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A ticking clock for the production of sequential actions: Where does the problem lie in schizophrenia?[☆]

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ABSTRACT

Schizophrenia has been associated to a distorted time clock. By subtracting contact duration from Inter Response Interval, we report evidence for preserved internal clock in schizophrenia, with normal spontaneous tapping tempo. Contact durations were however increased in patients suggesting a specific problem in the fast integration of incoming haptic feedback with outgoing motor efferences. This integration deficit would emerge at an early phase, since Ultra High Risk patients also revealed abnormal tapping stability. Tactile screens revealed to be a simple and low cost apparatus that may constitute a suitable measuring kit for the characterisation of sensory motor deficits in clinical settings.

1. Introduction

For over a century, schizophrenia has been related to systematic distortions of time (Lewis, 1932; Davalos et al., 2003) with subjective time being experienced as lengthened relative to objective time (Tysk, 1983). Experimental psychological studies have revealed abnormal estimations of temporal durations (Tracy et al., 1998) as well as impaired patterns of results when required to produce or reproduce temporal intervals (Wahl and Sieg, 1980; Carroll et al., 2009), ranging from several seconds to two minutes. Overall these results have been interpreted as reflecting a distorted ticking frequency of a hypothetical "internal clock" (Gibbon and Church, 1984) in schizophrenia.

One way to probe timing abilities in the motor domain, and more specifically the well functioning of the internal clock, is to ask participants to *produce a spontaneous and regular sequence* of finger taps (Vanneste et al., 2001). This measure has the advantage of requiring no subjective or explicit decision-making. Nevertheless, even such a simple motor task needs complex motor planning. Indeed, as there is no external cueing, spontaneous tapping requires subjects to produce a self-paced series of motor actions, which consist in the execution of a rhythmic sequence of individual elements {finger down/finger up – wait – finger down/finger up – wait …}. As such, in addition to an internal clock, the regular and stable production of a spontaneous tempo depends on motor attention for fluent sequential action planning (Stelmach et al., 1989), which is abnormally allocated in schizophrenia (Delevoye-Turrell et al., 2006). Thus, a confounding factor in using spontaneous tempo for investigating internal clock in schizophrenia is that the origins of the deficit may be diverse.

Through the use of a touch screen, we propose to measure Inter Response Interval (IRI), i.e., the dependent variable traditionally measured in finger tapping studies, but to decompose each IRI as the sum of two new variables. First, Contact Duration (CD) was defined as the time interval during which the finger is in contact with the screen. This indicator is associated to the time needed by the sensorimotor system to detect that the finger has made contact (finger down) and that the next element can thus be initiated (finger up). Hence, contact duration is an indicator of the brain capacity to quickly integrate incoming sensorimotor (haptic) afferences with outgoing motor efferences. The second parameter is the Flight Time (FT), i.e., the time during which the finger is moving from one target to the next. This parameter is planned in a predictive manner on the basis of an open loop that cycles at the ticking frequency of the internal clock (finger down … finger down …). As such, it does not depend

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Table 1
Demographic characteristics are given for the four experimental groups. Specifics on clinical characteristics and treatment are also provided for the two patient groups.

Characteristics	SZ (N = 24)		CS (N = 22)	Statistics		UHR (N = 15)	ADO (N = 17)	Statistics	
Demographic characteristics	N (ET)		N (ET)		*p*	N (ET)	N (ET)		*p*
Age (years)	40.62 (8)		39.41 (8.03)	T = −0.30	.76 (ns)	18.2 (2.6)	18.4 (3.8)	T = 0.23	.82 (ns)
Education (years)	11.45 (2.3)		13.78 (2.3)	T = 4.027	<.01 (s)	10.3 (1.8)	11.5 (3.1)	T = 1.32	.19 (ns)
Gender (M/F)	14/10		13/9	$X^2 = 0.39$	.84 (ns)	10/5	11/6	$X^2 = 0.14$	.90 (ns)
Handedness (R/L)	23/1		21/1	$X^2 = 0.24$	.62 (ns)	12/3	15/2	$X^2 = 0.41$	.52 (ns)
Clinical characteristics	Mean	SD							
Positive and negative syndrome scale									
Positive component	16.3	(5.7)							
Negative component	23	(6.3)							
General component	37.8	(10)							
Total Component	77.1	(18)							
Duration of illness (years)	16.1	(8.4)							
IQ						101	(17)		
Processing speed index	82.39 (8.9)	(12)				88	(19)		
Treatment measures (dose per day at testing)	Mean	SD				Mean	SD		
Chlorpromazine equivalents (mg)	290	(250)				97	(74)		
Untreated (N)	0					5			

on sensorimotor integration but requires clock-based mechanisms and may thus reveal the pure ticking frequency of the timer.

In the present study, we question the nature of the deficit characterising time distortions in schizophrenia. By measuring FT and CD specifically, we aim to show that time distortions in patients are due to a deficit in the sensorimotor integration of afferent and efferent information for regular spontaneous tempo production rather than to a distorted internal clock per se. We propose furthermore that the integration deficit may emerge during the early phase of the illness, as early as the prodromal phase of schizophrenia.

2. Materials and methods

Two groups of outpatients participated in the current study. The *UHR Group* was composed of 16 young patients who fulfilled the Ultra High Risk criteria (Yung et al., 2005). These patients were characterised by initial signs foreshadowing psychosis, and did not meet DSM IV-TR criteria for schizophrenia. The *SZ Group* was composed of 24 chronic patients suffering from schizophrenia. Diagnoses were based on a structured clinical interview that was given by a single psychiatrist following the DSM-IV-TR. Symptom severity was evaluated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989). All patients were rated on the Symbol Search and the Digit Symbol Coding subtests of the WAIS III allowing the evaluation of a processing speed index. Two control groups were constituted (ADO *Group*; CS *Group*) and were pair-matched for age and sex with the UHR and the SZ groups, respectively. Detailed information about the participants is presented in Table 1. For all groups, exclusion criteria were substance dependence, mental retardation, history of epilepsy and physical illnesses. The present study was approved by the local ethics committee,[1] and all participants provided written informed consent after the procedure had been fully explained.

Subjects were seated comfortably on a chair in front of a touch screen (Elo Touch, 23 cm ∗ 36 cm ∗ 30 cm), which was placed on a narrow support at knee-height. Each trial started with the presentation of a visual image that was made of 6 black circles (Fig. 1—left). The subjects' task was to point each circle one after the other, clockwise, starting from the bottom-right circle. Subjects were asked to use their preferred hand and to tap as regularly as possible, at their preferred rate. No sound was ever heard. A trial was ended after the production of 30 taps, and a total of 12 trials were recorded.

With Matlab software (under the LINUX operating system), we used an Elo tactile screen to measure the X-Y-Z components of each touch down at a frequency of 100 Hz. For each tap series, it was thus possible to measure Inter Response Intervals (IRI in ms), Contact Durations (CD in ms) and Flight Times (FT in ms). Fig. 1—right provides an illustration of how these three variables were calculated. In addition, for each trial, the ratio of IRI_{n+1} over IRI_n was calculated to get an indication of the subjects' regularity (ratio in ms); the coefficient of variance was calculated as the ratio of $IRI_{variation}$ over IRI_{mean} to obtain for each participant a global estimation of performance stability (CV in %). Force pressure was also measured but not reported. A one-way ANOVA with Group as independent factor was conducted to reveal the effects of pathology. The significance level was set at $p = 0.05$ and the LSD post hoc test was used when required.

3. Results

Participants performed mean ratios very close to 1, suggesting that all groups were able to follow instructions and produce regular series of taps. The mean group values that are presented in the next section are presented in Table 2.

3.1. Comparing group means

Statistical analysis revealed a significant Group effect on mean IRI duration [$F(3,148) = 9.3938$; $\eta_p^2 = 0.159$; $p = 0.001$]. Post hoc analyses confirmed that values were similar for UHR and ADO ($p = 0.344$). However, values were significantly greater in SZ than in CS ($p < 0.001$). Group effect was also significant for mean CV [$F(3,148) = 3.189$; $\eta_p^2 = 0.061$; $p = 0.026$], suggesting that both patient groups were more variable in interval production than controls. Indeed, post hoc tests confirmed that mean CV in UHR and SZ were similar ($p = 0.156$) whereas UHR results were more variable than in ADO ($p = 0.014$) and SZ results were more variable than in CS ($p = 0.004$). Overall, these results confirm previous findings indicating a slower and more variable spontaneous tempo in patients than in age-matched controls.

In order to determine what aspect of IRI production was abnormal in the patients, each IRI was subdivided in the time spent in the air (Flight Time, FT) and the time spent in contact with the tactile screen (Contact Duration, CD). Analysis revealed an absence of Group effect for mean FT duration [$F(3,148) = 2.385$; $\eta_p^2 = 0.046$; $p = 0.071$] with similar FT for all groups. Post hoc tests further confirmed that FT duration was similar in UHR and ADO ($p = 0.077$) and in SZ and CS ($p = 0.053$). An absence of Group effect was also observed for mean FT variability [$F(3,148) = 0.436$; $\eta_p^2 = 0.109$; $p = 0.728$].

Analysis on mean CD duration revealed a significant Group effect [$F(3,148) = 10.151$; $\eta_p^2 = 0.170$; $p = 0.001$]. The UHR group revealed similar CD durations than ADO ($p = 0.444$); the SZ applied significantly

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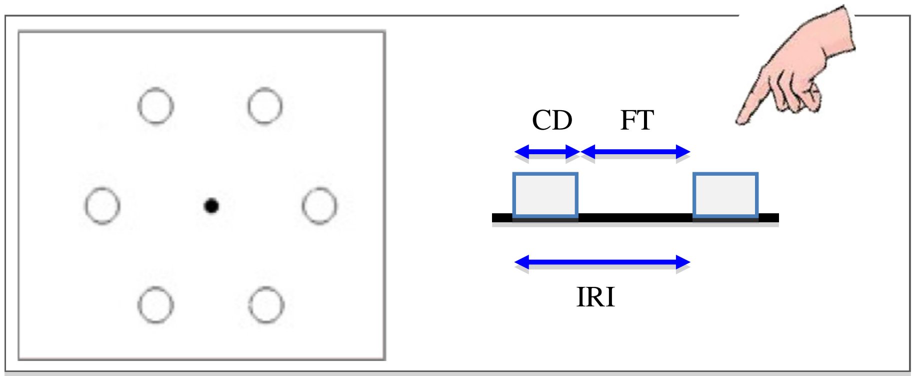

Fig. 1. Left is a top view of the tactile screen on which the picture was displayed throughout each trial. Right is a side view of the setup, with white squares illustrating a sequence of two successive taps for which the fingers contacted the tactile screen (black line). The time during which the finger is in contact with the screen is referred to as the Contact Duration (CD). The time during which the finger is in midair is referred to as the Flight Time (FT). Thus, the Inter Response Interval (IRI) is the sum of CD and FT, in ms.

longer CD durations than CS ($p<0.001$). Group effect was none significant for mean CD variability [$F(3,148)=0.277$; $\eta_p^2=0.005$; $p=0.841$].

3.2. Correlation analyses

A first correlation analysis was conducted for the two patient groups. Results showed that treatment level was not correlated with the timing parameters. However, processing speed was negatively correlated with both mean IRI durations ($r^2=0.478$), and mean CV ($r^2=0.348$) suggesting that slower cognitive speed was associated to slower and more variable tempo pace.

The second series of analyses were conducted in all four groups of subjects on IRI, FT and CD durations to reveal performance strategy. For SC, ADO and UHR groups, IRI duration was correlated the strongest to FT duration, which explained 76% of IRI variance in SC ($p<0.001$), 53% in ADO ($p=0.001$), and 88% in UHR ($p<0.001$). For the SZ patients, IRI duration was correlated the strongest to CD duration, which explained 82% of IRI variance ($p<0.001$). These findings suggest that patients with schizophrenia plan sequential actions differently than controls and that contact durations are the principle cause of the abnormal decrease in spontaneous tempo.

4. Discussion

In patient populations, for which a distorted time clock may have various causes, a unique analysis of Inter Response Intervals (IRI) does not provide the means to distinguish abnormal spontaneous tempo (ticking frequency of the internal clock) from deficits in fine sensorimotor integration processes. One study did propose to isolate the flight time from contact duration when studying elderly individuals (Cousins et al., 1998) but to our knowledge, the present study is the first to propose such an analysis in pathology.

In the present report, chronic patients with schizophrenia were able to produce regular sequences of spontaneous taps but at a slower rate than that measured in age-matched controls (IRI of 628 ms vs. 487 ms for patients and controls, respectively). These results are consistent with previous studies reporting (1) IRI of around 500 ms in healthy adults (McAuley et al., 2006) and (2) general movement slowness in patients with schizophrenia (Morrens et al., 2007). Interestingly, tempo slowness was positively correlated to the slowdown of cognitive speed in patients, which suggests a central origin for the deficit. Finally, even though young patients with Ultra High Risk of psychosis (UHR) did not reveal slower tempo (IRI of 520 ms), they were nevertheless characterised by more variable rhythmic patterns (CV and IRI variance) to a similar extent to that observed in the chronic patients. These findings suggest that some fragility exists in the central mechanism involved in the production of rhythmic sequences as early as the prodromal phase of schizophrenia. These results need now to be confirmed in a larger sample.

Through the use of a touch screen with an original time performance subdivision, our analyses revealed that an overall mean Flight Time (FT) of 350 ms was displayed across experimental groups (330, 335, 369, 379 ms for controls, chronic and young patients, respectively). Coherent with an absence of group effect, our results argue in favour of a normalised ticking frequency of the internal clock in chronic and stabilised patients with schizophrenia, with furthermore similar timing stability (FT variability) in both patients and healthy individuals. These results resemble those reported in the early 80s in studies investigating spontaneous eye-blink rates, with normalised spontaneous rates in stabilised patients under neuroleptic treatment (Karson, 1983).

Our chronic patients were characterised nevertheless with significantly longer Contact Durations (CD) than controls (see Table 2), which argues in favour of a specific problem in the fluent production of the finger down/up rhythmic movement in schizophrenia. Indeed, as suggested in studies with anaesthetised digits, simple manual actions are impaired severely in the absence of haptic afferences (Kilbreath et al., 1997; Nowak and Hermsdörfer, 2003). Thus, it is possible that the general psychomotor slowness reported here in schizophrenia is not related to frequency distortion of the internal clock but rather to a specific deficit in the sensorimotor integration of incoming afferences with outgoing efferent commands. Such

Table 2
Group means (standard deviation) for the timing variables are provided for the patients at Ultra High Risk (UHR) and their controls (ADO) as well as for the patients suffering from chronic schizophrenia (SZ) and their controls (CS). The Inter Response Interval (IRI) is given as a measure of spontaneous tempo rate; ratio and CV are indicators of timing regularity and stability, respectively.

	Tempo IRI (ms)	Regularity ratio	Stability CV (%)	Internal clock Flight time (ms)	Sensori-motor integration Contact time (ms)
ADO (n = 17)	490 (70)	1.003 (.007)	10.8 (9.1)	335 (71)	158 (80)
CS (n = 22)	487 (107)	1.004 (.007)	10.3 (9.6)	328 (78)	161 (74)
UHR (n = 15)	519 (134)	1.008 (.016)	18.7 (21.1)	380 (129)	140 (65)
SZ (n = 30)	610 (155)	1.010 (.014)	13.4 (9.2)	369 (115)	246 (133)

interpretations are similar to those reported in other studies (Lencer et al., 2010) and are furthermore reinforced by (1) the strong statistical power of the group effect for contact duration ($\eta_p^2 = 0.17$) and not for flight time ($\eta_p^2 = 0.04$), and (2) the correlation analyses, which demonstrated that contact duration explained over 80% of IRI tempo variance in chronic patients with schizophrenia. Note that the contrasting effects on FT and CD exclude an explanation in terms of a generalised deficit due to extra-pyramidal symptoms.

It has been proposed that schizophrenia may be associated to a deficit in generating neuronal synchrony, which would lead to problems in maintaining normal time phenomenology (Varela, 1999). Indeed, abnormal long latencies in the cortical loops have been reported as a possible cause for synchrony abnormalities in schizophrenia, which at a behavioural level would express itself as abnormal relative timing of incoming afferences with outgoing efferences. In this view, Giersch and collaborators have demonstrated in patients with schizophrenia difficulties in the discrimination of simultaneous from asynchronous stimuli, thus revealing a difficulty in time event coding (Foucher et al., 2007; Giersch et al., 2009; Lalanne et al., 2010). With a difficulty in distinguishing physical past and present events, the coding of the passage of time could be impaired with direct consequences on the capacity to correctly time and integrate sequences of multiple events. These deleterious effects would further be troublesome for cognitive operations that require the precise timing of afferent and efferent integration, e.g., sensory-motor coordination, language and action fluency (DeLisi et al., 1997; de Gelder et al., 2003; Docherty et al., 2006; Delevoye-Turrell et al., 2007). It is also the case that rhythmic initiation of an action in response to the action made by others is necessary for joint-interaction recognition. Specific difficulties in time event coding could thus also be the source of certain abnormal social behaviours adopted by patients when trying to interact with their outer world (Park et al., 2009; Delevoye-Turrell et al., 2011).

In conclusion, we report evidence of a preserved internal clock in schizophrenia, with normal spontaneous tapping tempo. Contact durations were however significantly increased in patients suggesting a specific problem in the integration over time of afferent (sensory) and efferent (motor) information for fluent motor execution in schizophrenia. Tactile screens revealed to be a simple and low cost apparatus that may constitute a suitable measuring kit for the characterisation of sensory motor deficits in clinical settings.

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Contributors

Authors HW, YT and AG designed the study and wrote the protocol. Author HW managed the literature searches and the data collection. Authors YT and HW conducted the data analyses. YT wrote the first draught of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

YT, HW and AG report no competing interests.

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