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Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

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ABSTRACT

Schizophrenia (SZ) and Bipolar Disorder (BD) are associated with deficits in both timing and cognitive control functions. However, the underlying neurological dysfunctions remain poorly understood. The main goal of this study was to identify brain structures activated both by increases in cognitive activity and during timing tasks in patients with SZ and BD relative to controls.

We conducted two signed differential mapping (SDM) meta-analyses of functional magnetic resonance imaging studies assessing the brain response to increasing levels of cognitive difficulty: one concerned SZ, and the other BD patients. We conducted a similar SDM meta-analysis on neuroimaging of timing in SZ (no studies in BD could be included). Finally, we carried out a multimodal meta-analysis to identify common brain regions in the findings of the two previous meta-analyses.

We found that SZ patients showed hypoactivation in timing-related cortical-subcortical areas. The dysfunction observed during timing partially coincided with deficits for cognitive control functions. We hypothesize that a dysfunctional *temporal/cognitive control network* underlies the persistent cognitive impairment observed in SZ.

1. Introduction

Since both perception and action take place over time, timing is a key component of information processing in the central nervous system (Piras et al., 2014). Indeed, temporal processing has been described as a fundamental neuropsychological domain with a broad influence on cognitive functioning (Fuster et al., 2013; Head et al., 2008).

In view of the impact that a timing dysfunction might have on human cognition and behaviour, researchers have undertaken to understand the role of timing in neuropsychiatric diseases. Pathophysiological distortions in time processing have been reported in different disorders, such as schizophrenia (SZ).

1.1. Timing in schizophrenia and bipolar disorder

The idea that a disrupted experience of time might play a fundamental role in the pathophysiology of SZ dates back at least to the first half of the twentieth century (Minkowski, 1933). It is now nearly two decades since Andreasen (1999) commented on how a disturbance in time perception was involved in the processes of psychosis and suggested the study of timing in SZ as a way to discover more about the core symptoms of the disease, which she termed *cognitive dysmetria*. She further proposed that the underlying disorder involved the cortico-cerebellar-thalamic-cortical circuit. Nowadays, few would doubt the relevance of the study of timing to our understanding of neurobiological and cognitive abnormalities in SZ. Despite increased academic interest in timing in SZ and despite various proposals of new time-dependent conceptualizations of SZ pathophysiology, there has been little research that directly examines timing in SZ. Furthermore, due to inconsistent definitions and different methodologies, the findings of studies are not always in clear agreement (Texeira et al., 2013).

Recent research suggests that timing abnormalities may be a feature not only of SZ but of psychosis more generally (Schmidt et al., 2011). SZ and psychotic affective disorders, including schizoaffective disorder and psychotic BD, show more severe neurocognitive impairment than non-psychotic BD (Simonsen et al., 2011), and these findings suggest that psychosis symptoms are better predictors of neurocognitive impairment than diagnostic category (Bolbecker et al., 2014). Individuals

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without a diagnosis of SZ but who are prone to visual hallucinations (Coy and Hutton, 2013), who present schizotypal features (Lee et al., 2006), and who are deemed to have a high genetic risk for developing SZ (Penney et al., 2005) demonstrate alterations in time estimation that resemble those observed in individuals with SZ. Thus, a timing dysfunction might be considered as an endophenotype of SZ and schizotypal personality disorder, and, more generally, alterations in temporal perception may represent a psychosis-related phenotype and constitute a trait dysfunction that crosses diagnostic categories (Ciullo et al., 2015).

With regard to BD, although research on timing in BD is scarce, theory and the empirical evidence suggest that interval-timing mechanisms are disrupted in BD, regardless of symptom status (Koch et al., 2009). The disruption has been attributed to a failure in the neural circuitries involved in sub-second timing (cerebellum, basal ganglia and prefrontal cortex), which have also been implicated in the pathophysiology of BD (Texeira et al., 2013). In a recent study, Bolbecker et al. (2014) found significantly increased variability in timing in BD with and without psychotic features. Such increased variability in timing is not found in schizoaffective disorder, however. In conjunction, the two findings suggest a more nuanced view of the relative contributions of psychotic and affective symptoms to the disruption of the brain mechanisms underlying temporal processing; in this context it will be recalled that temporal processing is argued to be an important substrate of neurocognitive functioning (Andreasen, 1999).

1.1.1. Neuroimaging studies

There are only a few published fMRI studies on timing that focus specifically on neurofunctional substrates in SZ. One such study (Volz et al., 2001) used an auditory time estimation task and a frequency discrimination task and revealed timing specific differences between patients and controls in terms of activity in the posterior putamen, anterior thalamus, and right medial prefrontal cortex, with patients showing relative hypoactivity. More recently, Davalos et al. (2011) evaluated the effects of task-difficulty in temporal processing and found that patient and control groups showed different patterns of brain activation. Differences were found at two levels of task difficulty. In particular, the study identified a network of brain regions that showed reduced temporal processing-related responses in patients. The network included the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), thalamus, striatum, and insula/operculum. Deficits in the latter two regions were especially pronounced in SZ under conditions of high task difficulty. In conclusion, functional brain imaging findings confirm the notion that SZ patients have difficulties in recruiting key areas that mediate temporal processes.

1.2. Cognitive control in schizophrenia and bipolar disorder

Cognitive control is defined as a set of cognitive processes linked to the function of a distributed neural network that involves the DLPFC, anterior cingulate cortex (ACC), and the inferior parietal lobes (IPL) (Niendam et al., 2012). Since it can be designated as the level of perceived difficulty of the cognitive task and the subsequent mental effort that the individual applies to achieve the cognitive aim (Radua et al., 2014a), constitutes an aspect of every cognitive process. It has been suggested that, in SZ, cognitive control is disrupted across a range of cognitive domains (Lesh et al., 2011), and that there are reductions in the function of the frontal-cingulate-parietal cognitive control network (Minzenberg et al., 2009).

Timing and other cognitive processes, such as, attention, automatic or controlled behaviour change, working memory, and adjusting degree of concentration to task difficulty, are known to share brain networks (Gómez et al., 2014). Indeed, accurate cognitive control requires participation of neuroanatomical and functional components of time perception. Consequently, performance at timing tasks has been proposed as a sensitive measure of cognitive functioning and a reliable assay of damage to the underlying neural substrate (Suh et al., 2006).

1.3. Relationship between timing and cognitive control

Given the inextricable functional interrelation between timing and other neuropsychological domains such as attention, WM, or executive functions, the neuroscientific study of temporal processing can be a model system to examine cognitive dysfunction (Balci et al., 2009). On the one hand, temporal cognition has been described as a "basic unit of ability" that mediates other cognitive and behavioural processes (Allman and Meck, 2012) ranging from basic motor coordination (Buonomano, 2007) to higher goal-directed behaviour. On the other hand, since timing is defined as the ability to perceive, remember, and organize behaviour in periods ranging from seconds to minutes, timing can be regarded as being dependent on other cognitive resources (Ciullo et al., 2015).

Although SZ has been characterized as a deficiency in the temporal coordination of information processing in the brain (Andreasen et al., 1999), recent evidence (Papageorgiou et al., 2013; Penney et al., 2005; Peterburs et al., 2013; Roy et al., 2012) challenges the notion of a genuine time perception disorder in SZ: timing impairments are suggested to be secondary to disease-related cognitive deficits. Some of the arguments used in this debate hinge on the notion of two distinct timing mechanisms (Rammsayer, 2006). The "automatic" timing system measures time without cognitive modulation and is primarily involved in timing intervals in the subsecond range. The "cognitively controlled" mechanism, on the other hand, is primarily based on higher-level cognitive circuits that are recruited for estimations of time intervals of longer durations (Lewis and Miall, 2003).

A recent meta-analysis by Ciullo et al.'s (2015) examines - as far as we are aware for the first time - whether timing disturbances in SZ arise from disease-related cognitive impairments or from defective timing *per se*. The study found that in SZ patients the impairment in timing of events was equal whether the events involved intervals of milliseconds or intervals of seconds. In other words, the temporal processing deficit in SZ was independent of the length of the interval to-be-timed, with the implication that the deficit is not dependent on a cognitively-controlled timing mechanism, is independent of more generalized cognitive impairments (Carroll et al., 2009; Elvevåg et al., 2003), and, therefore, is pervasive and primary in SZ (Ciullo et al., 2015).

Attempts to identify the functional regions active specifically during temporal processing and not during other cognitive processes (Livesey et al., 2007) have not considered any possible effect of cognitive effort. A recent meta-analysis of results for healthy individuals (Radua et al., 2014a) shows that specific brain regions traditionally associated with time perception are significantly more active with relatively difficult non-temporal cognitive tasks than with easier versions of the same tasks. Does task difficulty have a similar effect in SZ? Our previous, preliminary, study (Alústiza et al., 2016) found a pattern, primarily in the right hemisphere, of fronto-parietal and basal ganglia activation common to timing and increased cognitive effort in SZ.

We aimed to determine whether SZ and BD patients show a dysfunctional activity pattern in a timing circuit, and whether such a pattern matches that involved in cognitive control. To this end, we conducted two signed differential mapping (SDM) meta-analyses of functional magnetic resonance imaging (fMRI) studies assessing the brain response to increasing levels of cognitive difficulty: one meta-analysis concerned SZ patients, the other BD patients. We also conducted a similar SDM meta-analysis on neuroimaging of timing in SZ. Then, we carried out a final multimodal meta-analysis to identify common brain regions in the findings of the two previous SDM meta-analyses that explored cognitive difficulty and timing, respectively, in SZ (no studies in BD could be included). We hypothesize that an impaired temporal/cognitive control network underlies disruptive