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Predictive timing disturbance is a precise marker of schizophrenia

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ABSTRACT

Timing disturbances have being proposed as a key component of schizophrenia pathogenesis. However, the contribution of cognitive impairment to such disorders has not been clarified. Here, we investigated duration estimation and predictive timing in 30 patients with DSM-5 diagnosis of schizophrenia (SZ) compared to 30 healthy controls (HC). Duration estimation was examined in a temporal and colour discrimination task, fully controlled for working memory (WM) and attention requirements, and by more traditional temporal production and temporal bisection tasks. Predictive timing was measured in a temporal and spatial orienting of attention task. Expectations about stimulus onset (temporal condition) or location (spatial condition) were induced by valid and invalid symbolic cues. Results showed that discrimination of temporal and colour stimulus attributes was equally impaired in SZ. This, taken with the positive correlation between temporal bisection performance and neuropsychological measures of WM, indicates that duration estimation impairments in SZ are underpinned by WM dysfunction. Conversely, we found dissociation in temporal and spatial predictive ability in SZ. Unlike controls, patients were selectively unperturbed by events appearing at an unexpected moment in time, though were perturbed by targets appearing at an unexpected location. Moreover, patients were able to generate temporal expectations more implicitly, as their performance was influenced by the predictive nature of the flow of time itself.

Our findings shed new light on the debate over the specificity of timing distortions in SZ, providing evidence that predictive timing is a precise marker of SZ, more sensitive than duration estimation, serving as a valid heuristic for studying the pathophysiology of the disorder.

1. Introduction

Timing is a key component of cognition and the ability to process event duration and to integrate contextual information into a predictive framework plays a pervasive role in the continuity of consciousness (Fuchs, 2013). Indeed, disorders in which the constitution of reality is disturbed, like schizophrenia (SZ) and psychotic conditions are characterized by alterations in the experience of time. That's why temporality and its disturbances have been a major topic in psychopathology, and the transdisciplinary link between psychiatry and philosophy (Fuchs and Van Duppen, 2017).

Notably, since temporal cognition is a fundamental "*basic unit of ability*" on which other cognitive and behavioural processes are based (Allman and Meck, 2012), some models integrate time perception as a key component of schizophrenia pathogenesis (Andreasen et al., 1998; Fuchs and Van Duppen, 2017; Vogeley and Kupke, 2007). However, although the notion of mistimed information transfer in schizophrenia (i.e. cognitive dysmetria) -which is one of the most popular theories on the cognitive impairments and clinical outcomes in the disorder-, assumes that distorted temporal processing may underlie SZ symptoms (Andreasen et al., 1998), the existence of a genuine time perception deficit in the illness is still unproven (Roy et al., 2012). As a matter of fact, the significant correlation between time perception and cognitive performance in processes typically affected in SZ (Lee et al., 2009) casts doubt as to whether deficits in timing tasks reflect a pure temporal perception dysfunction or schizophrenia-related cognitive disturbances (Roy et al., 2012). Interpretation of the handful of studies investigating the impact of concurrent impairments in cognitive processes required for timing abilities -such as attention and working memory (WM)- (Bolbecker et al., 2014; Carroll et al., 2008; Elvevåg et al., 2004; Lee

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et al., 2009; Penney et al., 2006; Roy et al., 2012) is rather problematic as the neuropsychological tests used (e.g. Digit Span) likely tap different WM components than those required to estimate duration, thus impeding a definitive conclusion.

Likewise, current neurocognitive and computational theories propose that the positive symptoms of schizophrenia are due to an abnormality in the brain's inference mechanism, such that a failure in the integration and exchange between incoming sensory information and expectations is related to the emergence of delusions and hallucinations (Adams et al., 2013; Fletcher and Frith, 2009; Fuchs, 2007; Sterzer et al., 2016). Indeed, patients appear to have difficulty in predicting events over very short time intervals (Giersch et al., 2016; Lalanne et al., 2012) and in efficiently coding events in time suggesting that prediction impairments in patients may concern the prediction of time in particular (Giersch et al., 2015; Peterburs et al., 2013; Waters and Jablensky, 2009). Predictive timing disturbances in SZ have been mostly inferred from electrophysiological studies (Todd et al., 2003, 2008; Umbricht and Krljesb, 2005) although a recent behavioural investigation has established a link between predictive timing and clinical symptoms of SZ (Martin et al., 2017). Nevertheless, no significant difference in predictive timing performance between SZ and healthy controls was found in the abovementioned study.

Therefore, either level of explanation, one assuming that the fundamental problem underlying positive symptoms in SZ is the abnormal perception of time, or the other that dysfunctional predictive timing may cause both abnormal perceptions and abnormal beliefs, lack conclusive experimental evidence.

The present study has a threefold objective: (i) to investigate the extent of SZ's potential impairment in time estimation as a function of interval duration and task demands; (ii) to assess the contribution of comorbid WM and attention impairments on possibly reduced accuracy and precision in explicit duration estimation in SZ; (iii) to examine whether SZ patients have alterations in predictive coding, particularly in forming temporally specific expectations. Time perception performance was investigated using tasks for which the goal was to provide an overt estimate or representation of elapsed time (i.e. *explicit timing*: events duration discrimination, comparison of temporal stimuli to a reference, time intervals production) and a temporal and spatial orienting task in which predictive cues provided information on *where* (spatial condition) or *when* (temporal condition) a target will occur *(implicit timing*) (Piras and Coull, 2011).

2. Methods

2.1. Participants

An a priori power calculation in G*power was used to determine the minimum sample size (Supplementary Materials). Thirty patients with a DSM-5 (American Psychiatric Association, 2013) diagnosis of SZ were enrolled in the present study. Diagnosis of SZ was made by a senior psychiatrist and confirmed using the Structured Clinical Interview for DSM-5 Disorders- Clinician Version (First, 2016a). Inclusion criteria for all participants were: (1) age between 18 and 60 years, (2) at least 8 years of education, and (3) sufficient attentional resources to perform the experimental tasks (i.e. mean omission rates < 20%). Full exclusion criteria are given in Supplementary Materials. Antipsychotic dosage was converted to chlorpromazine equivalents (CPZE); no patient was undertaking benzodiazepine-type drugs. Psychotic symptoms were rated using the Positive and Negative Syndrome scale -PANSS- (Kay et al., 1989).

Thirty healthy controls subjects (HC), age-sex matched, were recruited from the same geographical area. All HC were screened for current or past diagnosis of any DSM-5 Axis I or II disorder using the SCID-5 Research Version edition (First et al., 2015) and the SCID-5-Personality Disorders Interviews (First, 2016b). The same exclusion criteria for SZ patients were applied to HC.

All subjects underwent an attentional and WM cognitive evaluation which included: the Trail Making Test (TMT) (Reitan, 1992) and a non-verbal, non visuo-spatial working memory task, the *Delayed Item Recognition task (DIR,* see Supplemental Fig. 1) (Habeck et al., 2012) to measure the maintenance component of WM necessary for timing tasks. All participants gave written informed consent to participate after the procedures had been fully explained. The study was approved and carried out in accordance with the guidelines of the IRCCS Santa Lucia Foundation Ethics Committee.

2.2. Experimental procedure

Duration estimation was investigated with two perceptual timing tasks (i.e. temporal and colour discrimination task, temporal bisection task) and with a motor timing task (temporal production task). A temporal and spatial orienting of attention task assessed predictive timing. Detailed description of the temporal bisection and production tasks, analyses and results for the DIR task, the neuropsychological evaluation and the correlational analyses are included in Supplementary Materials.

In the *temporal and colour discrimination task* (Coull, 2004; Coull et al., 2008, 2012) participants were asked to judge either the relative duration (shorter, equal to, longer) or the colour (redder, equal to, bluer) of two consecutive stimuli, by pressing one of three response buttons (Fig. 1). Stimulus colour was not uniform but it flickered rapidly. This colour manipulation was crucial for equating sustained attention and WM demands across the two conditions since, like perception of elapsed time, perception of colour required the integration of information *throughout* stimulus presentation. A response screen was presented for 5 s, and any slower response was not recorded.

An adaptation of the *temporal and spatial orienting of attention task* (Coull and Nobre, 1998), measured reaction time (RT) to targets appearing after one of three intervals in one of three boxes depicted on the computer screen (Fig. 2). Subjects were asked to press a response button to detect the target, as quickly as possible, using information provided by one of three types of cue. In the majority of trials (80%) informative cues validly predicted where (spatial) or when (temporal cue) the target would appear ("valid" trials). In the remaining 20% of trials, the cue incorrectly predicted the spatial location or temporal onset of the target ("invalid" trials). In the neutral condition, no spatial or temporal information was provided. The three experimental conditions (spatial/temporal/neutral) were presented separately in three blocks of trials.

2.3. Data analysis

Demographic data were compared using unpaired *t-tests* for age and educational attainment and chi-square test for gender.

2.3.1. Time and colour discrimination task

d-prime accuracy was computed for time and colour conditions separately, and analyzed in one repeated measures ANOVA with diagnostic group (SZ/HC) as between-subjects factor and stimulus attribute (time/colour) as within-subjects factor.

2.3.2. Temporal bisection task

Individual mean proportion of longer than sample p(long) responses was plotted as a function of each probe duration (699, 816, 933, 966, 1033, 1066, 1183, 1299 ms), and analyzed in one 2×8 repeated measures ANOVA with diagnostic group (SZ/HC) as between-subjects factor and duration as within-subjects factor. Psychometric curves were fitted to individual subjects' data and two measures of temporal sensitivity calculated: the bisection point (i.e. Point of Subjective Equality -PSE-, a measure of temporal sensitivity), and d-prime (Green and Swets, 1966) a general index of perceptual discrimination accuracy. PSE and d-prime were analyzed as dependent variables in two factorial one-way ANOVAs, with group (SZ/HC) as independent variable.