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## **Time processing impairments in neurological and psychiatric disorders**

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## **Abstract**

A central question in understanding cognition and pathology-related cognitive changes is how we process time. However, time processing impairments across several neurological and psychiatric disorders remains seldom investigated, with no unified understanding. In this review, an international group of experts from different backgrounds (cognitive psychologists, neurologists, psychiatrists, and clinical neuropsychologists) present their reflections for a taxonomy of time processing, and a neuropsychological approach of their various impairments. Four main temporal aspects are discussed: duration processing, simultaneity perception and synchrony, passage of time, and mental time travel. We review time processing impairments in several neurological and psychiatric disorders (e.g., schizophrenia, autism, Alzheimer's dementia, PTSD) and highlight the most promising avenues for improving diagnostic and therapeutic approaches to time processing alterations.

## **Towards a neuropsychology of time processing**

Although certainly one of the most fundamental dimensions of cognitive functioning, time and its processing by the brain, together with its various impairments, are seldom studied and understood. Time is indeed intertwined with many mental processes, such as **sensorimotor integration**, motor planning, attention and memory[1]. For example, playing music or understanding speech relies on the accurate perception of time (intervals, durations) at the millisecond scale. Time processing covers different temporal scales ranging from a few milliseconds to several seconds, minutes, hours or even years, with different mechanisms underlying the processing of each temporal dimension. It is also crucial for **mental time travel** in the personal past and the future, providing meaning in life and its temporal passage. Given this critical role for cognition and its extended neural bases, time processing is highly sensitive to developmental and pathological changes. Yet, knowledge about timing impairments across several neurological and psychiatric disorders remains limited, with no unified understanding of its associated cognitive and neural alterations.

The diversity of psychological and neuropsychological models of time processing has been the focus of several reviews in the previous decades[2–4]. Here, we do not propose to review the theoretical and experimental findings related to timing. Instead, we will focus on time processing impairments across several neurological and psychiatric disorders. Indeed, there is currently a gap between fundamental research on time processing and clinical applications across disciplines (i.e., development, psychiatry, neurology). Adopting a neuropsychological perspective on time processing alterations would have a twofold advantage: a) it would lead to a better understanding of patients' subjective difficulties, and b) it would deepen our knowledge of time processing by specifying how it differs across pathologies as well as its development throughout the lifespan.

In this review, an international group of experts from different backgrounds (cognitive psychologists, neurologists, psychiatrists, and clinical neuropsychologists) present their reflections on the nature of time processing and on a neuropsychology of its various impairments. As such, this article benefits from a growing body of work on clinical aspects of time processing while also providing a clear taxonomy of timing mechanisms and their associated disorders. Four main temporal aspects are discussed (Figure 1): I) **Duration processing**; II) **Simultaneity and temporal order**; III) **Feeling of the passage of time**; IV) **Mental time travel**. In this article, we review time processing impairments in several neurological and psychiatric conditions (e.g., schizophrenia, autism, Alzheimer's disease) and highlight the most promising avenues for improving diagnostic and therapeutic approaches to time processing alterations. Finally, we provide concluding remarks and recommendations for future work.

### **Duration production, reproduction, and comparison**

Asking participants to produce, to reproduce or to compare durations ranging from about 500ms to about 30s is the most common method of assessing duration processing, yielding measures of duration representation and temporal comparison. The neural bases of these measures have been described in recent reviews[4,5] (Figure 2), with the identification of two neural networks. A first network is engaged in the processing of time intervals of less than one second, and mainly involves the cerebellum and subcortical regions[5]. A second network is involved in the processing of intervals of more than one second (up to about tens of seconds), and includes cortical regions such as medial frontal regions, the supplementary motor area, superior temporal gyrus and inferior parietal lobe. Regarding the **M/EEG** brain rhythms involved, reduced alpha (8-13Hz) peak frequency has been associated with longer temporal productions[6], suggesting an association between individual oscillatory characteristics and time processing performance. In this line, the more alpha synchrony is observed with a displayed stimulus, the longer the

perceived duration[7]. Furthermore, an association between beta-band power (13-30 Hz) and temporal decisions has been highlighted, with increased beta oscillations associated with longer durations[8].

Investigation of duration processing provides information about normal and pathological developmental trajectories. Time perception develops early, through the perception by the fetus of maternal **circadian rhythms**, of their mother's movements and speech **prosody** [9,10], then through parent-child interactions [11]. Implicit duration estimation abilities have been reported in babies [12], and show developments during childhood mainly through motor and spatial representations [13]. The transition to explicit time perception (i.e., rules based on a concept of time) has been reported in children between five and seven years [14], and is associated with the development of attention and working memory abilities [14][15].

Relative to young adults, older adults produce longer durations and make shorter estimations[16]. These age-related differences were larger for intervals over a second and were associated with working memory and processing speed performance[17]. Most importantly, a larger variability of duration production and discrimination have been consistently reported in older individuals[18]. Findings were interpreted as reflecting a *slowing down of the internal clock*, and a less precise maintenance and encoding of temporal information with advancing age, associated with decreased memory and attentional capacities[17]. Aging effects on time processing may emerge as a consequence of even subtle dysfunction of fronto-striatal circuits[19], and age-related changes in time processing could be considered as a marker for cognitive decline in older adults[20].

Impairments in duration processing can result in incorrect estimation or production of time intervals, which are judged as being shorter or longer than their objective durations. Timing difficulties may also result in increased variability of performance across trials and tasks, in line with a decreased precision of temporal representations. Time processing difficulties have been

extensively described in attention-deficit/hyperactivity disorder (ADHD), and may be related to its core symptoms (i.e., inattention, impulsivity, hyperactivity)[21]. Children and adolescents with ADHD tend to overestimate durations[22], which may suggest a *faster internal clock* in this condition. In adolescents, duration underestimations of intervals over a second have been reported in **anorexia nervosa**[23], while duration overestimations of intervals over a second were observed in obesity[24]. Mixed results have been reported about duration estimation in autism[25,26], with a trend towards underestimations of intervals over a second.

Parkinson's disease (PD) is the first identified disease impacting time processing, mainly in supra-second intervals, which led to the identification of the critical role of dopamine [27]. Indeed, PD patients are impaired in duration production and discrimination tasks, with altered comparisons performance, and duration overestimations relative to controls[28]. However, the exact nature of time processing impairments in PD remain unclear, because of varying and sometimes uncontrolled dopaminergic medication[29]. Cerebellar disorders (e.g., strokes, tumors, or genetic degenerative disease), have also been associated with impaired duration processing. This impairment was mainly observed for short durations (below two seconds) and in timing motor tasks[30]. Recent meta-analyses of time processing in depression[31,32] also revealed that individuals with depression tend to overproduce short durations and underproduce longer durations relative to controls[33]. Although this should be further investigated, as lower working memory and attention abilities may contribute to altered temporal performance, changes associated with depressions were interpreted as reflecting a slower internal clock in depressed individuals[31], with a *slower internal clock*. This highlights the influence of emotions on duration estimation abilities, along with other temporal aspects (see the felt passage of time section). Finally, adults suffering from post-traumatic stress disorder (PTSD) showed overestimations of intervals over a second[34].

### **Simultaneity and temporal order**

Perception of simultaneity and temporal order are assessed using tasks involving decisions about the timing of two distinct events (as to whether they occur at the same time or follow each other), and the detection of deviations in rhythmic series of stimuli. Tasks asking subjects to press a button in synchrony with a stimulus, which also require sensory-motor adjustments, are also used. This section includes both simultaneity and temporal order, although discussions exist in the literature regarding the common or distinct processes involved[35]. One may further distinguish between rhythmic information (i.e., repeated signals), and simultaneity/order when it is explored with only two stimuli. The literature on rhythm vs. simultaneity/order often addresses different questions, respectively the synchronization with an external rhythm[36], in the context of music[36], language[37] or dancing[38], and the temporal structure of mental activities[39], in which successive events may occur irregularly. Here, we group these topics, consistent with some previous work [40], and given the fact that rhythms, simultaneity and order all participate in the timing of perceptions, as opposed to the perception of time. At the neural level, simultaneous and synchronized activity correspond to major properties of brain activity that have been associated with cognitive functioning. EEG studies have associated pre-stimulus alpha band activity with visual simultaneity judgements[41]. Sustained synchronized activity between frontal and parietal regions has also been associated with the maintenance of temporal representations and detection of deviations[42,43]. Neuroimaging studies also highlighted the implications of the left temporal and parietal cortices in simultaneity processing [44], whereas rhythm, and more specifically the perception of beats has been related to basal ganglia[45].

Even before birth, the intrauterine environment provides many rhythmic stimuli to the fetus, both auditory and vestibular, and the fetus also produces numerous endogenous and motor rhythms (heart rhythm, sucking rhythm, kicking rhythm[46]). Consequently, at birth, newborns are able, under certain conditions, to synchronize their own spontaneous motor tempo with the



rhythmic stimuli of their environment[47]. Because the cerebellum plays a critical role in timing sub-second intervals[48], children with a medulloblastoma, a highly malignant embryonic tumor of the cerebellum, exhibit longer and more variable inter-tap intervals in their spontaneous motor tempo and their rhythmic synchronization activity than control children[49]. Throughout the lifespan, simultaneous and synchronized events' occurrence play a decisive role in the processes that enable the encoding of perceptual experiences in the form of synaptic traces. At the cellular level, associative memory is indeed determined by a temporal factor of simultaneity, based on long-term depression and long-term potentiation[50].

Alterations to the perception of simultaneity and temporal order between two stimuli or behaviors have been associated with the feeling that time disappears or is disorganized, suggesting that both simultaneous and successive information processing provides an important sense of continuity in experienced events. Conversely, atypical rhythmic patterns of parent-child interactions have been reported in maternal depression[51], and autism[52]. Individuals with schizophrenia self-report strange experiences of time, like a fragmentation of the experience of time[44]. Yet, patients have difficulties in verbally describing their experiences, and the lack of a clear taxonomy of the different timing mechanisms complicates the investigation of these disorders. Recent work revealed that sequences of visual signals were predicted in time in healthy controls, allowing them to automatically anticipate and follow incoming signals at the millisecond level[53]. However, many asynchronies are not pertinent in daily life, and are ignored in healthy volunteers, thus producing the experience of living in a stable environment[54]. Individuals with schizophrenia have difficulties in detecting whether two successive visual signals are asynchronous or simultaneous[55]. Yet, short and undetected asynchronies incidentally affect the behavior of those individuals, suggesting they are abnormally sensitive to short, sub-threshold asynchronies [54]. In fact, short asynchronies seem to be more difficult to ignore in patients than in controls. The disruption induced by these short

asynchronies has been associated with a decreased feeling of control in patients during motor actions, when the sensory consequence of the action is slightly delayed [54], which highlights the association between millisecond-level synchrony impairments and clinical disorders (the altered sense of self and delusions of control).

Temporal aspects of cognitive functioning critically rely on extended processing and integration time windows. Neural synchrony is a fundamental principle that provide the functional basis for these time windows[56]. The temporal resolution for information integration measured by M/EEG has been proposed to involve gamma oscillatory cycles(30+Hz)[56], while theta (4-8Hz)/alpha oscillatory cycles would reflect a window for the encoding of sensory information[2]. Such complex and temporally specific communication organization is expected to be highly sensitive to pathology effects. Perturbations of neural synchrony could therefore be central in the investigation of pathology effects on time processing [57,58]. Patients with PD show increased temporal variability of short interval estimations, in association with reduced EEG delta (1-4Hz) midfrontal synchrony[59]. Importantly, such delta reduction predicted the precision of subsequent behavioral temporal estimations, and general cognitive performance scores[60]. Relatedly, patients with schizophrenia showed a reduced parietal alpha synchrony[61] during completion of a simultaneity discrimination task, which was associated with an abnormal sensitivity to short asynchronies in patients.

### **The feeling of the passage of time**

Marcel Proust wrote in *Within A Budding Grove* (1919) that “*the time which we have at our disposal every day is elastic; the passions that we feel expand it, those that we inspire contract it; and habit fills up what remains*”. While being a widely accepted and intuitive phenomenon, the mechanisms underlying the feeling of the passage of time and the influence of emotions have long remained elusive[62]. This phenomenological experience of time has been assessed using questionnaires and self-report scales, together with retrospective assessments of the

durations of past events, which can appear as accelerated or dilated as a function of the context or individuals' characteristics[3]. At the neural level, sustained brain oscillations, and ramping brain activity over time have been interpreted as reflecting the activity of the system accumulating time passage at a faster or a slower pace[2,4]. Recently, bursting activity in the alpha band at rest has been associated with the participant's retrospective estimate of the session's duration[63]. This accumulation has also been associated with activity in the supplementary motor area (SMA[64]), and the insula[65]. However, the feeling of the passage of time also involves understudied high-level cognitive processes related to consciousness, including self-awareness in time[62].

A disrupted sense of the passage of time can lead individuals to interrupt an activity they just started, thinking "enough time" has passed, or conversely to pursue an activity for an exaggerated period of time[66]. Mixed evidence for a faster passage of time in normal and pathological aging has been reported in previous decades, depending on whether the passage is assessed in short (present passage of time) or long periods of life (e.g., 5-10 years). No age effect was observed for the present passage of time judgment. However, from the age of 50 years, a small yet significant increase in the feeling that the passage of time accelerates as one gets older has been reported[67]. Conversely, other work[68] found no general age effect on the subjective passage of time, but age-related differences were observed when controlling for routines and daily activities, possibly partly reflecting the decreased frequency of new life experiences with advancing age[68]. A faster passage of time has also been reported in patients with mild cognitive impairment[69] and Alzheimer's disease[70] relative to age-matched controls, which has been associated with episodic memory impairments.

In retirement homes, negative mood and a feeling of a slower present passage of time have been reported in older individuals[71]. Emotions indeed play a critical role in modulating the daily experience of time[72]. Mood and affective disorders have been associated with accelerated or

slowed down passage of time[73], with for example anxiety disorders being associated with slowed down passage of time[74]. Regarding depression, recent meta-analyses[31,32] highlight an interesting double dissociation of how time is differently perceived and represented. Depressive patients frequently report perceiving time as passing very slowly at the scale of days or weeks, while present felt passage of time can appear as going too fast[75]. Because such slowing in felt passage of time has been associated with suicide contemplation[76], changes could constitute an indicator of impaired cognitive functioning or mental health issues.

An MEG study[77] investigated the neural activity involved in estimating a one-minute duration using MEG in medicated and unmedicated adults with ADHD, relative to a control group. Unmedicated, individuals with ADHD were less accurate in estimating elapsed time passage and had reduced gamma activity in the anterior cingulate, supplementary motor area, and left prefrontal cortex compared with controls. Medication in these same individuals was associated with an increased gamma activity and reduced behavioral differences. A persistent alteration of temporal processing has also been observed in PTSD, with a reported feeling of being “stuck in time”[78]. However, the investigation of judgment of long durations of several minutes is still very rare, and the underlying mechanisms remain poorly understood[79].

### **Mental time travel**

Mental time travel refers to the ability to flexibly navigate across layers of temporal representations that encapsulate a person’s life, including memories of the past and simulations of future events[80]. Retrospective time judgments and the recall of past events, together with the anticipation and planning of future activities, are intimately related[81], and involve partly similar processes[82]. Remembering past events and simulating future events commonly engage regions of the **default mode network**, including the medial temporal lobes, midline cortical structures, and temporal and inferior posterior parietal cortices[83]. Temporal order judgments in memory, as well as the encoding and retrieval of event sequences, have

specifically been associated with the hippocampus, and ordering autobiographical events also involves the left superior temporal gyrus and medial frontal gyrus[84].

Neuropsychological studies have shown the presence of parallel deficits in episodic memory and future thinking in various populations, including patients with hippocampal lesions[85], healthy older adults[86], and patients with Alzheimer's disease[87]. Other evidence has also highlighted the role of semantic memory in the construction of future thoughts[88]. Future thinking abilities have indeed been associated with the functional integrity of bilateral superior medial frontal gyri and anterior hippocampus, and were impaired in patients with semantic dementia[89], while episodic autobiographical memory was relatively preserved. This suggests a pivotal role of semantic memory in providing schemas and meaning to construct a plausible scenario of personal events in the future[90]. Furthermore, general knowledge about the self (e.g., personal traits and goals), and one's life allows one to place recalled and imagined events in a personal temporal context, on a personal timeline representing one's life story[80].

Many psychological disorders—including depression, anxiety, schizophrenia, and personality disorders—are also associated with deficits in memory and future thinking[91,92]. A reduced capacity for mental time travel has been reported in autistic children[90], while neurotypical children learn to plan or prepare for the future between age five and nine years[93]. **Diachronic thinking** also poses difficulties for autistic individuals[94]. Another paradigmatic example of future thinking impairment is schizophrenia. Individuals with schizophrenia not only have difficulties remembering specific events from their personal past, but are even more impaired at imagining specific events that might happen in their personal future [95]. Furthermore, individuals with schizophrenia use temporal landmarks and contextual details less frequently to locate events in time, and make more errors when determining the order of past and future events [96]. Difficulties in organizing and making sense of past and anticipated events are common to both schizophrenia [97] and autism[90,98], and may contribute to alterations in the

sense of self and identity. Altered memory mechanisms may also prevent individuals with PTSD from distancing themselves from the traumatic event and lead to difficulties in imagining and pre-experiencing detailed future events [99]. Indeed, imagined future events appear strongly negative, or related to the initial traumatic event[100]. As a result, individuals with PTSD are more likely to attribute a central role to the traumatic event in their self-image, with this experience becoming a reference point in the organization of autobiographical knowledge and in the individuals' identity[101]. Given the various forms that future thinking can take (i.e., simulation, prediction, intention, and planning[102]), important work remains to specify the nature of altered mental time travel processes across pathologies.

### **Concluding remarks and future perspectives**

The present consortium work was a unique opportunity for exchanges between clinicians and researchers exploring different aspects of time processing, and for discussions on their developmental changes and alterations in pathology. In this article, we focused on time perception and timing abilities in patients and across the lifespan to emphasize the need for a neuropsychological approach to time processing, based on a growing body of developmental, neurological, and psychiatric work. This approach remains in its infancy and has not yet been integrated into common clinical practice. This could partly reflect the recency of models of time perception and their behavioral validation[2], and that previous experimental research focused on the psychophysical sense of time (i.e., time perception) in healthy individuals. This could also come from the elusive nature of time (*"What is time then? If nobody asks me, I know; but if I were desirous to explain it to one that should ask me, plainly I do not know"*, St Augustine). We propose that time processing could represent a key characteristic of several developmental changes and pathological processes. In turn, research on developing or altered timing abilities may also help moving forward towards understanding time processing. This approach could

provide a mechanistic and unified account of timing impairment, and evidence-based approaches for enhancing time processing abilities and associated brain activity.

First and foremost, it is crucial, if we want to accurately identify the diversity of time processing impairments, to ask patients about the different facets of time reviewed in this article: changes in felt passage of time, difficulties estimating durations, difficulties following other's rhythms and synchronizing to it, difficulties following the flow of information, and alterations in mental time travel. Temporal processing should indeed be assessed in a more in-depth and detailed way than the temporo-spatial orientation included in general cognitive tests. A key step towards a neuropsychology of time also involves using tasks with high sensitivity and specificity to temporal aspects of cognition. Although we have discussed different aspects of time processing in separate sections, they operate concurrently and mutually affect each other. However, the formalization of the involved processes and their interaction remain a work in progress. Here, we emphasize that some well-documented patient difficulties previously interpreted as planning, memory, or attention deficits could potentially be reconceptualised as reflecting time processing impairments. As an example, the reduced speed of processing with advancing age is highly related to longer temporal representations[17]. Moreover, memory impairments could involve impaired temporal ordering abilities, and altered future projection capacities.

The reviewed work and current questions also pave the way to new non-pharmacological interventions that could target time processing aspects, and aim at enhancing cognitive performance. Virtual reality can causally influence the subjective feeling of time passing, and enable the assessment of time processing abilities in ecological situations[103]. Communication-focused therapies have also been proposed to increase parent-child synchrony[104] in children with autism. Moreover, mindfulness meditation has been associated with faster felt passage of time and increased precision of temporal representations[105,106], which suggests it could be promoted in a variety of clinical situations. Finally, music could

entrain and enhance brain rhythms of time processing. Indeed, brain's oscillatory activity is sensitive to the rhythmic structure of sensory input, and neuronal rhythms tend to align to external rhythmic output[107]. Because of neural entrainment, fast music leads to duration overestimation, and slow music to underestimations[108]. Musicians were also found to outperform non-musicians in temporal tasks by showing higher temporal sensitivity for small temporal differences between stimuli, and showing a smaller variability in temporal estimates[109], in line with the potential long-term effects on the encoding and retrieval of temporal representation.

Several open questions remain, as for example whether asynchrony detection and ordering difficulties overlap, although distinct impairment of one or the other have been reported[110]. The potential link between time processing processes across the different timescales also remains an open question. Specifying these points could provide critical information about the time scales that could be the most relevant to a given neurological or psychiatric impairment. Future research may thus aim at identifying associations and dissociations of impairments across these aspects and across time scales. The proposed taxonomy of time processing could further our understanding of both individual variability and differences across disorders. Importantly, other tasks and temporal aspects have not been addressed in the present work. For example, the temporal perspective refers to the focus and valence relative to present, past, and future personal events[111]. Although this was not the main focus of this article, individual differences and impairments in various pathologies have been reported in temporal perspective[112,113]. Progressing towards a neuropsychology of time processing will further our understanding of temporal impairments in clinical disorders for different types of temporal judgments and at different time scales.



## Figures

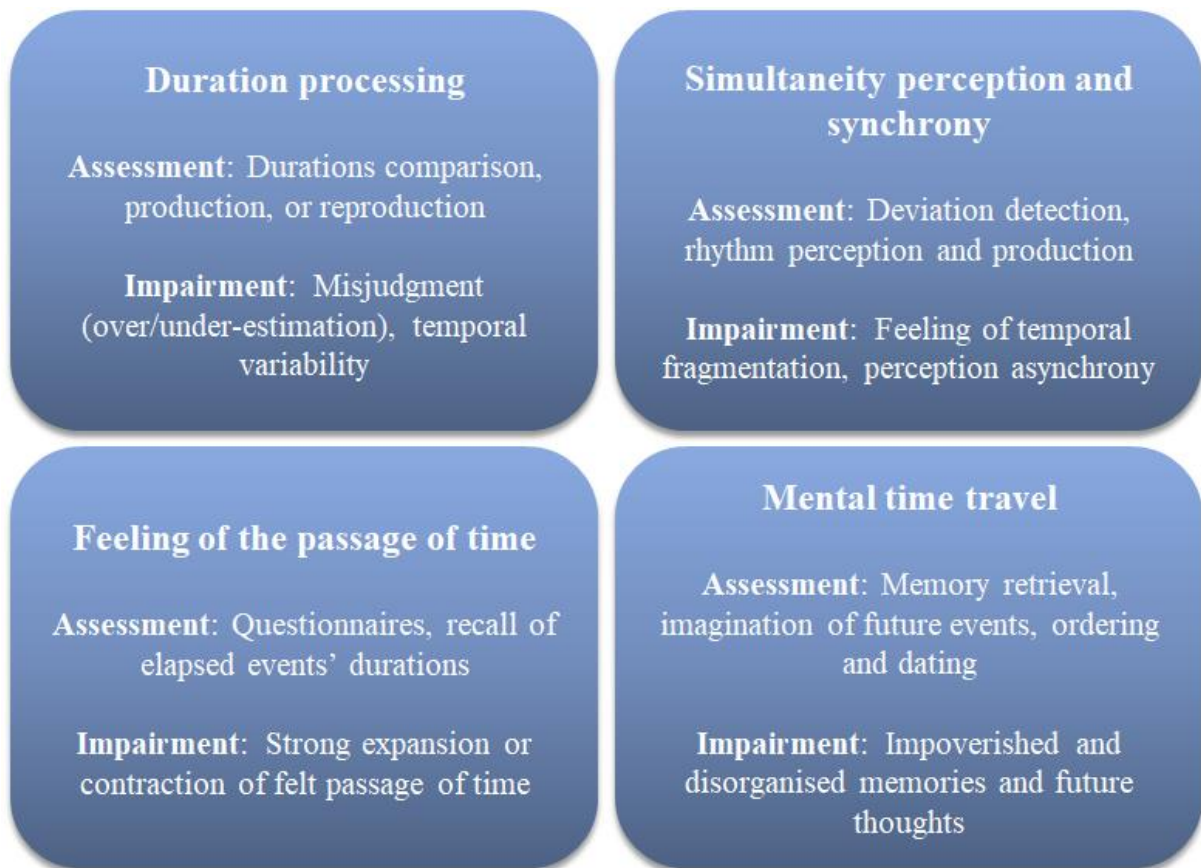


Figure 1: Summary of the four main aspects of time processing, their assessments and a tentative summary of possible difficulties associated with their impairment.

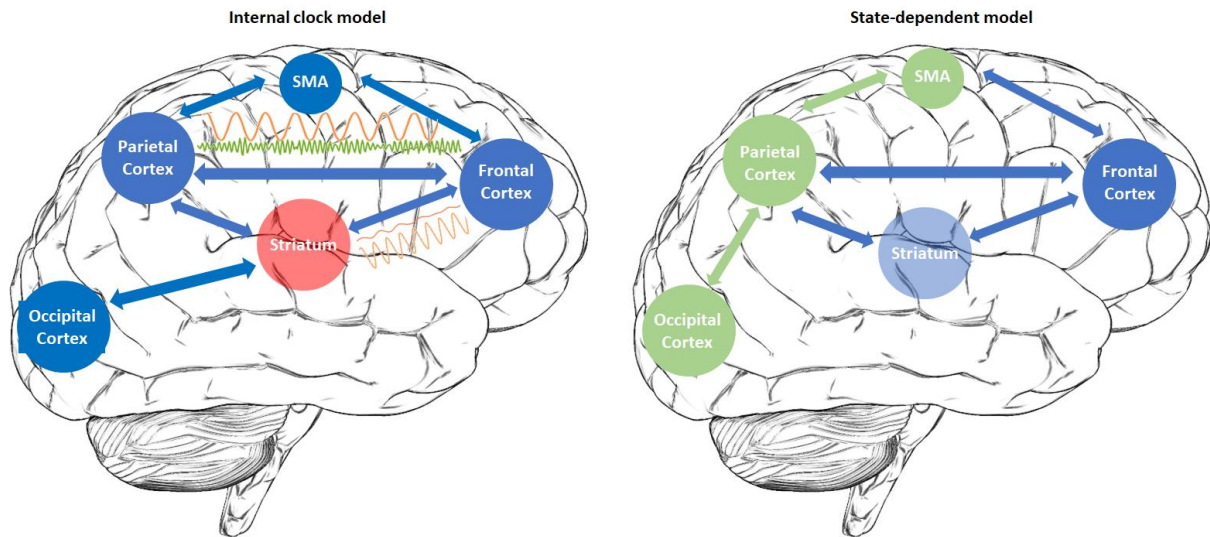


Figure 2: Summary of the two frameworks of the neural bases of cognitive time: In the Internal clock model, a centralized timing mechanism in the striatum (red) generates temporal information based on the detection of neural synchrony across cortical regions in different frequency bands (orange and green); In the state-dependent model, temporal representations A (green) and B(blue) are encoded in distinct spatial and temporal states of network activity. According to the SBF model, temporal representations are associated with pulsatory activity in the striatum, while they reflect a given network state in a distributed model. SMA: Supplementary Motor Area.

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