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**Time perception and its neuropsychological correlates in patients with
schizophrenia and in healthy volunteers**

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Abstract

Disordered time perception has been reported in schizophrenia. We investigated time perception dysfunction and its neuropsychological correlates in patients with schizophrenia. Thirty-eight patients and thirty-eight age and sex matched healthy volunteers were compared in an auditory temporal bisection paradigm using two interval ranges (a 400/800ms condition and a 1000/2000ms condition). In the temporal bisection, subjects were required to categorise a probe duration as short or long, based upon the similarity with two reference durations. All subjects also completed a battery of neuropsychological tests measuring sustained attention, short- and long-term memory and executive function. In the 400/800ms condition, patients judged durations significantly shorter than did control subjects. Patients also exhibited decreased temporal sensitivity in both conditions. We found in both groups a negative association between temporal sensitivity and sustained attention for the 400/800ms condition, and between temporal sensitivity and long-term memory for the 1000/200ms condition. In patients, short-term memory performance was negatively associated with duration judgement in both conditions, while executive dysfunction was correlated to a general performance deficit in the 400/800ms condition. These findings suggest the possibility that time perception abnormalities in schizophrenia are part of neuropsychological dysfunction and are likely to adversely impact upon activity of daily living.

Key words: temporal bisection, sustained attention, Wisconsin Card Sorting Test, Scalar Property of timing

1. Introduction

Patients with schizophrenia show a marked deviation between time as they actually experience it and time as it is measured in standard units (Lewis, 1932; Freedman, 1974). In these subjective accounts, some patients complain that they experience time as passing painfully slow while the other patients experience inconsistent perceptions of the passage of time. Such time distortion is pronounced during the acute stage of their illness, which may be associated with their disorganised, fragmented and distorted cognitive processes, as well as subjective feelings of confusion and anxiety. In longer term, disordered time sense may affect patients' continuity of self (i.e., the feeling of loss of continuity), leading to a passivity experience in which patients perceive themselves as completely changed (Sims, 1995). Timing impairments may also impact on communication skills, such as discerning when to respond appropriately in everyday conversations. This may manifest itself as miss-timing of verbal responses (e.g., interrupting others before they finished speaking or awkward long periods of silence in response to others' questions) (Clegg et al., 2007).

Earlier experimental studies provide a general consensus that patients with schizophrenia overestimate time intervals, hence they sense that more time has elapsed than has actually passed. Time intervals used in these studies range from milliseconds to hours (Rabin, 1957; Weinstein et al., 1958; Pearl and Berg, 1963; Rammsayer, 1990). Longitudinal studies have shown that patients tend to either under- or overestimate, and whichever category they fall into is consistent over time (Rabin, 1957; Melges and Fougrouse, 1966; Tysk, 1984). Furthermore, Davalos and colleagues showed that patients with schizophrenia exhibit deficits on both auditory and visual temporal discrimination tasks (Davalos et al., 2002). Despite these findings, time perception in schizophrenia has rarely been the focus of detailed investigation (Tracy et al., 1998; Rammsayer, 1990).

The investigation of time perception is pertinent to the understanding of neurobiological and cognitive abnormalities of schizophrenia. Firstly, brain lesion and neuroimaging studies have shown that critical brain structures engaged in time perception include the prefrontal and parietal cortices (lateralised to the right), thalamus, basal ganglia and cerebellum (Gibbon et al., 1997; Ivry and Spencer, 2004; Matell and Meck, 2004). These brain areas have been implicated in the pathophysiology of schizophrenia, in terms of impaired coordination of activity among these regions (Andreasen et al., 1999). Secondly, pharmacological studies indicate that time perception performance is highly sensitive to dopaminergic modulation. For example, dopamine agonists such as metamphetamine and cocaine produce lengthening of perceived time, whereas the dopamine antagonist haloperidol causes subjective shortening of time (Meck, 1996). In schizophrenia, it has long been hypothesised that positive symptoms are related to increased dopamine type-2 receptors in the basal ganglia, whereas negative symptoms are associated with decreased activity of dopamine type-1 receptors in the dorsolateral prefrontal cortex (Davis et al., 1991). Finally, according to the scalar expectancy theory, processing temporal information involves multiple cognitive processes that are working in concert: an internal clock, (short- and long-term) memory and decisional processes (Gibbon and Church, 1990; Wearden, 1999; Malapani, 2002). In patients with schizophrenia, cognitive abnormalities of attention, memory and decision making have been reported (Heinrichs and Zakzanis, 1998; Fioravanti et al., 2005).

The temporal bisection task has been used in patients with schizophrenia (Elvevåg et al., 2003). In this task, subjects are presented two reference stimuli of different duration and asked to categorise test stimuli as long or short, in relation to the reference stimuli. For the analysis, the mean proportion of “long” responses is plotted against stimulus duration, yielding a “psychophysical function” from which the bisection point (indicating leftward or rightward shift of the function) and difference limen (representing the gradient of the function) are determined. Elvevåg and

colleagues used 200ms and 800ms as reference stimuli in their temporal bisection task. Patients with schizophrenia showed an increase in bisection point value (a rightward shift of psychophysical function, hence, perceived shortening of time) and an increase in difference limen (flattened psychophysical function, representing decreased temporal sensitivity or precision). They interpreted these observations as indicating a long-term memory impairment in patients, because if the long-term memory for the standard durations was distorted (or noisier so that they are remembered as longer than they were) than the right-ward shift could occur. However, this interpretation was based upon the framework of the scalar expectancy theory, rather than upon a direct correlation between temporal bisection performance and memory function in schizophrenia. In the present study, we utilised the temporal bisection task, because it demonstrates significant advantages over traditional time perception tasks (Zakay, 1990). For example, some of compounding effects of estimation strategies (tapping or counting) or motor response delay in verbal estimation or temporal reproduction tasks are minimised in the temporal bisection. Moreover, we have previously demonstrated that temporal bisection performance with an interval range under 1s was affected by repetitive transcranial magnetic stimulation (rTMS) over the cerebellum (Lee et al., 2007a). Hence it is likely that the locus dysfunction in patients with schizophrenia using this particular task involves the cerebellum.

We wished to compare patients with schizophrenia and healthy volunteers using an auditory temporal bisection paradigm with two interval ranges (a 400/800ms condition and a 1000/2000ms condition). As noted earlier, time perception involves several cognitive processes working in concert. Hence, once time perception dysfunction was observed in schizophrenia, it would be difficult to decide the fundamental source. Therefore, we operationally defined the a priori external markers of time perception processes to be attention (as an indicator of the internal clock; Lejeune, 1998), short- and long-term memory, and executive function (as a proxy of

decision process) (Gibbon and Church, 1990; Wearden, 1999; Malapani, 2002). All subjects were administered the neuropsychological tests to evaluate the relative contribution of each cognitive processes to time perception performance. In addition, we also examined the effect of antipsychotic medication and clinical symptoms on measures of time perception in schizophrenia. We hypothesised that patients with schizophrenia would show time perception dysfunction which in turn would be associated with abnormalities in the cognitive domains of attention and executive function.

2. Method

2.1 Subjects

Forty-four patients with schizophrenia (DSM–IV) participated in this study. Data from six schizophrenia subjects were analysed and reported separately (referred to hereafter as the ‘unused schizophrenia subgroup’), because it was not possible to numerically analyse their temporal bisection data (see data analysis section). The final patient sample for group-comparison comprised thirty-four males and four females, with a mean age of 37.3 years ($SD = 10.4$). Healthy control subjects (thirty-four males and four females) were age-matched individually within 3 years (mean age of 35.5 years, $SD = 8.8$). Neither IQ (as estimated by the National Adult Reading test) nor years of education (Table 1) were significantly different between the groups.

Schizophrenia symptoms were assessed using the Schedule for the Assessment of Positive symptoms (SAPS) (Andreasen, 1984) and Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Illness duration was determined by a psychiatrist (AM) after interviewing patients and reviewing their medical record. After a complete description of the study to the subjects, written informed consent was obtained. The study was approved by the local Research Ethics Committee.

Table 1 about here

All 38 patients were receiving antipsychotic medication at the time of this study. The mean daily dose in chlorpromazine equivalents was 617.67mg. 33 patients were receiving atypical antipsychotics (clozapine [$n=10$], olanzapine [$n=11$], risperidone [$n=9$], quetiapine [$n=3$], amisuphrine [$n=1$], aripiprazole [$n=1$]; two were receiving more than one) and 5 patients were receiving typical antipsychotics. In the unused schizophrenia subgroup, two patients were not on any medication. One patient was on

a typical antipsychotic (fluphenazine), while three others were on atypical antipsychotics (clozapine, risperidone, or olanzapine).

2.2 Temporal bisection task

All subjects participated in two experimental conditions, a 400/800ms condition and a 1000/2000ms condition. In the 400/800ms condition, the reference auditory stimuli were of 400ms ('short') and 800ms ('long') durations. Auditory stimuli presented during the testing phase included durations of 400, 467, 533, 600, 667, 733, and 800ms. In the 1000/2000ms condition, the reference auditory stimuli were of 1000ms ('short') and 2000ms ('long'). Test auditory stimuli were of 1000, 1170, 1340, 1500, 1660, 1830 and 2000ms duration. A Power Macintosh computer controlled experimental events and recorded data with Psyscope (Cohen et al., 1993). Responses were made on the right and left buttons of a Psyscope response box. The stimuli used in the bisection tasks were 700 Hz tones produced by the computer speaker.

Subjects were trained and tested for each condition separately. The order of conditions alternated across subjects in each group. In the training phase, subjects heard two reference tones, each repeated five times. Subsequently, they were trained to press one button on the response box in response to the reference 'short' and 'long' tones, each of which were presented 20 times. In the testing phase, subjects were asked to respond whether a randomly presented tone from the seven test stimuli (reference 'short' and 'long' together with five intermediate stimuli) was more *similar* to the reference "short" or "long" tone, by pressing the left button for "short" or the right for "long". Each stimulus was presented 20 times (140 trials in total in each condition). The total testing lasted approximately 20 minutes.

2.3 Neuropsychological testing

Sustained attention was assessed with an auditory continuous performance task (CPT) in which 30 targets (sound of the letter “a”) were presented with 270 non-target stimuli (Seidman et al., 1997). Short-term memory was assessed using the digit span test from the WAIS-III. The Hopkins verbal learning test-revised (HVLT-R) was used to examine long-term memory (Brandt and Benedict, 1991). A 64-card version of the Wisconsin Card Sorting Test (WCST) (Kongs et al., 2000) was used to evaluate executive function.

2.4 Data analyses

2.4.1 Psychophysical data analyses

Proportions of ‘long’ responses were plotted against tone duration for each individual in each experimental condition. Then, sigmoidal curve-fitting was applied using a curve-fitting software (CurveExpert; Hyams, 2005), to determine the bisection point and difference limen. A sigmoidal curve model shown below showed the best fit for individual data, i.e., proportions of ‘long’ response ($P(L)$):

$$P(L) = \frac{ab + cx^d}{b + x^d}$$

The bisection point indicates the stimulus duration at which the subject provided 50% ‘long’ responses. The difference limen is calculated as half the difference between the durations providing 75% and 25% ‘long’ responses. The Weber’s fraction, a standardised performance measure of temporal bisection, was obtained by dividing the difference limen by the bisection point. Finally, an index of the scalar property of timing was obtained for each individual, by calculating the absolute difference between the Weber’s fractions for the 400/800ms and 1000/2000ms conditions.

Variations in ‘goodness-of-fit’ between model and data could be a potential confounding variable on between-group differences, because goodness-of-fit for individual data might be different across subjects. To address this issue, we calculated a residual (error term) for each distribution for each individual (Wichmann and Hill, 2001). The error term was used to examine the covariation effect of ‘goodness of fit’ on group differences.

2.4.2 Between- and within-group analyses

Between-group differences in the temporal bisection performance in each condition were examined using independent sample t-tests. Analysis of covariance (ANCOVA) was used to examine the effect of ‘goodness-of-fit’. In order to examine temporal bisection performance in relation to neuropsychological and clinical variables, Pearson’s correlation analysis was used.

In six patients (the unused schizophrenia subgroup), the fitted sigmoidal function did not reach either the bisection point or the 75% “long” responses, so that the bisection point obtained was not within the stimulus range. The Mann–Whitney *U*-test was used to examine whether this subgroup of schizophrenia patients were different in neuropsychological and clinical variables from the main schizophrenia group. All statistical test results reported in this study were two-sided and statistical significance was set at 0.05.

3. Results

3.1 Between group comparisons in each temporal bisection condition¹

Patients with schizophrenia had an increased bisection point when compared to healthy controls in the 400/800ms condition ($t_{74} = 2.9$, $P = 0.004$), but not in the 1000/2000ms condition ($t_{74} = 1.0$, $P = 0.313$) (Table 2 and Figure 1). Patients showed flattened gradients of the psychophysical functions in the 400/800ms ($t_{74} = 2.9$, $P = 0.006$) and 1000/2000ms conditions ($t_{74} = 3.2$, $P = 0.003$), compared to controls.

There were significant covariation effects of goodness of fit for the difference limen between groups in the 400/800ms condition ($F_{1,73} = 5.9$, $P = 0.018$) and the 1000/2000ms condition ($F_{1,73} = 9.3$, $P = 0.003$). However, when the effect of goodness of fit was controlled for, the group differences in difference limen remained significant for the 400/800ms condition ($F_{2,73} = 7.3$, $P = 0.001$) and similarly for the 1000/2000ms condition ($F_{2,73} = 10.3$, $P = 0.0001$). Within the patient group, medication (CPZ-equivalent dose) was not significantly correlated with temporal bisection variables.

Table 2 and Figure 1 about here

¹ Each experimental condition was further divided into two stages (i.e., first half and second half of trials) to test whether patients and controls showed a differential performance over time in each condition. We used a multiple analysis of variance (MANOVA), with group as a between-group variable, and ‘repetition’ (1st or 2nd half) and ‘task’ (400/800ms or 1000/2000ms conditions) as within-group variables. The group variable did not interact with ‘repetition’ or ‘task’ factors, suggesting that the performance pattern between patients and controls was not different across the first and second set of ten presentations and across each condition. The main effect of ‘repetition’ was significant ($F_{1,74} = 9.54$, $P < 0.01$) implying a shorter bisection point in the second half trials in both patient and controls. The effect of ‘group’ was significant for difference limen ($F_{1,74} = 14.5$, $P < 0.001$) and at trend level for bisection point ($F_{1,74} = 3.6$, $P = 0.06$) suggesting that patients showed an increase of difference limen and bisection point (a trend level of significance).

3.2 Temporal bisection in relation to neuropsychological, clinical and demographic variable variables

The correlations between temporal bisection and neuropsychological variables in both groups are presented in Table 3. In patients, increased difference limen values (flattened gradient) were associated with lower CPT scores (in the 400/800ms condition) and poorer delayed recall performance (in the 1000/2000ms), whereas in both conditions an increased bisection point was related to poor digit span performance. Poor WCST performance was related to increases in both the bisection point and difference limen in the 400/800ms condition. In controls, CPT and delayed recall scores exhibited the same relationship as in patients.

Total SANS scores were positively correlated with the difference limen in the 1000/2000ms condition ($r = .33, P=0.045$). Age or illness duration were not significantly associated with any temporal bisection variables. However, higher IQ scores were associated with a shorter bisection point in the 400/800ms condition in the patient group ($r = -0.48, P = 0.002$).

Table 3 about here

3.3 Scalar Property of timing

Patients with schizophrenia exhibited an increased scalar property value (the absolute difference between two Weber's fractions) (mean: patients 0.04 ± 0.06 ; controls 0.02 ± 0.02) ($t_{74} = 2.0, P = 0.048$). Post-hoc analyses showed that there was no significant co-variation effect of 'goodness of fit' (the 400/800ms condition residuals: $F_{1,72} = 1.7, P > 0.05$; the 1000/2000ms condition residuals: $F_{1,72} = 1.5, P > 0.05$).

Figure 2 about here

Within the patient group, the increased scalar property value was significantly associated with a decreased number of total correct responses in the CPT ($r = -0.3$, $P = 0.045$). However, the increased scalar property value was not significantly related to the digit span, the Hopkins memory test, or WCST scores. In healthy controls, the scalar property value was also significantly correlated with sustained attention ($r = -0.45$, $P = 0.005$) and Hopkins delayed recall score ($r = -0.39$, $P = 0.015$).

3.4 Characteristics of the unused schizophrenia subgroup excluded from the main analysis

Six patients with schizophrenia excluded from the group comparisons all had a rightward shift of the psychophysical function (see Figure 3). Two patients had the rightward shift in the 400/800ms condition and three patients had the shift in the 1000/2000ms condition. One patient had the shift in both conditions.

Figure 3 about here

Compared with patients included in the between group comparisons, these patients exhibited significantly more severe negative symptoms (Mann–Whitney U -test, $U=33$, $P = 0.005$), lower total correct responses in the CPT (mean 17.7, SD 7.2, Mann–Whitney U -test, $U = 36$, $P = 0.007$) and total Digit Spans scores (mean: 13.3, SD 4.5, Mann–Whitney U -test, $U = 33$, $P = 0.005$) (Table 1).

4. Discussion

We investigated time perception dysfunction in patients with schizophrenia in relation to their sustained attention, short- and long-term memory and executive function. Patients with schizophrenia showed a rightward shift and a flattened gradient of the psychophysical function in the 400/800ms condition. Our results are consistent with findings of Elvevåg and colleagues who used a temporal bisection task with interval ranges 200ms to 800ms (Elvevåg et al., 2003). Furthermore, we observed that the rightward shift was associated with poor short-term memory and executive performance in patients with schizophrenia. The cerebellum is involved in perception of intervals below 1 second, in an automatic and preattentive way (Lewis and Miall, 2003; Näätänen et al., 2004). Consistent with this is our previous finding that suppressing activity in the cerebellum using 1-Hz rTMS produced a leftward shift of psychophysical function in the 400/800ms condition, but not in the 1000/2000ms condition (Lee et al., 2007a). Taken together, the relationship between executive dysfunction and poor performance in the 400/800ms condition indicated that accurate time perception within the hundreds of milliseconds range may make a key contribution to the executive system that is more generally disturbed in schizophrenia. We suggest that this dysfunction may be associated with cerebellar functional and structural abnormalities (Lee et al., 2007b)

Because our control subjects also underwent an identical neuropsychological testing to that of schizophrenia subjects, we were able to identify neuropsychological variables that were common to the time perception performance in both groups, as well as some other variables that were specifically related to the time perception abnormalities found in the patient group. In both groups, we found that increased accuracy on the continuous performance test related to smaller difference limen values in the 400/800 ms condition. This suggests that there is an association between better sustained attention function and high temporal sensitivity for sub-second time

perception. The observation that better long-term memory performance was associated with higher temporal sensitivity in the 1000/2000ms condition supports the idea that memory systems are important for temporal sensitivity of > 1 sec durations. In patients, poor short-term memory performance was associated with the rightward shift of the psychophysical function in both temporal bisection conditions. A rightward shift of the function would occur if subjects perceived test tone durations shorter than they actually were. Hence their subjective time is shortened (Wearden et al., 1999). Similarly, Franck and colleagues reported that patients with schizophrenia estimated time intervals between sequential movements shorter than healthy volunteers, demonstrating a “contraction of time” (Franck et al., 2005). Our result suggests that a deficit in the transient online storage and retrieval of temporal information may lead to the shortening or contraction of time in patients with schizophrenia.

Poor neuropsychological test performance in the unused schizophrenia subgroup (six patients excluded from the main analyses) further strengthened the evidence that time perception dysfunction was associated with neuropsychological abnormalities in patients with schizophrenia. The patients had more severe negative symptoms and were more impaired in sustained attention and short-term memory compared to the rest of the patient sample. Tracy and colleagues (1998) found that a dual task paradigm which engaged attention and short-term memory produced a larger performance decline in temporal accuracy among patients with schizophrenia. These findings are consistent with our own results.

In a temporal bisection task in experimental animals, administration of a dopamine releasing agent, methamphetamine, induced a leftward shift of psychophysical function, whereas dopamine D2 receptor agonist, haloperidol produced the opposite effect (Maricq et al., 1981; Maricq and Church, 1983; Meck, 1986). One might therefore speculate that our finding of the rightward shift of psychophysical function

was simply the effect of antipsychotic medication in patients. However, in our study we found no significant association between medication and horizontal shift of psychophysical function in patients. Previous studies of the effects of typical antipsychotic medication on time perception in patients with schizophrenia have been inconsistent (Angle, 1973; Goldstone et al., 1979). Hence, we conclude that time perception dysfunction in patients with schizophrenia in this study is unlikely to be associated with the effects of antipsychotic medication.

Weber's law in timing (the scalar property) has been reliably observed in experimental animals and humans (Droit-Volet & Wearden, 2002). Because Weber's fraction (the difference limen divided by the bisection point in the present study) is a standardised measure of performance, Weber's fractions in different conditions should be the same in each individual. As shown in Table 2, group means values for Weber's fraction in patients with schizophrenia remained the same across two interval ranges, so that impaired scalar property of time would be canceled out at the group level. However when calculated at the individual level, patients exhibited a significant increase of the scalar property value (i.e., greater difference between Weber's fractions: Figure 2), which, in turn, was associated with impaired sustained attention. Weber's law observed in the domains of perception and cognition is a characteristic feature of many biological systems, from single neuronal level to organism's behavioural level (Gisiger, 2001; Nieder & Miller, 2003). In this study, the increase of the scalar property value in patients was associated with poor CPT performance. Although preliminary, our results indicate a disturbance of the scalar property of timing in schizophrenia. Hence, further exploration of Weber's law in other domains of perception and cognition in schizophrenia may be of interest.

There are some issues to consider in interpreting the results of this study. No statistical correction procedures to adjust for possible type I errors were included in the associations between neuropsychological and temporal bisection variables (Table

3). Therefore the results must be interpreted with caution. However they may provide a basis for generating a new hypothesis in future studies (minimising the likelihood of type II errors). The relationship between sustained attention and time perception can be further examined using a more complex version of the continuous performance test (e.g., examining D prime as a measure of signal detection sensitivity), given that poorer than normal performance on sustained attention tasks in schizotypy (Chen et al., 1997) and in schizophrenia (Liu et al., 2002) has frequently been reported. Studies on time perception in schizophrenia using neuroimaging tools could be beneficial in examining the underlying neural basis of time perception and identifying the neural pathology involved in this disorder (e.g., Volz et al., 2001; Davalos et al., 2005).

In conclusion, this study highlights the significant associations of sustained attention and negative symptoms to time perception dysfunction, and provides evidence for neuropsychological and clinical relevance of time perception in patients with schizophrenia. Elucidation of the exact nature of time perception dysfunction in schizophrenia, however, will require a substantial amount of further research. For instance, investigating time perception intervals below 1 second could usefully examine whether cerebellar dysfunction directly contributes to abnormalities in sub-second time perception and executive function in patients with schizophrenia.

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References

- Andreasen, N.C., 1983. Scale for the Assessment of Negative Symptoms (SANS).
University of Iowa, Iowa City.
- Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SAPS).
University of Iowa, Iowa City.
- Andreasen, N.C., Nopoulos, P., O'Leary, D.S., Miller, D.D., Wassink, T., Flaum, M.,
1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its
neural mechanisms. *Biological Psychiatry* 46, 908-920.
- Angle, H.V., 1973. Role of chlorpromazine in maintaining timing behavior in chronic
schizophrenics. *Psychopharmacologia* 28, 185-194.
- Brandt, J., Benedict, R.H.B., 1991. Hopkins verbal learning test-revised. Professional
manual. Psychological Assessment Resources, Florida.
- Chen, W.J., Hsiao, C.K., Lin, C.C., 1997. Schizotypy in community samples: the
three-factor structure and correlation with sustained attention. *Journal of
Abnormal Psychology* 106, 649-654.
- Cohen, J.D., MacWhinney, B., Flatt, M., Provost, J., 1993. PsyScope: A new graphic
interactive environment for designing psychology experiments. *Behavioral
Research Methods, Instruments, and Computers* 25, 257-271.
- Clegg, J., Brumfitt, S., Parks, R.W., Woodruff, P.W., 2007. Speech and language
therapy intervention in schizophrenia: a case study. *International Journal of
Language and Communication Disorders* 42, 81 - 101.
- Davalos, D.B., Kisley, M.A., Freedman, R., 2005. Behavioral and
electrophysiological indices of temporal processing dysfunction in
schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences* 17,
517-525.
- Davalos, D.B., Kisley, M.A., Ross, R.G., 2002. Deficits in auditory and visual
temporal perception in schizophrenia. *Cognitive Neuropsychiatry* 7, 273-282.

- Davis, K.L., Kahn, R.S., Ko, G., Davidson, M., 1991. Dopamine in schizophrenia: a review and reconceptualization. *American Journal of Psychiatry* 148, 1474-1486.
- Droit-Volet, S., Wearden, J. 2002. Speeding up an internal clock in children? Effects of visual flicker on subjective duration. *The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology* 55, 193-211.
- Ellevåg, B., McCormack, T., Gilbert, A., Brown, G.D., Weinberger, D.R., Goldberg, T.E., 2003. Duration judgements in patients with schizophrenia. *Psychological Medicine* 33, 1249-1261.
- Fioravanti, M., Carlone, O., Vitale, B., Cinti, M.E., Clare, L., 2005. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology review* 15, 73-95.
- Franck, N., Posada, A., Pichon, S., Haggard, P., 2005. Altered subjective time of events in schizophrenia. *Journal of Nervous and Mental Disease* 193, 350-353.
- Freedman, B.J., 1974. The subjective experience of perceptual and cognitive disturbances in schizophrenia. A review of autobiographical accounts. *Archives of General Psychiatry* 30, 333-40.
- Gibbon, J., Church, R.M., 1990. Representation of time. *Cognition* 37, 23-54.
- Gibbon, J., Malapani, C., Dale, C.L., Gallistel, C., 1997. Toward a neurobiology of temporal cognition: advances and challenges. *Current Opinion in Neurobiology* 7, 170-184.
- Gisiger, T., 2001. Scale invariance in biology: coincidence or footprint of a universal mechanism? *Biological Reviews of the Cambridge Philosophical Society* 76, 161-209.
- Goldstone, S., Nurnberg, H.G., Lhamon, W.T., 1979. Effects of trifluoperazine, chlorpromazine, and haloperidol upon temporal information processing by schizophrenic patients. *Psychopharmacology (Berl)* 65, 119-124.
- Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12, 426-445.

- Hyams, D. 2005. CurveExpert. Hixson, Tennessee.
- Ivry, R.B., Spencer, R.M., 2004. The neural representation of time. *Current Opinion in Neurobiology* 14, 225-232.
- Kongs, S.K., Thompson, L.L., Iverson, G.I., Heaton, R.K., 2000. Wisconsin Card Sorting Test-64 Card Version (WCST-64). PAR Assessment Resources, Lutz, Florida.
- Lee, K.-H., Egleston, P.N., Brown, W.H., Gregory, A.N., Barker, A.T., Woodruff, P.W., 2007a. The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation. *Journal of Cognitive Neuroscience* 19, 147-157.
- Lee, K.-H., Farrow, T.F, Parks, R.W, Newton, L., Mir, N., Egleston, P.N., Brown, W.H., Wilkinson, I.D, Woodruff, P.W, 2007b. Increased cerebellar vermis white-matter volume in men with schizophrenia. *Journal of Psychiatric Research* 41, 645-651.
- Lejeune, H., 1998. Switching or gating? The attentional challenge in cognitive models of psychological time. *Behavioural Processes* 44, 127-145.
- Lewis, A., 1932. The experience of time in mental disorder. *Proceedings of the Royal Society of Medicine* 25, 611-620.
- Lewis, P.A., Miall, R.C., 2003. Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia* 41, 1583-1592.
- Liu, S.K., Chiu, C.H., Chang, C.J., Hwang, T.J., Hwu, H.G., Chen, W.J., 2002. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. *American Journal of Psychiatry* 159, 975-982.
- Malapani, C., 2002. Scalar timing in animals and humans. *Learning and Motivation* 33, 156-176.
- Maricq, A.V., Church, R.M., 1983. The differential effects of haloperidol and methamphetamine on time estimation in the rat. *Psychopharmacology (Berl)* 79, 10-15.

- Maricq, A.V., Roberts, S., Church, R.M., 1981. Methamphetamine and time estimation. *Journal of Experimental Psychology: Animal Behavior Processes* 7, 18-30.
- Matell, M.S., Meck, W.H., 2004. Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. *Brain Research. Cognitive Brain Research* 21, 139-170.
- Meck, W.H., 1986. Affinity for the dopamine D2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. *Pharmacology, Biochemistry, and Behavior* 25, 1185-1189.
- Meck, W.H., 1996. Neuropharmacology of timing and time perception. *Brain Research. Cognitive Brain Research* 3, 227-242.
- Melges, F.T., Fougerousse, J.C.E., 1966. Time sense, emotions, and acute mental illness. *Journal of Psychiatric Research* 4, 127-140.
- Näätänen, R., Syssoeva, O., Takegata, R., 2004. Automatic time perception in the human brain for intervals ranging from milliseconds to seconds. *Psychophysiology* 41, 660-663.
- Nieder, A., Miller, E.K. 2003. Coding of Cognitive Magnitude: Compressed Scaling of Numerical Information in the Primate Prefrontal Cortex. *Neuron* 37, 149-157.
- Pearl, D., Berg, P.S.D., 1963. Time perception and conflict arousal in schizophrenia. *Journal of Abnormal and Social Psychology* 66, 332-338.
- Rabin, A.I., 1957. Time estimation of schizophrenics and non-psychotics. *Journal of Clinical Psychology* 13, 88-90.
- Rammsayer, T., 1990. Temporal discrimination in schizophrenic and affective disorders: evidence for a dopamine-dependent internal clock. *The International Journal of Neuroscience* 53, 111-120.
- Seidman, L.J., Caplan, B.B., Tolomiczenko, G.S., Turner, W.M., Penk, W.E., Schutt, R.K., Goldfinger, S.M., 1997. Neuropsychological function in homeless mentally ill individuals. *Journal of Nervous and Mental Disease* 185, 3-12.

- Sims, A., 1995. *Symptoms in the Mind: An Introduction to Descriptive Psychopathology* (2nd ed.). W. B. Saunders Company LTD, London.
- Tracy, J.I., Monaco, C., McMichael, H., Tyson, K., Chambliss, C., Christensen, H.L., Celenza, M.A., 1998. Information-processing characteristics of explicit time estimation by patients with schizophrenia and normal controls. *Perceptual and Motor Skills* 86, 515-526.
- Tysk, L., 1984. A longitudinal study of time estimation in psychotic disorders. *Perceptual and Motor Skills* 59, 779-789.
- Volz, H.P., Nenadic, I., Gaser, C., Rammsayer, T., Hager, F., & Sauer, H., 2001. Time estimation in schizophrenia: an fMRI study at adjusted levels of difficulty. *Neuroreport* 12, 313-6.
- Wearden, J.H., 1999. "Beyond the fields we know...": exploring and developing scalar timing theory. *Behavioural Processes* 45, 3-21.
- Wearden, J.H., Pilkington, R., Carter, E., 1999. 'Subjective lengthening' during repeated testing of a simple temporal discrimination. *Behavioural Processes* 46, 25-38.
- Weinstein, A.D., Goldstone, S., Boardman, W.K., 1958. The effect of recent and remote frames of reference on temporal judgments of schizophrenic patients. *Journal of Abnormal and Social Psychology* 57, 241-244.
- Wichmann, F.A., Hill, N.J., 2001. The psychometric function: I. Fitting, sampling, and goodness of fit. *Perception & Psychophysics* 63, 1293-1313.
- Zakay, D. 1990. The evasive art of subjective time measurement: Some methodological dilemmas. In R. A. Block (Ed.), *Cognitive models of psychological time*. Lawrence Erlbaum Associates, Hillsdale, pp. 59-84.

Table 1. Demographic, clinical, and neuropsychological variables

Variables	Schizophrenia Main Group (n=38)	Controls (n=38)	Unused Schizophrenia Subgroup (n = 6)
Sex (No. M/F)	34/4	34/4	5/1
Age (years)	37.3 ± 10.4	35.5 ± 10.7	33.3 ± 8.9
Estimated IQ ^a	105.1 ± 12.1	106.6 ± 11.4	98 ± 12.2
Education (years)	12.4 ± 2.3	13.4 ± 2.3	11.5 ± 1.4
Duration of illness (years)	11.7 ± 9.0	N/A	11.3 ± 10.6
Antipsychotic (Atypical /Typical / None)	33 / 5 / 0	N/A	3 / 1 / 2
CPZ equivalent dose (mg/day)	617.7 ± 730	N/A	1120 ± 2072
SANS total	7.5 ± 3.4	N/A	13.3 ± 4.5 **
SAPS total	7.0 ± 4.8	N/A	6.9 ± 4.8
CPT Total correct ***	25.5 ± 4.7	28.8 ± 1.6	17.7 ± 7.2**
Digit Spans Total correct **	12.5 ± 3.9	14.9 ± 3.9	7.2 ± 1.8**
Delayed recall total correct **	7.0 ± 3.0	9.5 ± 1.8	6.2 ± 2.3
WCST total correct ***	33.9 ± 11.8	42.8 ± 9.3	31.7 ± 12.3
WCST perseverative errors **	17.8 ± 11.6	10.8 ± 6.2	19.5 ± 14.9
WCST categories completed **	1.6 ± 1.3	2.5 ± 1.4	1.5 ± 1.4

^a Estimated from scores on the National Adult Reading Test (NART). Patients with schizophrenia (N = 38) exhibited significantly lower scores on all neuropsychological tests compared with their healthy controls, marked by * <0.05 ; ** <0.01 ; *** <0.001 . A subgroup of patients (N = 6) reported separately (see results section) had more severe negative symptoms as well as significantly lower total CPT and digit span scores compared with the rest of patients (Mann–Whitney *U*-test).

Table 2. Means and standard deviations of temporal bisection variables for each group

Bisection conditions	Schizophrenia (<i>n</i> = 38)	Controls (<i>n</i> = 38)
400/800 condition		
Bisection point **	609.6 (66.9)	571.5 (44.2)
Difference limen **	118.9 (55.1)	92.2 (15.3)
Weber's fraction *	0.19 (0.07)	0.16 (0.03)
1000/2000 condition		
Bisection point	1421.7 (174.2)	1386.8 (119.5)
Difference limen **	269.3 (88.4)	220.5 (32.5)
Weber's fraction **	0.19 (0.05)	0.16 (0.02)

* < 0.05; ** < 0.01

Table 3. Neuropsychological test result correlations with temporal bisection task variables within the patient group ($n = 38$) and the control group ($n = 38$)

	BP400/800	DL400/800	BP1000/2000	DL1000/2000
Patients with schizophrenia				
CPT total correct	-0.241	-0.572***	-0.082	-0.162
Digit span total correct	-0.415**	-0.258	-0.338*	-0.231
Delay recall total correct	-0.255	-0.186	-0.214	-0.366*
WCST total correct	-0.307	-0.334	-0.102	-0.159
WCST perseverative errors	0.422**	0.413**	0.221	0.266
WCST categories completed	-0.326*	-0.381*	-0.104	-0.197
Healthy controls				
CPT total correct	0.228	-0.327*	0.305	-0.067
Digit span total correct	-0.015	-0.246	0.092	-0.052
Delay recall total correct	0.276	-0.242	0.193	-0.339*
WCST total correct	0.21	0.229	0.158	0.037
WCST perseverative errors	-0.236	-0.263	-0.194	0.023
WCST categories completed	0.212	0.052	0.044	-0.187

BP: bisection point; DL: difference limen; * < 0.05 ; ** < 0.01 ; *** < 0.001

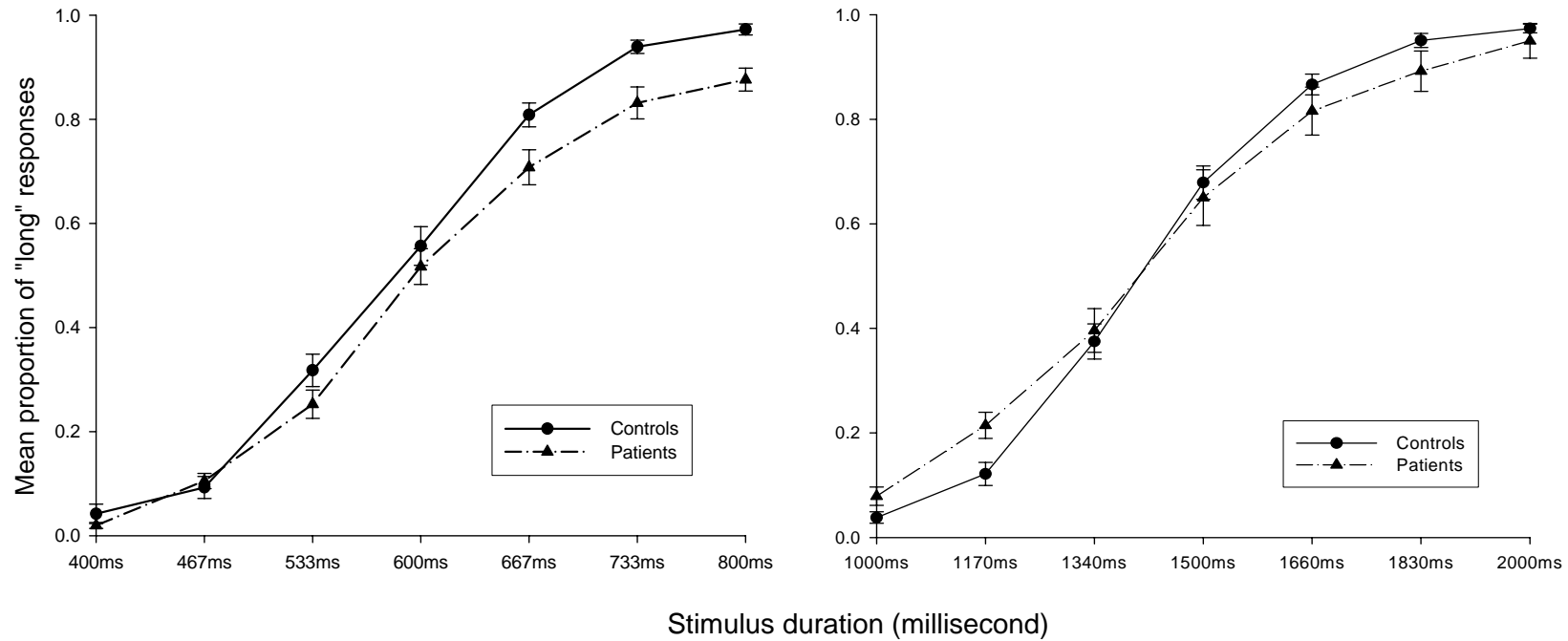


Figure 1. The mean proportion of "long" responses plotted against stimulus duration for 400/800ms (left panel) and 1000/2000ms (right panel) conditions. Patients with schizophrenia exhibited flattened and rightward shift of psychophysical function compared to healthy controls in the 400/800ms condition. Patients also showed flattened gradients of the psychophysical functions in the 1000/2000ms condition.

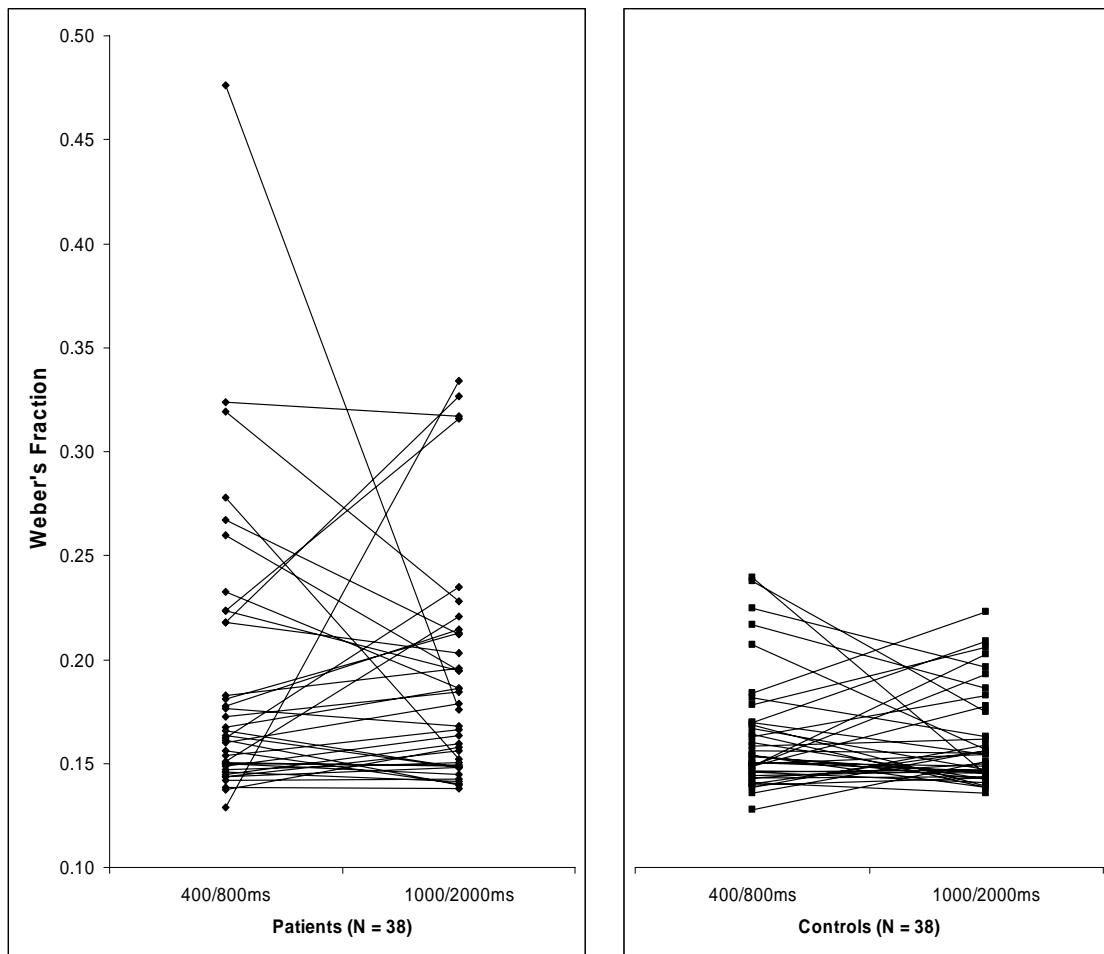


Figure 2. Weber's fractions for each individual in each condition. An index of the scalar property of timing was obtained for each individual, by calculating the absolute difference between the Weber's fractions. Patients showed an increase of the scalar property of timing index compared with controls. Impaired sustained attention was related to this increase.

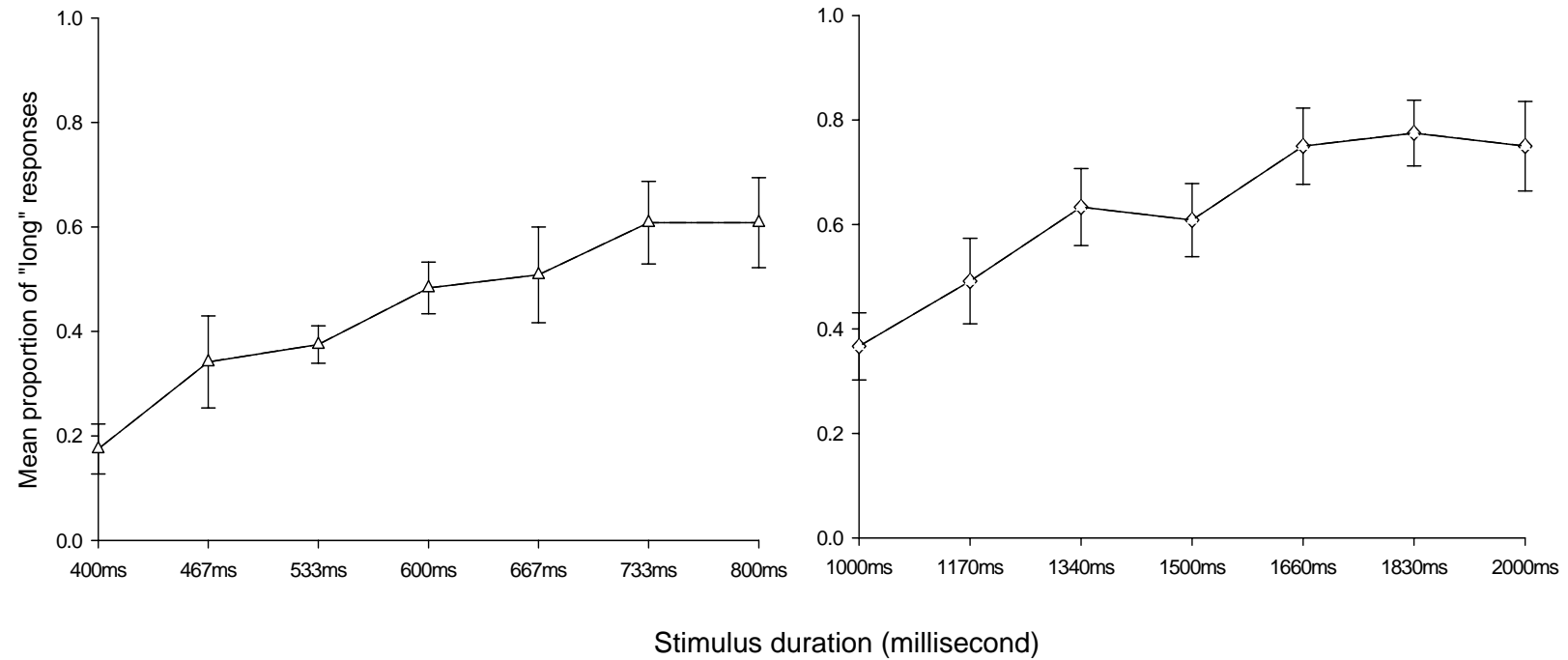


Figure 3. The mean proportion of “long” responses plotted against stimulus duration for 400/800ms (left panel) and 1000/2000ms (right panel) conditions in six patients with schizophrenia. The data were not included in the main between-group analyses, because their fitted sigmoidal function did not reach either the bisection point or the 75% “long” responses. This unused subgroup of patients had more severe negative symptoms and more impaired in sustained attention and short-term memory compared to the rest of the patient sample.