*, 350–353. doi:10.1097/01.nmd.0000161699.76032.09

Gibbon, J., & Church, R. M. (1990). Representation of time. *Cognition*, *37*, 23–54. doi:10.1016/0010-0277(90)90017-E

Gómez, J., Atakan, Z., & Ortuño, F. (2014). Time perception networks and cognition in schizophrenia: A review and a proposal. *Psychiatry Research*, *220*, 737–744. doi:10.1016/j.psychres.2014.07.048

Grondin, S. (2010). Timing and time perception: A review of recent behavioral and neuroscience findings and theoretical directions. *Attention, Perception and Psychophysics*, *72*, 561–582. doi:10.3758/APP.72.3.561

Harvey, P. D., & Bowie, C. R. (2012). Cognitive enhancement in schizophrenia: Pharmacological and cognitive remediation approaches. *The Psychiatric Clinics of North America.*, *35*, 683–698. doi:10.1016/j.psc.2012.06.008

Heilman, K. M., Watson, R. T., & Valenstein, E. (2003). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical neuropsychology* (4th ed., pp. 296–346). New York: Oxford University Press.

Hellström, A. (1985). The time-order error and its relatives: Mirrors of cognitive processes in comparing. *Psychological Bulletin*, *97*, 35–61. doi:10.1037/0033-2909.97.1.35

Jepsen, J. R., Christensen, Anne Marie R., Nordentoft, M., & Mortensen, E L. (2010). Deficient maturation of aspects of attention and executive functions in early-onset schizophrenia. *European Child and Adolescent Psychiatry*, *19*, 773–786. doi:10.1007/s00787-010-0126-4

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1989). The Positive and Negative Syndrome Scale (PANSS): Rationale and standardisation. *British Journal of Psychiatry.*, *155*, 59–67.

Kumra, S., Smith, A K., Arling, E., Albus, K., Hamburger, S D., McKenna, K., ... Jacobsen, L K. (2000). Neuropsychological deficits in pediatric patients with childhood-onset schizophrenia and psychotic disorder not otherwise specified. *Schizophrenia Research*, *42*, 135–144. doi:10.1016/S0920-9964(99)00118-8

Lee, K. H., Bhaker, R.S., Mysore, A., Parks, R W., Birkett, Paul B. L., & Woodruff, P. W. R. (2009). Time perception and its neuropsychological correlates in patients with schizophrenia and in healthy volunteers. *Psychiatry Research*, *166*, 174–183. doi:10.1016/j.psychres.2008.03.004

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). Oxford: Oxford University Press.

Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., & Robertson, I H. (2001). The differential assessment of children's attention: The Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *Journal of Child Psychology and Psychiatry*, *42*, 1065–1081. doi:10.1111/1469-7610.00806

Ortuño, F., Guillén-Grima, F., López-García, P., Gómez, J., & Pla, J. (2011). Functional neural network of time perception: Challenge and opportunity for schizophrenia research. *Schizophrenia Research*, *125*, 129–135. doi:10.1016/j.schres.2010.10.003

Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spatial Vision*, *10*, 437–442. doi:10.1163/156856897X00366

Penney, T. B., Meck, W.H., Roberts, S.A., Gibbon, J., & Erlenmeyer-Kimling, L. (2005). Interval timing deficits in individuals at high risk for schizophrenia. *Brain and Cognition*, *58*, 109–118. doi:10.1016/j.bandc.2004.09.012

Piras, F., Piras, F., Ciullo, V., Danese, E., Caltagirone, C., & Spalletta, G. (2014). Time dysperception perspective for acquired brain injury. *Front Neurol*, *4*, 217. doi:10.3389/fneur.2013.00217

Radua, J., del Pozo, N. O., Gómez, J., Guillen-Grima, F., & Ortuño, F. (2014). Meta-analysis of functional neuroimaging studies indicates that an increase of cognitive difficulty during executive tasks engages brain regions associated with time perception. *Neuropsychologia*, *58*, 14–22. doi:10.1016/j.neuropsychologia.2014.03.016

Ranganath, C., Minzenberg, M. J., & Ragland, J. D. (2008). The cognitive neuroscience of memory function and dysfunction in schizophrenia. *Journal of Biological Psychiatry*, *64*, 18–25. doi:10.1016/j.biopsych.2008.04.011

Rao, S. M., Mayer, A. R., & Harrington, D. L. (2001). The evolution of brain activation during temporal processing. *Nature Neurosciences*, *4*, 317–323. doi:10.1038/85191

Roy, M., Grondin, S., & Roy, M. A. (2012). Time perception disorders are related to working memory impairment in schizophrenia. *Psychiatry Research*, *200*, 159–166. doi:10.1016/j.psychres.2012.06.008

Van Os, J. I. M., Driessen, G. E. R., Gunther, N., & Delespaul, P. (2000). Neighbourhood variation in incidence of schizophrenia. *The British Journal of Psychiatry*, *176*(*3*), 243–248. doi:10.1192/bjp.176.3.243

Ward, R. D., Kellendonk, C., Kandel, E.R., & Balsam, P D. (2012). Timing as a window on cognition in schizophrenia. *Neuropharmacology*, *62*, 1175–1181. doi:10.1016/j.neuropharm.2011.04.014

Wechsler, D. (2000). *WAIS III: Administration and scoring manual: Wechsler adult intelligence scale*. New York: Psychological Corporation.

World Medical Association. (2008). *Declaration of Helsinki. Ethical principles for medical research involving human subjects*. Retrieved from http://www.wma. net/e/policy/b3.htm