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Temporal processing in schizophrenia: Review

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ABSTRACT

We review the main contributions of the cognitive neuroscience literature in the field of time processing in schizophrenia. First, we summarize the theoretical concepts and terminology related to time and time estimation and the characterization of this deficit in the illness. Second, we thoroughly review the neuroanatomical basis of this deficit and its interactions with other cognitive processes and clinical symptoms. Third, we specifically highlight the main findings of studies that have analyzed temporal discrimination using cognitive tasks performed during functional neuroimaging.

Summary: This review aims to summarize the main findings of the neuroscientific and cognitive literature on temporality in schizophrenia. First, we will provide a brief introduction regarding the theoretical and conceptual issues and then will delve into the importance of their disturbance in this disorder, particularly underlying brain structures and the interactions they have with other cognitive dysfunctions and psychopathological symptoms. This review includes different studies that describe both behavioral and neuroscientific approaches, although it focuses especially on tasks of temporal discrimination on the milliseconds scale and on the studies that use functional neuroimaging techniques.

1. Introduction

Temporal processing, relevant in human behavior and cognition, interests various disciplines, such as Philosophy, Medicine and Psychology. In the literature, studies on dysfunctions in temporal processing in people with brain pathology, pharmacological/toxicological inductions or psychiatric disorders, such as schizophrenia, stand out (Grondin, 2010).

Since the beginning of last century, phenomenological, clinical, and neurobiological observations point to alterations in temporal processing in this disorder (Bonnot et al., 2011). Such alterations are considered key by some models of its pathogenesis, such as *cognitive dysmetria* (Andreasen, 1999). Neuropsychological research on temporality in schizophrenia facilitates understanding of its neurobiological and cognitive disturbances and how they contribute to the condition's symptoms.

There are several terms and classifications to define this function. There is a distinction between *temporal perception*, referring to more passive elements, such as the perception of intervals, and *motor temporality*, which refers to the temporal organization of motor or cognitive acts (Neufang et al., 2008).

2. Theoretical approaches

Faced with the more traditional approach, which defends the existence of a central mechanism or internal clock, other approaches propose a differentiation according to the information used for temporal estimation. While chronobiological models are based on environmental information, cognitive models consider the contribution of attentional and memory processes. Among the latter, *Temporal Oscillator* (Treisman, 1963) and *Scalar Timing* (Gibbon et al., 1984) processes stand out. The latter is the most quoted contemporary model and consists of five components distributed into three processes: clock (pacemaker and switch), memory (accumulator or working memory and reference memory) and decision (comparator). It can also be defined as a time processing system made up of three levels: clock (pacemaker-switch-accumulator), memory (working and reference memory) and decisional.

The idea of a simple pacemaker-accumulator system has been abandoned because of its lack of neurobiological plausibility. Matell and Meck (2004) have proposed the *Striatal Beat Frequency Model*, whereby a cortico-striatal circuit underlies temporal processing.

3. Experimental paradigms

The psychophysical approach distinguishes between two classical paradigms of evaluation. The one paradigm as *temporal perception, estimation of intervals or discrimination of duration*, implies comparing time intervals. The so-called *temporal production, tapping or motor timing* is the vocal or physical reproduction of a series of tones at a certain rhythm (Correa et al., 2006).

Another possible classification distinguishes between tasks of estimation and temporal comparison, highlighting two versions: *temporal generalization* and *temporal bisection* (Grondin, 2010).

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Coull and Nobre (2008) distinguish between *explicit* and *implicit* temporality. Finally, the paradigm of *temporal discrimination* evaluates the simultaneity threshold by showing pairs of identical stimuli separated by an inter-stimulus variable interval (Pastor et al., 2006).

4. Anatomical and functional correlates

The study of temporal representation in the brain questions whether there is a specialized structure or a neural circuit distributed between different structures. Research using functional magnetic resonance imaging (Buhusi and Meck, 2005) or positron emission tomography (Ortuño et al., 2002) proposes the activation of a cortico-subcortical network during the execution of temporality tasks.

In his research using functional neuroimaging in a healthy population, two recent meta-analyses (Ortuño et al., 2011; Wiener et al., 2010) stand out. They agree on the involvement of a group of cortical and subcortical regions: the left inferior frontal, the bilateral supplementary motor area, the left inferior parietal, the temporal regions (bilateral insula) and the left putamen. The consensus on specific circuits underlying the different time scales is increasing: subcortical structures on the order of milliseconds and cortical ones on the order of seconds. In schizophrenia, a dysfunctional involvement of these networks has been observed, with widespread hypoactivation of the right hemisphere.

The cortico-cerebellar-thalamic circuit underlying temporality is involved in the pathophysiology of schizophrenia. This circuit includes the bilateral supplementary motor area, the middle frontal cortex, the inferior parietal, the posterior cerebellum, the thalamus, the right middle frontal gyrus, the insula, the left putamen and the left superior temporal gyrus. Compared to healthy controls, these patients show signs of dysfunction in neuroanatomical regions involved in this function (i.e., the supplementary motor area, the striatum and the insula/operculum); these dysfunctions become more pronounced with increasing task difficulty (Davalos et al., 2011).

Evidence of the participation of each particular region comes from studies of brain injury and transcranial magnetic stimulation. Disturbances in temporal perception tasks in patients with lesions in the cerebellum, basal ganglia, supplementary motor area, prefrontal cortex, inferior parietal areas and right parietal supramarginal gyrus have been observed (Gómez et al., 2014).

5. Electrophysiological studies

The physiology of temporality, dependent on synchronized neural oscillations, particularly on dopaminergic neurotransmission systems, is deficient in schizophrenia (Waters, 2013). Abnormal dopamine activity (DA) in the fronto-striatal network means more clock speed and an underproduction of intervals (Penney et al., 2005). This abnormal activity contributes to the temporal deficits observed in dopaminergic disorders such as schizophrenia, attention deficit disorder and hyperactivity disorder (ADHD) or Parkinson's disease (Carroll et al., 2009). Pharmacological studies suggest a hypersensitivity of this function to dopaminergic modulation, but research on the effects of its administration is inconsistent. While agonist agents of DA (cocaine and methamphetamine) produce a slowing of perceived time, antagonists (e.g., haloperidol) generate a shortening of subjective time (Papageorgiou et al., 2013).

6. Genetics

Both individuals with schizophrenia and those at high risk of developing it have shown deficits. Temporal disturbance seems to share genetic risk factors to schizophrenia and can be used as a specific marker in identifying individuals who are at high risk of developing the disorder (Ward et al., 2011). Meck (1986) argues that the D2 receptor modulates the internal clock speed. It is not surprising that its dysfunction, as in schizophrenia, can lead to poor processing of intervals. Wishart et al. (2011) postulate that genetic variations in the dopamine system can act together to generate individual differences in cognitive ability. According to Gómez et al. (2014), genetic factors (e.g., catechol-O-methyltransferase [COMT] or ankyrin repeat and kinase-containing domain 1 [ANKK1]) are thought to be associated with both temporality and schizophrenia.

7. Behavioral studies

Although evidence of temporal deficit in schizophrenia is consistent, its description remains nonspecific (Roy et al., 2012). Ward et al. (2011) propose it as a general cognitive phenotype of this disorder. Comparison of the results obtained is complex due to the differences between the experimental conditions and the lack of a standardized and validated test.

Several authors agree in their observation of a tendency to overestimate and underproduce temporal durations (Papageorgiou et al., 2013). While initial studies report conflicting results about the direction of the deficit (both overestimations and underestimations), other more recent studies show greater consistency in their results. They define this dysfunction as "highly variable" without leaning towards a specific direction (Lee et al., 2009).

8. Interaction with other cognitive processes

Temporality and other cognitive processes, such as attention, automatic or controlled behavior change, working memory and the degree of concentration required depending on the level of difficulty of the task share some brain networks (Gómez et al., 2014).

According to the theory of scalar timing, poor discrimination of intervals in schizophrenia stems from a dysfunction of the comparator in the decisional stage coupled to the memory stage. The greater speeds of production and reproduction variability suggest a decline in the accuracy of the internal clock (Papageorgiou et al., 2013).

The difficult objective assessment of the supposed internal clock has led to dependence on tasks involving both a temporal component and other non-specific cognitive domains for time (Lee et al., 2009). Execution appears disturbed in tasks sensitive to frontal, temporal, and parietal functions and those of the hippocampus, striatum and cerebellum. This cognitive deficit is characterized by disturbances in working memory, attention and executive functions, which are essential for precise temporal processing (Gómez et al., 2014). Such a deficit shows lesser cognitive involvement in the discrimination of short durations and automated processes; in its assessment, short intervals (50–500 msg) and pre-conscious measures are used (Roy et al., 2012).

The difficulty in controlling the involvement of other cognitive domains in execution contributes to the continued debate over the specificity of the temporal dysfunction. It is questionable if temporal dysfunction is associated with a disturbance in the central temporal processes or if it is attributable to cognitive or biological dysfunction (Bonnot et al., 2011).

Temporality and other executive components, such as interference control, seem to share a neuroanatomical basis in the early stages of development, postulating the requirement of neuroanatomical and functional components of the temporal processing for proper cognitive control (Radua et al., 2014).

A further aspect of any cognitive process is *cognitive effort*, the perceived level of difficulty of the task and the consistent applied mental effort required to achieve its objective. To examine whether there is a brain region simultaneously involved in all of these