Review

Neural networks engaged in milliseconds and seconds time processing: evidence from transcranial magnetic stimulation and patients with cortical or subcortical dysfunction

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Here, we review recent transcranial magnetic stimulation studies and investigations in patients with neurological disease such as Parkinson's disease and stroke, showing that the neural processing of time requires the activity of wide range-distributed brain networks. The neural activity of the cerebellum seems most crucial when subjects are required to quickly estimate the passage of brief intervals, and when time is computed in relation to precise salient events. Conversely, the circuits involving the striatum and the substantia nigra projecting to the prefrontal cortex (PFC) are mostly implicated in supra-second time intervals and when time is processed in conjunction with other cognitive functions. A conscious representation of temporal intervals relies on the integrity of the prefrontal and parietal cortices. The role of the PFC becomes predominant when time intervals have to be kept in memory, especially for longer supra-second time intervals, or when the task requires a high cognitive level. We conclude that the contribution of these strongly interconnected anatomical structures in time processing is not fixed, depending not only on the duration of the time interval to be assessed by the brain, but also on the cognitive set, the chosen task and the stimulus modality.

Keywords: time perception; timing; stroke; transcranial magnetic stimulation; repetitive transcranial magnetic stimulation; Parkinson's disease

1. INTRODUCTION

Although, at first glance, time can be considered as a linear function, the way in which the brain builds up a mental representation of the passage of time seems to be a much more complex phenomenon. Our brain needs to estimate the passage of brief intervals of time with very high precision in order to perform extremely elaborate actions, such as athletic or artistic performances. On the other hand, this cognitive function is crucial for everyday life, as it is necessary for the accomplishment of the most usual activities in which we continuously keep in mind the passage of time, during several seconds or minutes (i.e. making a coffee, waiting for a traffic light). Moreover, our perception of time is flexible since we continuously experience subjective changes in the flow of time depending on

the current emotional or cognitive context (i.e. Nobre & O'Really 2004; Droit-Volet & Meck 2007; Eagleman 2008; Wittmann & Paulus 2008). In the past years, efforts have been made by neuroscientists to elucidate how all these complex interplays are coded by the brain. On the basis of recent studies conducted in animal models, in healthy subjects and in patients with neurological diseases, a new framework is emerging. Specific and interconnected brain regions are involved in processing time intervals depending on the duration, the task or the stimulus modality. The basal ganglia and the cerebellum have been proposed as time generators (Harrington *et al.* 1998a,b; Spencer *et al.* 2003; Ivry & Spencer 2004; Ivry & Scherf 2008), as well as many cortical areas such as the parietal and dorsolateral prefrontal areas whose role remains controversial (Lewis & Miall 2006). Even if incomplete, we will try to describe this picture in the current paper, focusing on the recent evidence provided by patients with neurological diseases such as Parkinson's disease (PD) and stroke, together with studies using repetitive transcranial magnetic stimulation (rTMS) to influence cortical excitability.

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One contribution of 14 to a Theme Issue 'The experience of time: neural mechanisms and the interplay of emotion, cognition and embodiment'.

2. SUB- AND SUPRA-SECOND INTERVAL TIME SCALES

Based on the relevant time scales and the presumed underlying neural mechanisms, temporal processing has been categorized into four time scales: micro-seconds; milliseconds; seconds; and circadian rhythms (Mauk & Buonomano 2004). Interval timing in the seconds to minutes range is crucial in decision making and foraging, whereas millisecond timing is required for motor control, speech, playing music and dancing (Buhusi & Meck 2005). Temporal processing of milliseconds and seconds time intervals may depend on different neural networks (Gibbon *et al.* 1997; Ivry & Spencer 2004) and a number of evidence suggests that these are possibly measured by independent brain mechanisms (Lewis & Miall 2003a). Michon (1985) argued that the temporal processing of intervals longer than approximately 500 ms is cognitively mediated, whereas the temporal processing of shorter intervals is supposedly of a highly perceptual nature, fast, parallel and not accessible to cognitive control.

In a first attempt to provide experimental evidence for two distinct timing mechanisms as a function of interval duration, Rammsayer & Lima (1991) found that temporal processing of intervals ranging from 50 to 100 ms is unaffected by a secondary cognitive task, whereas temporal processing of intervals in the range of seconds was markedly impaired by the same task. Based on these findings, they concluded that the timing mechanism underlying the temporal processing of intervals in the range of seconds could be influenced by concurrent cognitive processing. On the other hand, the timing mechanism involved in the temporal processing of intervals in the range of milliseconds appeared to be uninfluenced by concurrent cognitive processing and, thus, was considered highly sensory in nature and beyond cognitive control. This view has been supported by recent neuroimaging studies of timing (Lewis & Miall 2003a,b), which provided some evidence for two distinct neural timing systems: a more automatic timing system for measuring brief intervals in the subsecond range and a cognitively controlled system for temporal processing of intervals in the supra-second range.

3. SUBCORTICAL STRUCTURES: THE CEREBELLUM

The importance of the cerebellum in motor timing is well documented. Cerebellar dysfunctions such as dysdiachokinesia have traditionally been explained in terms of abnormalities of temporal coordination of muscle groups (Holmes 1939). Additionally, the cerebellum is thought to be involved in forward modelling of motor behaviour, and these forward models have a strong temporal aspect (Wolpert & Miall 1996). Patients with cerebellar damage exhibit increased temporal variability both in producing timed movements and in discriminating durations (Ivry *et al.* 1988; Nichelli *et al.* 1996; Mangels *et al.* 1998; Spencer *et al.* 2003). Therefore, cerebellar patients perform poorly even in those tasks in which they are required to estimate certain durations without necessarily performing movement. In fact, poor acuity in time discrimination

tasks has been reported in patients with lesions of the cerebellum in the range of both milliseconds and a few seconds (Ivry *et al.* 1988; Nichelli *et al.* 1996; Mangels *et al.* 1998). Malapani *et al.* (1998a,b), using a peak interval procedure, reported that the variability of time estimates increased in patients with focal lesion of the lateral cerebellum (cortex and nuclei) when they were trained to remember durations in the seconds range, in comparison with patients with lesions of the mesial cerebellum and vermis. Patients with neocerebellar damage were impaired not only in discriminating intervals in the milliseconds range but were also impaired in the seconds range (Mangels *et al.* 1998). A recent series of studies defined an important characteristic on the functional domain of cerebellar timing: cerebellar patients showed increased temporal variability when producing repetitive movements that entail discrete events demarcating successive intervals. For example, during finger tapping, contact with the table surface might constitute such an event; by contrast, these patients showed no-to-minimal impairment when producing repetitive movements in a smooth, continuous manner (Spencer *et al.* 2003). Ivry and colleagues suggested that the critical distinction between discrete and continuous movement timing is the way in which movements are controlled (Ivry *et al.* 2002; Spencer *et al.* 2003). For discrete movements, an explicit process mediated by the cerebellum specifies the timing of successive events. This event-timing hypothesis also provides a parsimonious account of the cerebellar contribution for temporal processing in perception and sensorimotor learning tasks. Importantly, all these studies tested time intervals within the millisecond temporal range (approx. 500 ms).

Additional evidence for the involvement of the lateral cerebellum in neural control of temporal intervals emerged from recent rTMS studies. With this approach, it is possible to induce a temporary modulation of the excitability of the cerebellar cortex (i.e. Oliveri *et al.* 2005, 2007), hence to investigate whether changes in cerebellar neural activity would interfere with specific timing tasks. Using a visual time reproduction task in which subjects were required to reproduce time intervals in the range of hundreds of milliseconds (500 ms) or few seconds (2 s), we (Koch *et al.* 2007a) observed that cerebellar rTMS selectively disrupted subject's performance for the millisecond time interval targets (figure 1). This was evident only when the magnetic pulses were applied during the reproduction phase but not during the encoding phase; conversely, prefrontal rTMS interfered with reproduction of longer intervals (Koch *et al.* 2007a). In another related study, the same rTMS procedure was applied while subjects were performing a finger-tapping task with similar temporal targets (Fernandez Del Olmo *et al.* 2007); there again, cerebellar rTMS interfered selectively when subjects were required to tap their index finger following an auditory cue at a higher frequency (2 Hz, corresponding to an interstimulus interval of 500 ms) but not when the intervals between the cues were longer (0.5 Hz, corresponding to an interstimulus interval of 2000 ms). In this case also, tapping performance with longer intervals was disrupted by rTMS over the prefrontal and premotor cortices, but not over the supplementary motor areas (SMAs;

Figure 1. (a) For cerebellar rTMS investigations, precise anatomical information about the brain area stimulated was obtained by performing a T1-weighted image magnetic resonance imaging on a sample subject after marking the cerebellar scalp sites with capsules containing soya oil. In the milliseconds range, significant differences were selectively found for (b) the left cerebellar but not for (d) the right dorsolateral prefrontal cortex (DLPFC) stimulation. In the supra-second intervals, right DLPFC stimulation altered (e) time perception, whereas no effect was found for (c) the left cerebellar stimulation. The x - and y -axis values are expressed in milliseconds. Pre-rTMS, grey bars; Post-rTMS, black bars. Error bars indicate 1 s.e.m. * $p < 0.05$. Adapted from Koch *et al.* (2007a).

Fernandez Del Olmo *et al.* 2007). Similar results were obtained in another rTMS study testing the role of the cerebellum in sub- and supra-second time intervals (400/800 and 1000/2000 ms) using a different experimental procedure. Subjects were asked to respond whether a randomly presented tone from the test stimuli was more similar to a standard short or long tone (Lee *et al.* 2007). The results provided direct evidence for the involvement of the cerebellum in perceiving subsecond intervals. On the other hand, there was an absence of cerebellar involvement in the perception of supra-second time intervals. The results of this study are in line with the proposal that different neural systems are involved in sub- and supra-second timing, with the former mainly subserved by the cerebellum (Lee *et al.* 2007). On the basis of these evidences, we suggested (Koch *et al.* 2007a) that cerebellar rTMS may alter time processing within the millisecond range through transient inhibition

of the Purkinje cells or of groups of interneurons of the posterior and superior lobules of the lateral cerebellum. In this regard, additional evidence of the cerebellar involvement in time processing emerges from animal studies showing that Purkinje cells are activated during acquisition and coding of learned timing (Kotani *et al.* 2003). Moreover, long-term depression of these cells was found to be necessary for learning-dependent timing of Pavlovian-conditioned eyeblink responses in the milliseconds range (Koekkoek *et al.* 2003).

From a stricter neuroanatomical perspective, disturbances in temporal estimation have been associated with medial and/or lateral damage to the middle- to superior cerebellar lobules, within the lateral cerebellar hemispheres (Ivry *et al.* 1988; Harrington *et al.* 2004). These findings are in keeping with most functional imaging studies in healthy adults showing that more posterior and superior cerebellar lobules

including the anterior lobe (IV and V) are activated during motor timing tasks (Jueptner *et al.* 1995; Schubotz *et al.* 2000; Smith *et al.* 2003). A distinction based on patient studies has been put forward in which the posterior cerebellum is involved in non-motor aspects of cognition, whereas the anterior cerebellum is involved in motor functions (Schmahmann & Sherman 1998; Exner *et al.* 2004). Moreover, the posterior cerebellum has connections with association cortex including the prefrontal cortex (PFC; i.e. Kelly & Strick 2003), such as the dorsolateral prefrontal area 46 in a closed loop with the thalamus and the dentate.

A recent review of neuroimaging studies examining papers in which neural activity was associated with time measurement has shown that most of the papers involving measurement of millisecond intervals report activity in the cerebellum, whereas only four of the seven which scanned the cerebellum and examined intervals longer than 1 s reported activity there (Lewis & Miall 2003a). In an interesting study, O'Reilly *et al.* (2008) developed a novel paradigm similar to the 'real-world' scenarios in which participants used their observations of a moving object to extrapolate its trajectory which was occluded during 600 ms. Participants made perceptual judgements which either required integrated spatial and temporal information (judgements of velocity), or required only spatial information (judgements of direction). They found that a region in the posterior cerebellum (lobule VII crus 1) was engaged specifically during the velocity judgement task (O'Reilly *et al.* 2008), reinforcing the idea that this region is involved in timing processes.

Taken together, these works indicate that the posterior cerebellum provides representation of the precise timing of salient events, determining the onset and offset of movements or the duration of a stimulus mainly in the shorter intervals lasting hundreds of milliseconds (Ivry *et al.* 2002).

4. SUBCORTICAL STRUCTURES: THE BASAL GANGLIA

The basal ganglia have been associated with temporal processing in the range of both milliseconds and seconds. A substantial amount of information regarding the role of basal ganglia in time processing was put forward by studies showing that manipulation of dopamine in rats and humans alters the rate of perceived time (Meck 1996; Meck & Benson 2002; Rakitin *et al.* 2006). Indeed, recent experiments showed that the integrity of the striatum and its afferent projections from the substantia nigra pars compacta (SNPC) are crucial for both temporal production and temporal perception (for a review see Meck 1996; Matell & Meck 2004). In these studies, rats with excitotoxic lesions of the striatum or selective dopaminergic lesions of the SNPC are unable to regulate their responses with respect to the amount of time that has passed in a trial. Moreover, striatal neuron firing patterns are peak shaped around a trained criterion time, a pattern consistent with substantial striatal involvement in interval timing processes (Matell *et al.* 2003).

Administration of dopaminergic drugs in rats (Maricq & Church 1983; Matell *et al.* 2004) or in

humans (Rammsayer 1993) directly alters the speed of interval timing processes. An immediate, proportional, leftward shift in perceived time (responding earlier in time than under control conditions) is evident following systemic dopaminergic agonist administration (e.g. methamphetamine or cocaine), whereas an immediate, proportional, rightward shift (responding later in time than controls) occurs following systemic dopaminergic antagonist administration (e.g. haloperidol). Moreover, neuroimaging studies in healthy subjects have constantly demonstrated that time processing is related to basal ganglia activity (Rao *et al.* 1997; Nenadic *et al.* 2003; Coull *et al.* 2004; Hinton & Meck 2004; Jahanshahi *et al.* 2006).

Results from the study of PD patients have provided further knowledge regarding the role of basal ganglia in time processing. Most studies on these patients have been based on repetitive movement tasks (i.e. finger tapping), in which subjects have to perform simple movements with precise timing cued by an external signal, with time intervals in the range of hundreds of milliseconds. PD patients may have abnormal temporal processing in repetitive rhythmic movement tasks because their performance is more variable than that of controls (Artieda *et al.* 1992; O'Boyle *et al.* 1996; Harrington *et al.* 1998a,b). Therefore, abnormal findings in temporal processing of brief intervals observed in PD patients (Artieda *et al.* 1992; Rammsayer & Classen 1997; Harrington *et al.* 1998a,b) have been interpreted along with the hypothesis that timing in the subseconds range is modulated by dopaminergic activity in the basal ganglia.

However, other authors found that PD patients performed as accurately as normal subjects on these tasks, even when they were tested off medication (Spencer & Ivry 2005). In this regard, an interesting recent study explored the abilities of PD patients to process temporal information across different timing tasks using intervals in the range of hundreds of milliseconds (Merchant *et al.* 2008). Cluster and discriminant analyses revealed heterogeneity of temporal performance with a subgroup of high variability timers throughout all tasks, and a subgroup of PD patients with a temporal variability that did not differ substantially from control subjects. Therefore, these results corroborate the hypothesis that PD patients cover a wide spectrum of clinical phenotypes, with subgroups that can be defined on the basis of different rates of clinical progression, age of PD onset, dose of levodopa, different cognitive performances in a number of neuropsychological tests (Foltynie *et al.* 2002; Lewis *et al.* 2005; Schrag *et al.* 2006) and now temporal processing (Merchant *et al.* 2008). Moreover, given the high ratio of variance associated with timing during repetitive movements, such tasks may present some limitations for the assessment of timing functions in patient populations with severe motor deficits, such as PD (Shea-Brown *et al.* 2006).

Another experimental approach widely used to test time processing in PD patients is the time reproduction task. In this task, participants are required to produce behavioural responses (i.e. pressing a response button) based on memorized time intervals in the seconds range, thus necessitating cognitively controlled time

measurement (Lewis & Miall 2003a). In a study by Pastor *et al.* (1992), time intervals between 6 and 27 s were investigated in a sample of PD patients in different modalities (by internal counting or by using their preferred strategy); a greater overestimation was found for the longer duration estimations than for the shorter duration ones. Interestingly, administration of levodopa (L-dopa) led to a significant improvement in the estimated time. However, Perbal *et al.* (2005) did not replicate these findings (intervals spanning 5–38 s), although the variability tended to be higher in PD patients than in control participants. Jones *et al.* (2008) found that PD patients performing a seconds range (30–120 s) time production task when tested ‘on’ medication showed a significantly different accuracy profile compared with controls. However, no differences in accuracy were found on a time reproduction task and a warned reaction time task requiring temporal processing within the 250–2000 ms range. On the other hand, variability was altered in this latter task, suggesting that PD patients may present atypical temporal processing mechanisms independently from dopamine. The authors suggested that the time production task uses neural mechanisms distinct from those used in the other timing tasks (Jones *et al.* 2008).

In another study, Malapani *et al.* (1998a,b) asked PD patients to reproduce two learned target durations (8 and 21 s) for which they received feedback for responding. Results revealed that medicated PD patients’ performances were comparable with those of healthy control participants. By contrast, when off medication, PD patients overestimated the short duration (8 s), underestimated the long duration (21 s) and showed a higher variability for the short interval than for the long one. Effects on temporal accuracy and variability were observed when patients were trained to learn two target durations (i.e. dual training condition) and were no longer observed when they were trained to learn only one of the two target durations (i.e. single training condition). The authors attributed this effect to a dysfunctional representation of memory for time (migration effect). In particular, the authors proposed that memory retrieval might be the source of migration, resulting from dysfunction of the decoding system, in comparison with the currently elapsing time (Malapani *et al.* 2002). Our group obtained similar results using a slightly different procedure (without feedback), testing intervals of 5 and 15 s (Koch *et al.* 2004a,b, 2005a). We observed that when PD patients without L-Dopa therapy were asked to reproduce different time intervals intermingled within the same session, they overestimated the shorter one (5 s) and underestimated the longer one (15 s). Such abnormalities were reverted by both subthalamic deep brain stimulation (DBS; Koch *et al.* 2004a) and L-dopa supplementation (Koch *et al.* 2005a,b). Moreover, in a following investigation, we aimed to verify whether this behaviour was specific for the multisecond time scales or also emerged when millisecond time intervals were tested (Koch *et al.* 2008). We examined PD patients’ performance on a time reproduction task involving intervals of milliseconds (500 ms) and supra-second durations (2 s). When the different ranges were tested in the same session, PD patients without L-dopa therapy

presented a selective impairment for supra-second time intervals (underestimation) but their reproduction of millisecond time intervals was comparable with a control group of healthy subjects. On the contrary, when the different time intervals were tested in separate sessions, PD patients did not show any clear deficit of time estimation in either range. Therefore, these data seem to indicate that (i) cognitive time processing in PD patients for time intervals spanning up to 2 s is unimpaired and (ii) selective abnormalities in this temporal range emerge only when timing involves further cognitive processes such as memory and attention. One possibility is that these dysfunctions emerge only when longer time intervals are processed together with the shorter, subsecond duration because an increased cognitive load is required.

Taken together, these investigations in PD patients seem to suggest that the basal ganglia dysfunction characterizing this disease alters the perception of time when the tested intervals are longer and that clearer deficits emerge when processing of time intervals requires additional cognitive functions such as working memory and attention.

In this regard, it is important to note that in addition to the mesostriatal dopaminergic pathway projecting from the substantia nigra to the striatum, the dopaminergic system includes a mesocortical pathway with projections from the ventral tegmental area to the PFC. Dopamine modulates cortical networks subserving working memory and motor function via two distinct mechanisms: nigrostriatal projections facilitate motor function indirectly via thalamic projections to motor cortices, whereas the mesocortical dopaminergic system facilitates working memory function via direct inputs to PFC (Mattay *et al.* 2002). This provides a direct route by which dopaminergic inputs might act upon the PFC to influence time perception (Rammsayer 1997). Rammsayer (1997) found that remoxipride, an atypical neuroleptic agent, which blocks dopamine D2 receptors mainly in the mesocortical system but not in the nigrostriatal system, disrupts comparison of durations in the seconds range, without affecting comparisons of durations in the milliseconds range. The same study showed that haloperidol, which blocks D2 receptors in both systems, impairs the timing of both short- and long-duration processing and also interferes with movement timing. These data support the role of mesocortical dopamine in a cognitive timing system, which draws upon working memory and attention, and of nigrostriatal dopamine in both this cognitive system and a more automatic timing process (Rammsayer 1997). This suggestion is corroborated by the observation that Parkinsonian patients experience more severe deficits in temporal processing in the late stages of the disease, when cells in the ventral tegmental area have been destroyed (Artieda *et al.* 1992). Additionally, the recent demonstration of temporal deficits in several other dopaminergic disorders involving the PFC, such as Huntington’s disease (Paulsen *et al.* 2004) and schizophrenia (Elvevåg *et al.* 2004), is also in line with this view.

Along this vein, we have recently observed that PD patients with implantation of DBS of the subthalamic nucleus ameliorated their abnormal performance in a

time reproduction task when the stimulator was turned on, paralleling the effects of L-dopa administration (Koch *et al.* 2004a). We suggested that the observed effects might be mediated by activation of striato-cortical projections following subthalamic DBS. Therefore, we provided additional evidence to support the hypothesis that the mesocortical dopaminergic system plays an important role in cognitively controlled timing.

Further evidence was provided in a recent study, in which psychophysical tests assessing several aspects of auditory temporal processing were administered to a group of PD patients treated with bilateral subthalamic DBS and to a normal control group (Guehl *et al.* 2008). In this study, each patient was tested in three clinical conditions: without treatment; with levodopa therapy; and during subthalamic nucleus (STN) stimulation. PD patients showed a significant deficit in the detection of very short temporal gaps and in the discrimination between the durations of two well-detectable time intervals (50 ms). The authors proposed that the deficit observed in the gap-detection test was probably due to a dysfunction of the auditory cortex, impairing its ability to track rapid fluctuations in sound intensity, being a consequence of an impairment in memory and/or attention rather than in the perception of time *per se*. Remarkably, the patients' deficits were not diminished by levodopa therapy; by contrast and overall, STN stimulation slightly improved performance. Nevertheless, the effects of subthalamic DBS on prefrontal cognitive functions are still controversial with some studies showing worsening of performances in chronic follow-up (Witt *et al.* 2008).

In another investigation, we observed that the performance of PD patients on a time reproduction task was ameliorated by high-frequency rTMS of the dorsolateral prefrontal cortex (DLPFC; Koch *et al.* 2004b). When delivered at frequencies higher than 5 Hz, such as the one adopted in our study, rTMS is known to increase the excitability of the stimulated area. Whereas low-frequency off-line rTMS protocols (1 Hz) have been reported to induce a long-lasting inhibition, high-frequency off-line protocols (more than 5 Hz) may lead to enhancement of cortical activity. In our study, we observed that rTMS over the right DLPFC but not over SMA was able to improve time perception in patients with PD, suggesting that reduced DLPFC activity owing to decreased striatocortical projections could be involved in cognitive timing deficit in PD (Koch *et al.* 2004b).

Despite these findings, it is still unclear whether the temporal processing of brief intervals is selectively dependent on the effective level of dopaminergic activity rather than representing a more general function of the integrity of the basal ganglia. Timing mechanisms involved in the temporal processing of milliseconds and seconds intervals might not be completely independent of each other (Hellström & Rammsayer 2004), but may share some common mechanisms (Lewis & Miall 2003a,b). According to this notion, both timing mechanisms may depend on dopaminergic systems, with some tasks being more dependent on dopamine than others, and when working memory, attention or other cognitive processes are

more engaged, and when timing of longer intervals is required (Lewis & Miall 2006).

5. ROLE OF THE CEREBRAL CORTEX

Cognitive time processing seems to depend on a right hemispheric cortical network (Gibbon *et al.* 1997; Harrington *et al.* 1998a,b; Mimura *et al.* 2000; Pouthas *et al.* 2000; Koch *et al.* 2002, 2003; Smith *et al.* 2003; Lewis & Miall 2006). A right prefrontal–inferior parietal cortex circuit for time processing in the range of milliseconds has been first proposed by Harrington *et al.* (1998a,b) on the basis of lesion overlays using a duration perception task. They found that patients with right but not left hemispheric stroke showed disruption in their discrimination of brief time intervals (300–600 ms). In particular, lesion overlap analysis showed that the right inferior parietal lobe and areas of the PFC, including the frontal eye field (BA 6) and DLPFC (BA 8, 9 and 46), were associated with abnormal timing. On the other hand, lesions in the same regions in the left hemisphere were associated with normal functions. The results implied a role for anterior and posterior regions of the right hemisphere in temporal computations, which is compatible with the reciprocal connections between the inferior parietal cortex and corresponding frontal cortical areas in monkeys (Selemon & Goldman-Rakic 1988).

(a) DLPFC: time and working memory

Other lesion studies stressed the PFC as having a more primary role in time estimation processes, especially in the range of seconds (Mangels *et al.* 1998; Koch *et al.* 2002, 2003). Mangels *et al.* (1998) used a time discrimination task with intervals ranging 400 ms or 4 s in groups of stroke patients with lesion in the PFC or in the cerebellum. The duration of the standard was 400 ms in the short-duration task and 4 s in the long-duration task. The patients with neocerebellar lesions were impaired on both short-duration (400 ms) and long-duration (4 s) discrimination tasks. By contrast, the frontal patients only exhibited a significant timing deficit when judging 4 s intervals. Additionally, patients with prefrontal lesions exhibited a significant rightward shift in determining the point of subjective equality, not observed in neocerebellar patients or control subjects, suggesting that such alteration may reflect a systematic lengthening of the duration stored in reference memory.

Koch *et al.* (2002) described a 49-year-old man admitted in the acute neurological ward and presenting mental confusion and difficulty with concentration. Cranial magnetic resonance imaging showed an ischaemic lesion in the right frontal lobe (DLPFC, BA 46/9). Few days after this acute episode, when he came back to his daily activities, the patient noted that he had trouble estimating the duration of events, judging them as shorter than they actually were. He had difficulty in evaluating how much time had elapsed since the beginning of a determinate event, e.g. he was not able to judge when the working day was over, leaving the office earlier than the scheduled time. When he was asked to estimate the duration of time intervals indicated by visual markers ranging 5–90 s, he was

significantly less accurate as compared with control subjects in the evaluation of the longer intervals, showing a clear tendency to underestimate real time (Koch *et al.* 2002). In a subsequent study, we tested the effects of inhibitory rTMS in a sample of healthy volunteers. We observed that subjects underestimated time periods in a time reproduction task with intervals lasting for 5–15 s after 600 rTMS stimuli at 1 Hz were applied over the right but not the left DLPFC (Koch *et al.* 2003). We suggested that time underestimation induced by rTMS could depend either on a decreased encoding rate into the memory store or on a possible impairment in the decision phase when the current time had to be compared with the reference time. Therefore, these results were in line with the idea that right DLPFC may be critical in perceiving and keeping the flow of time in memory, contributing to the formation of a conscious representation of subjective time for short and long intervals. Since in that study (Koch *et al.* 2003) subjects read aloud a series of numbers varying in order and presentation time, they performed time processing in the context of a dual task. This could imply increased attentional load, and thus increased activation of the brain areas involved in attention and working memory. In this regard, TMS of the DLPFC is known to disrupt both attention (Oliveri *et al.* 2000) and working memory processes (Oliveri *et al.* 2001; Mottaghy *et al.* 2002, 2003; Koch *et al.* 2005a,b); therefore, the observed effects of rTMS on time perception (Koch *et al.* 2003) could be partially explained by interference with these cognitive functions. Similar results using rTMS were provided by Jones *et al.* (2004). In contrast to the study of Koch and colleagues, Jones *et al.* (2004) tested milliseconds and seconds intervals to determine whether the short/long dichotomy supported by functional imaging results was a key issue in the differential roles of the SMA and the right DLPFC in temporal processing. In fact, functional magnetic resonance imaging studies evidenced the right DLPFC as an area involved in time processing but activation of the superior frontal gyrus, the SMA and the inferior parietal cortex has also been reported (Rao *et al.* 2001; Ferrandez *et al.* 2003; Smith *et al.* 2003; Macar *et al.* 2006). A time reproduction task involves two distinct phases: an estimation phase and a reproduction phase. Jones *et al.* (2004) stimulated the brain during both phases such that the influence of the SMA and right DLPFC on the timing processes occurring in each phase would be investigated. Results showed that subjects underestimated the duration of longer (2 s on average) intervals if rTMS was given to the right DLPFC during the reproduction phase of the task, while there were no effects of right DLPFC stimulation in the short (500 ms on average) interval estimation and there were no significant effects of SMA stimulation. The authors proposed that the disruption produced by rTMS over the right DLPFC reflects interference with memory processes, implying that longer intervals are more vulnerable than short intervals to task-oriented memory processes subserved by prefrontal areas (Jones *et al.* 2004).

In neuroimaging studies, timing tasks activate the right DLPFC more frequently than any other brain

area (Lewis & Miall 2003a). Importantly, right DLPFC activity is much more common in cognitively controlled timing tasks than in those classified as automatic (Lewis & Miall 2003a). This part of the PFC is strongly associated with working memory functions as shown by numerous studies using targeted lesions and single-unit recordings in monkeys as well as patient work and a vast collection of neuroimaging data (i.e. Goldman-Rakic 1995; Passingham & Sakai 2004). Therefore, it is unsurprising that the DLPFC is essential to some timing tasks and that many neurons in this area show phasic increases in activity that depend on the duration of the preceding delay period (Genovesio *et al.* 2006). Interestingly, the post-delay signal seemed best suited to index event durations relevant to the current task and not to code precisely time intervals (Genovesio *et al.* 2006).

Overall, these data put forward the notion that the DLPFC, known to be important for working memory, is also essential for cognitively controlled time measurement (Lewis & Miall 2006) with an apparent bias to the right hemisphere. The neural activity of the PFC therefore seems to increase with timing tasks depending on the duration of the stimulus and on the cognitive load.

(b) *Posterior parietal cortex: time and space*

Other evidence suggested a role of the posterior parietal cortex (PPC) in timing processes on the basis of the study of behaviour of right-brain-damaged (RBD) patients in temporal tasks. In fact, the relationship between time and space can be usefully approached in the context of unilateral neglect, a neuropsychological syndrome in which patients fail to perceive or respond to stimuli in the contralateral hemifield, behaving as if that half of space did not exist. Traditional models characterize neglect exclusively in spatial terms but based on recent investigations of RBD patients, they also present abnormal temporal dynamics in the distribution of attention.

If space and time are integrated in the right parietal cortex, then one could expect that in RBD patients, the greater the spatial deficit, the greater temporal deficits will be. Basso *et al.* (1996) were the first to explore temporal perception in a right parietal patient with spatial neglect, showing that visual stimuli in the left neglected space were judged to be longer than stimuli in the rightmost positions. In particular, the patient was less accurate when presented with a short duration in leftmost positions and with a long duration in the rightmost positions. This behaviour seems to be consistent with the hypothesis of a left-to-right-oriented mental time line which, when disrupted by right parietal damage, could invert its direction.

Likewise, Snyder & Chatterjee (2004) documented that the ability to distinguish between two successive events was worse in contralesional than in ipsilesional space of a patient with right temporoparietal stroke. These findings could be interpreted as reflecting a longer refractory period of stimuli in the contralesional space (di Pellegrino *et al.* 1998) and concur with those of Harrington *et al.* (1998a,b) and Rao *et al.* (2001) in keeping a role for the right PPC in timing. Moreover, by documenting that the right temporoparietal cortex

Figure 2. Schematic of the connections between the subcortical and cortical structures involved in time processing of time intervals with different durations and cognitive loads. The arrow in the left indicates length of time intervals and the arrow in the right indicates the difficulty of the task being performed. PPC, posterior parietal cortex; PFC, prefrontal cortex; VLp, anterior ventrolateral nucleus; VLp, posterior ventrolateral nucleus; VIm, intermediate ventral nucleus.

integrates spatial with temporal information, these results support the theory of magnitude proposed by Walsh (2003), according to which the right parietal cortex is critically involved in sensorimotor transformations with regard to space, time and other magnitudes (see also the paper by Buetti & Walsh 2009).

Recently, by testing RBD patients with verbal reproduction of supra-second intervals, Danckert *et al.* (2007) have showed that patients with spatial neglect were the most impaired in the task, showing significant underestimations of presented time intervals compared with both healthy controls and RBD patients without neglect. Since there was no correlation between the severity of neglect and the severity of timing deficits, it appears that temporal deficits are not an epiphenomenon of neglect. The authors suggested that temporal deficits are part of the group of cognitive deficits occurring in neglect, such as impaired spatial working memory (Danckert & Ferber 2006). The combination of these deficits commonly leads to the loss of awareness of contralesional space that is characteristic of neglect.

Thus, it appears that visual neglect is a disorder of directing attention to both time and space, thus supporting the hypothesis that elapsing time could be internally mapped onto spatial representations (Becchio & Bertone 2006).

Additional evidence for a link between time and space came from a recent study in which we observed that, in healthy subjects, duration judgements of visual digits are biased depending on the side of space where the stimuli are presented and on the magnitude of the stimulus itself (Vicario *et al.* 2008). Different groups of healthy subjects performed duration judgement tasks on various types of visual stimuli. In the first two experiments, visual stimuli were digit pairs (1 and 9) presented in the centre of the screen or in the right and

left space. In a third experiment, visual stimuli were black circles. The duration of the reference stimulus was fixed at 300 ms. Subjects had to indicate the relative duration of the test stimulus compared with the reference one. The main results showed that, regardless of digit magnitude, duration of stimuli presented in the left hemispace is underestimated and that of stimuli presented in the right hemispace is overestimated. Overall, these findings fit with the prediction that time could be cognitively represented by means of spatial coordinates, with a left-to-right-oriented linear representation, in analogy with numbers and other types of ordered material, such as numbers, sound pitches, months and letters.

(c) Visual, temporal and parietal cortex: stimulus modality matters

Modality-dependent activation of different cortical areas during temporal tasks has been observed. In a previous TMS study, Buetti *et al.* (2008a) transiently disrupted activity in the extrastriate visual cortex (V5/MT) and in the left and right inferior parietal cortex, while subjects discriminated visual and auditory durations. They found that the right PPC was important for timing of auditory and visual stimuli and that MT/V5 was necessary only for timing of visual events. In a subsequent study, the same authors investigated the role of the auditory cortex in auditory timing, stimulating the left and right superior temporal cortex (Buetti *et al.* 2008b). When rTMS was applied over the right superior temporal gyrus, temporal discrimination of auditory stimuli in the range of hundreds of milliseconds (from 560 to 640 ms) was significantly impaired. The authors proposed that many cortical areas are able to compute time depending on the task, the stimulus modality and whether the duration is in the range of milliseconds or seconds, although it seems

highly unlikely that this decentralization is absolute and that the modality-specific mechanisms contain unique time generators.

6. CONCLUSIONS AND PERSPECTIVES

The studies discussed in the present paper do not provide a clear segmentation of different subcortical and cortical areas in timing functions. However, it seems likely that a wide range-distributed neural network is useful to process time information, with a prevalent involvement of specific structures that depend not only on the duration of the time interval to be assessed by the brain, but also on the cognitive set, the task adopted and the stimulus modality.

The neural activity of the cerebellum seems more crucial when subjects are required to quickly estimate the passage of brief intervals and when time is computed in relation to precise salient events. On the other hand, the circuits involving the striatum and the substantia nigra with their projections to the PFC are mostly implicated in the processing of supra-second time intervals, i.e. when time is processed consciously and in conjunction with other cognitive functions. The conscious representation of temporal intervals also relies on the integrity of the prefrontal and the parietal cortices. A predominant role is related to the PFC activity when time intervals have to be kept in memories, with a greater involvement related to longer supra-second time intervals and when the task requires higher cognitive level. On the other hand, the parietal cortex seems crucial when time information has to be processed together with spatial information, for both sub- and supra-second time intervals.

It is important to note that all these neural structures are connected through specific neural networks. Not only dense corticocortical connections exist between the parietal and frontal regions (i.e. Battaglia-Mayer et al. 2003; Koch et al. 2007b), but it is also well known that cerebello-thalamo-cortical and the striato-thalamocortical pathways project to adjacent portions of the cortex. Moreover, recent evidence has pointed out that these systems are not fully independent (figure 2). For instance, it has recently been shown that the cerebellum directly influences the activity of the striatum through disynaptic projections (Hoshi et al. 2005). Besides, following cerebellar lesions, a significant facilitation of glutamate transmission in the contralateral striatum was observed (Centonze et al. 2008), suggesting that the cerebellum and the striatum are more interconnected than commonly believed. In this regard, it is interesting to mention that O'Reilly et al. (2008) showed that, in a timing task, the posterior cerebellum showed functional connectivity with the anterior putamen bilaterally, hence raising the intriguing possibility that these two sets of structures, implicated in timing, interacted in the temporal prediction task adopted in the study.

Within this anatomo-functional framework, it is likely that different aspects of temporal information can be mediated by the activity of these interconnected neural networks that present different points of interaction. This could be important to make the brain able to process temporal information in a wide variety of circumstances.

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