Chapter 7

General discussion: A review of electro-magnetic correlates of interval timing, before, during and after the to-be-timed interval period.
Research has associated a number of neural signatures with the perception and reproduction of supra-second time intervals. More specifically, the perception of supra-second intervals has been associated with the slow buildup of electromagnetic brain activity, commonly instantiated by the CNV. This ramping activity has been ascribed to the accumulation of temporal pulses that are generated by the internal pacemaker (Macar, Vidal, & Casini, 1999; Pfeuty, Ragot, & Pouthas, 2005; see Figure 1 in Chapter 1). In this thesis, I challenge the notion that the CNV is a marker of temporal accumulation and investigate alternative explanations regarding the functional role of the CNV in interval timing. Additionally, I propose novel EEG markers that index the perception and reproduction of time, and that predict subjective time better than the CNV. Unlike the slow electromagnetic fields, these new markers do not focus on the timed interval but instead indexes processes immediately before or after the onset or offset of the interval. An overview of EEG/MEG components that are known to index time-estimation processes before, during, and after a timed interval is shown in Figure 1.

![Figure 1. Overview of EEG/MEG components recorded from human participants associated with time estimation. Red color indicates components that were investigated in this thesis.](image)

The components marked red were investigated in the studies reported in this thesis. This chapter discusses the implications of these findings for theories and mechanisms of timing and time perception, and neural markers of interval timing observed in the animal electrophysiology literature where relevant.

In the remainder of this Chapter, I will introduce and discuss neural phenomena that have been linked to interval timing: intensively debated climbing neural activity, and pre- and post-interval components. I will also discuss how these components add to the debate on the role of the SMA in interval timing.
Climbing neural activity and interval timing

Whenever participants are presented a stimulus that has to be associated with a subsequent stimulus or action this initial stimulus typically triggers a slow neuronal activity. This slow neuronal activity that persists even in the absence of a physical stimulus, often described as climbing neural activity (CNA, for review see, Durstewitz & Deco, 2008; Simen, 2012; Wittmann, 2013), has been associated with anticipation, planning, and working memory maintenance (Durstewitz & Seamans, 2006), with discriminative performance (Romo & Salinas, 2003), but also with the encoding of temporal information (Durstewitz, 2003; Reutimann, Yakovlev, Fusi, & Senn, 2004). Besides the fact that a typical CNA pattern alludes to some sort of cumulative process, there is little evidence that the value of CNA at a given time reflects some cumulative neural quantity (e.g., Durstewitz & Deco, 2008). Several theories have been proposed to account for rise of CNA. For example, Durstewitz (2003, 2004) proposed that the stable configuration of a so-called line attractor (i.e., a network of elements that is recurrently connected and exhibits a stable pattern such as stable firing rates) can be disrupted at the level of single neurons by feedback from Ca$^{2+}$ currents, resulting in the buildup of a CNA. Another proposal conceives CNA at a global neuronal level and assumes that the climbing activity in excitatory neurons is caused by a firing rate adaptation of inhibitory neurons (Reutimann, Yakovlev, Fusi, & Senn, 2004). Yet another model poses that groups of neurons that give rise to CNA are bistable (Deco, Ledberg, Almeida, & Fuster, 2005; Durstewitz & Deco, 2008; Kitano, Okamoto, & Fukai, 2003), but assumes that averaging over many neurons result in an observed climbing activity. Interestingly, apart from neuronal recordings that resemble the CNA, studies have identified many more neuronal patterns. For example, Jin, Fujii, and Graybiel (2009) identified neurons which activity was tied to specific event and the passage of time since that event. If such time-stamp activity is averaged over many trials it will result in the CNA (Durstewitz & Deco, 2008).

Although the exact neural mechanism driving CNA remains unknown (for a review, see Durstewitz & Deco, 2008), it is assumed to be a very general neural process as a CNA-like ramping pattern has been found in many different brain areas such as the thalamus (Komura et al., 2001; Tanaka, 2007), the prefrontal cortex (Watanabe, 1996), in motor and premotor structures (Lebedev, O'Doherty, & Nicolelis, 2008; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009), and in the striatum (Hassani, Cromwell, & Schultz, 2001).

The claim that the CNA reflects interval timing is supported by at least two arguments. Firstly, a CNA-like pattern has been shown to be present during interval timing in a broad range of intervals. Secondly, the slope of the CNA is a function of the length of the interval, suggesting that the mechanisms underlying the CNA are sensitive to the intended duration (Mita et al., 2009). Interestingly, besides this classical CNA trace that resembles an accumulation pattern, a recent study has shown a much richer pallet of CNA-like patterns at the level of individual spiking neurons (Merchant, Zarco, Pérez, Prado, & Bartolo, 2011). This work classified four types of ramping patterns: motor cells, relative timing cells, absolute timing cells, and time accumulator cells and demonstrates that CNA has more functions than has
been previously thought. In line with these results, theoretical work has proposed the idea that these neuronal patterns that are typically interpreted as evidence accumulation can also serve as a threshold mechanism that could be distinguished from more gradual accumulator-like activations (Simen, 2012). Additionally, recent evidence also challenges the notion that CNA exhibited by individual neurons is directly linked to time accumulation (Schneider & Ghose, 2012; Simen, 2012; Cook & Pack, 2012, Goel & Buonomano, 2014; cf., Wittmann, 2013).

Interestingly, Schneider & Ghose (2012) demonstrated that at the level of individual spiking neurons, time judgments can be associated with a decrease of the spiking rate. They trained monkeys to perform self-timed rhythmic sequences of saccades. Whereas most studies in animals showing an increase in spiking activity have scheduled reward at predictable time on each and every trial, Schneider and Ghose (2012) minimized reward anticipation by delivering the reward at random times in the sequence of the saccades. Crucially they showed that the decrease in activity of the lateral interparietal area between saccades was predictive of intersaccadic interval length. Importantly, the CNA account is based on the assumption that an increase in neural activity reflects process of neural integration (cf., Mita et al., 2009). Such decrease in activity (Schneider & Ghose, 2012; also see Cook & Pack, 2012), has consequences for the idea of neural integration of temporal pulses. This decrease in activity is clearly at odds with the idea of accumulation of pulses over time as a cumulative value cannot be expressed as decreasing neuronal activity.

CNA instantiated as the CNV and its relation to interval timing

The first and most commonly studied type of CNA in the context of interval timing is the contingent negative variation (CNV). However, Chapters 2, 4, and 5 of this thesis present crucial evidence against, and arguments questioning the direct link between the CNV amplitude and the temporal accumulator. Chapter 2 tested the assumption that the CNV as measured from the SMA and preSMA tracks the accumulation processes as has been proposed in the context of information processing theories of interval timing. However, the CNV amplitude did not correlate with the variations in temporal performance, questioning this widely cited assumption. Moreover, the CNV amplitude was influenced by time-on-task effects, such that over the course of the experiment the CNV amplitude was decreasing. This habituation effect is in contrast with the assumption that the CNV reflects a stable accumulation process, and is therefore not predicted by, or even evidence against the temporal accumulation hypothesis (Macar et al., 1999). On the basis of the empirical findings in Chapter 2, Chapter 3 evaluates CNV phenomena from the perspective of temporal accumulation and preparation for action accounts. In addition, Chapter 3 provides a theoretical discussion pointing out some of the inconsistencies between theories of interval timing and the experimental results that are often interpreted in favor of the temporal accumulation hypothesis (Macar et al., 1999). Together, Chapters 2 and 3 challenge the direct link between CNV and...
temporal (accumulation) processes. Hence, one cannot use these data to argue that the basis of temporal performance, the accumulator, is indexed by the CNV.

Moreover, over the course of the experiment, the CNV amplitude decreased. This observation is difficult to explain in the context of the hypothesis that the CNV reflects temporal accumulation hypothesis. That is, over the course of the experiment, the accumulation should - on average - always reach that value that represents the estimated interval. A strict temporal accumulation hypothesis should therefore predict that when habituation effects are observed, the estimated durations are shortened. As the habituation effect was not correlated with a shortening of produced duration, this effect argues against the temporal accumulation hypothesis (Macar et al., 1999).

Regardless of the habituation effect, a careful analysis of the empirical evidence and the theoretical models that provide the context in which the evidence is evaluated, shows that the reasoning on the basis of which it is suggested that the CNV represents the temporal accumulator is inconsistent with these theories (Chapter 3, this thesis). Instead of the indexing temporal accumulation assumption, Chapter 3 presents an alternative account of the CNV, proposing that the CNV reflects expectancy and readiness for an upcoming event. For example, O’Connel et al. (2009) demonstrated that the CNV amplitude preceding a target was larger in hit trials than in miss trials, suggesting that CNV determines a level of stimulus detectability. Alternatively, Boehm, Van Maanen, Fortsmann, and Van Rijn (2014) have shown that the CNV amplitude is higher in trials in which response-caution is low, suggesting that the CNV is negatively correlated with meticulous responding. These data suggest that expectation of and preparation for an event can be regulated through modulation of neural excitability (Elbert, 1993; Rockstroh, Muller, Wagner, Cohen, & Elbert, 1993). These examples show that neural excitability and CNA can be seen as general phenomena in which other cognitive processes can be structured and embedded (also see Kösem, Gramfort, & Van Wassenhove, 2014).

This expectation-based process is even visible in paradigms that reduce the involvement of motor activity in a temporal judgment task. For example, in a temporal generalization or bisection task, participants are asked to judge the length of an interval in comparison to one or more given standards. As the response indicating the judgement can be delayed, the perception of the interval is not associated with any motor actions. The most remarkable feature of the CNV in these tasks is that it starts to deflect at the time the temporal decision is made. For example, in a temporal generalization task, the CNV will deflect at around the point of time when the associated response switches from "shorter-than-the-standard" to "longer-than-the-standard". Based on the notion that the deflection reflects the end of the accumulation process, and thus the end of the process that keeps track of time, decisions made after the deflection of the CNV cannot be based on differential temporal information. This assumption was tested in Chapter 5. In line with earlier temporal-generalization studies, we showed that the CNV indeed deflects at the time of the memorized standard, and also showed that behavioral performance for durations longer than the standard, and thus when the CNV has deflected, was still a function of the amount of time that had passed. Whereas the CNV did not correlate with behavioral performance, the amplitude of N1P2 component evoked by the offset of the comparison interval increased as a function of the temporal
distance from the SI, and the latency of the P2 component followed the hazard rate of the CIs, indicating that timing processes continue after the resolution of the CNV. Based on these data, Chapter 5 provides the first direct EEG evidence that the subjective timing of multi-second intervals does not depend on climbing neural activity as indexed by the CNV, but that the subjective experience of time is better reflected by potentials evoked by the end of the interval.

An additional consequence of the hypothesis that the CNV reflects the accumulator is that longer durations should be associated with higher amplitudes (assuming an absolute accumulator, see Macar et al., 1999), or that different durations are associated with the same amplitude (assuming a relative accumulator, see Pfeuty et al., 2005). This assumption was tested in the experiment reported in Chapter 4 in which participants were asked to reproduce durations of 2, 3 and 4 seconds. Similarly to the original study by Elbert et al. (1991), the CNV amplitude was larger at the end of the interval for the 2 second duration than for the 3 and 4 second durations. The enhancement of the CNV amplitude in the 2 second condition is in line with the results of a temporal bisection study in which the amplitude of the CNV was larger in the context of shorter anchor and probe durations than in the context of longer durations (Ng, 2014). Moreover, at the level of individual subjects, the CNV amplitude showed a negative correlation with the reproduced duration, such that a larger amplitude was associated with a shorter duration, a finding diametrically opposed to any hypothesis relating CNV amplitude to the accumulation of time (but see Chapter 3, or Boehm et al, 2014, for a possible explanation).

Another hypothesis that can be derived from CNA theories is that the build-up of anticipation over time should be associated with a ramping pattern, as the passing of time is the driving factor behind the increased anticipation. Interestingly, electrophysiological studies in humans provide evidence that anticipatory activity is not necessarily associated with ramping patterns. For example, Ng, Tobin, & Penney (2011) used a duration bisection paradigm in which subjects are asked to categorize durations as either more similar to the short, or to the long anchor. In line with the expectations, Ng et al. (2011) observed a negative deflection that started at the onset of the duration that had to be categorized. However, as soon as the short anchor duration was reached, the CNV remained stable until the onset of the late anchor, and then resolved. We have also observed a similar pattern of results in a temporal orienting task in which a target could occur at an early or late time point (Boshoff, Kononowicz, & Van Rijn, unpublished observation). In line with the results of Ng et al. (2011) these results suggests that CNV can reflect persistent activity indexing sustained preparation and the development of this preparation in time. This hypothesis finds support in other electrophysiological measures as both single cell recordings (Janssen & Shadlen, 2005) and slow EEG activity (Trillenberg, Verleger, Wascher, Wauschkuhn, & Wessel, 2000) accurately reflects the expectation of event occurrence. Thus, as such, the CNV can be interpreted to mediate how the brain controls excitability in preparation for an upcoming internal or external stimulus (Elbert 1993, Boehm, et al., 2014; Plichta et al., 2013; Rockstroh et al., 1993). In another words, the CNA at a given time could reflect task-related brain states such as the level of preparation or the neural excitability that is needed to maintain a set of mental operations. Of course, for the optimization of resources the brain has to
rely on some kind of temporal information that would allow control of these processes over time. Thus, although these results suggest that the primary function of the CNV is the temporal organization of excitability, it is still conceivable that the CNV and CNA convey some sort of temporal information. However, although the CNV might be based on temporal information, it is unlikely that it is the source of temporal information for other cognitive processes.

**CNA instantiated as beta power and its relation to interval timing**

To investigate whether other EEG components could index timing during the to-be-timed interval, Chapter 6 investigates the role of oscillatory power in time estimation (also see Kononowicz & Van Rijn, 2014b). As previous studies have linked the ramping of oscillatory power in theta and beta frequency bands to the function of evidence accumulation (e.g., Donner, Siegel, Fries, & Engel, 2009; Van Vugt, Simen, Nystrom, Holmes, & Cohen, 2012), these two frequency bands are the potential candidates to index temporal performance. Based on a reanalysis of the data reported in Chapter 2, the analyses reported in Chapter 6 demonstrate that trial-to-trial variability in interval timing is predicted by beta oscillatory power measured immediately after the onset of the interval, suggesting that temporal reproduction is biased from the onset of a temporal interval. Interestingly, the slope of the down-ramp of beta oscillatory power within timed interval did not differentiate between time reproductions. In other words, beta power does not seem to reflect the slope of temporal integration, but in terms of drift diffusion models of temporal decision making (e.g., Simen, Balci, deSouza, Cohen, & Holmes, 2011) beta power effect could be interpreted as reflecting trial-to-trial fluctuations in the starting point of a decision process. This assumption suggests that beta power is involved in an early formation of temporal judgment. As beta power was measured at the onset of the reproduced duration, these results indicate that instead of just looking at the offset of reproduced durations as is typically done in interval timing studies, future studies should also take into account any differences at or before the onset of the interval.

**The role of SMA in interval timing**

The results presented in this thesis together with other studies investigating CNV in humans have demonstrated that this ramping pattern originates from the SMA and pre-SMA. Apart from studies on interval timing, the role of the SMA seems to be an important and hotly-debated topic in other fields of cognitive neuroscience, evidenced by the observation that studying the SMA increases the chances to publish one’s work in higher impact factor journals (Behrens et al. 2013). The SMA has been associated with phenomena that have an obvious temporal aspect, such as rhythmicity and beat perception, but also with phenomena that have a more indirect link to timing, such as intentions, volition, and movement preparation. For
example, Penfield and Welch (1951) reported that weak current stimulation of the SMA caused patients to feel the urge to move. Along the same lines, Lau, Rogers, Haggard, and Passingham (2004) found that the activation of the pre-SMA did increase when participants were asked to pay attention to the intention of movement (for review see Haggard, 2008; Tanji, 1994). More specifically related to timing, Coull, Vidal, Nazarian, and Macar (2004) and Liu et al. (2013, also see Schubotz, 1999) have reported that the activation of the SMA is a function of the attention devoted to a timing task, and other work has shown that it is also active during interval encoding and during interval comparison (Coull, Nazarian, & Vidal, 2008; c.f., Bueti & Macaluso, 2011). As climbing neural activity is often recorded in the SMA and premotor structures (Casini & Vidal, 2011; Van Rijn et al., 2014), a common view is that the SMA serves as the accumulator for the pulses generated in other parts of the brain (e.g., Bueti & Macaluso, 2011; Macar et al., 1999), presumably in the basal ganglia, or in more general terms, that the SMA is a crucial brain structure involved in interval timing tasks (e.g., Wiener et al., 2012). However, the work by Livesey, Wall and Smith (2006) showed that when a timing task was contrasted against a non-temporal but difficult task, the SMA was not more active during the timing task, suggesting that the SMA might reflect relative cognitive demands.

In this thesis, instead of contrasting timing tasks against a control task, the activity driving a timing task was correlated with timing behavior. The data presented in Chapter 2 and 4 nicely aligns with the notion that SMA is important in interval timing, but cannot be seen as a brain structure directly responsible for perception of temporal intervals. Chapter 4 investigated the relationship between behavioral performance in a time reproduction task and the amplitudes of the CNV and its magnetoencephalographic analogue, the CMV. Unlike earlier studies correlating CNV and CMV activity, participants in this study were asked to reproduce supra-second temporal durations. Chapter 4 had two crucial findings that add to the functional role of SMA in interval timing. Firstly, in contrast to the CNV, which shows a steady increase in amplitude from the onset until the offset of an interval, only the last part of the CMV, the so-called pre movement magnetic field (preMMF) which originated from the SMA, tracks the reproduction of supra-second temporal durations. The preMMF was most likely related to late movement preparation. As the signature of the CMV/preMMF differs from the CNV, we argue that additional information on the neural mechanisms of interval timing can be obtained when these two components are both assessed when investigating the role of SMA in reproduction of temporal intervals. The second finding was based on the positive correlations between behavioral performance and CNV amplitudes.

Unfortunately, there is currently no alternative proposal in the time perception literature that would describe the functional role of SMA in such a simple and mechanistic way as the temporal accumulation hypothesis. For example, the striatal beat frequency (SBF) model (Matell & Meck, 2004) posits that timing arises from coincidence detection between medial spiny neurons and cortical oscillators in prefrontal cortex and SMA (Gu, Van Rijn & Meck, 2014). However, it remains silent about the differentiation between these structures. Another possibility is that the SMA may play a less specific role than proposed by the temporal accumulator hypothesis. For example, the robust connectivity between the
General discussion

The role of pre and post-duration components in time perception

In a typical interval timing paradigm, a time interval is demarcated by brief sensory events (e.g., brief tone bursts or flashes of light) or indicated by continuous stimulation (Bueti & Macaluso, 2011; Coull et al., 2004). Typically, studies using neuroscience-methods to investigate interval timing (e.g., EEG, Praamstra, Kourtis, Kwok, & Oostenveld, 2006; Wiener et al., 2012; or single cell recordings Mita et al., 2009) have focused on brain signatures occurring during the timed interval. However, in the context of other cognitive tasks such as perceptual decision making, it has been demonstrated that behavioral response and the associated brain responses are not simply a function of stimulus-related processing, but that the perception of an event is influenced by the brain states before (e.g., Busch & Van Rullen, 2009; Deco & Romo, 2008; Engel, Fries, & Singer, 2001) and even after (Sergent, Wyart, Babo-Rebelo, Cohen, Naccache, & Tallon-Baundry, 2013) the event. Of course, this notion relates to other contemporary advancements in the cognitive neurosciences that propose that perception is an active process (Friston, 2010). All these considerations indicate that influences on the judgment of temporal
durations may not be temporarily constrained to the period of the temporal interval, but that pre- and post-interval neural activity may play a role in interval timing. However, there are only few studies that have explored post-interval periods (e.g., Genovesio, Tsujimoto, & Wise, 2006, 2009) whereas, to our best knowledge, the pre-interval period has not been investigated.

In Chapter 6 we investigated whether the activity measured before the onset of the interval influences the produced duration and we showed, for the first time, that beta power measured before the self-initiation of the time interval predicts the length of the produced duration. We hypothesized that dependency is driven by either pre-setting the level of motor inhibition or alternatively by adjusting the starting point of the decision process. Although the data did not allow for a specific claim with respect of the role of beta power in the context of information-processing models of interval timing, beta power could reflect several factors that might influence the internal clock (e.g., modulations of the clock speed, also see Burle & Casini, 2001). In the context of the SBF model, an explanation is more readily available, as beta power in pre-interval period can be linked to the tonic level of dopamine, a neurotransmitter crucial for biologically plausible models of interval timing such as the SBF (Mattel & Meck, 2004).

Whereas studying the pre-interval period might provide additional insight in the workings of the clock component - especially the starting phase - studying post-interval periods can be beneficial for unraveling the mechanisms associated with making a decision based on temporal information. Although most work has focused on the neural signatures observed during the interval, some studies have focused on the responses evoked by the end of the interval. For example, Brannon, Libertus, Meck, & Woldorff (2008) used a temporal oddball task and showed that the mismatch negativity increases as a function of the temporal difference between standard and deviating intervals. Similarly, Loveless (1986) showed that the amplitude of the N2/P3 complex increases as a function of temporal deviance. The amplitude modulation found in these studies has been interpreted as a reflection of a degree of deviance, suggesting that a currently elapsing interval is automatically compared to a template duration (see also Mento et al., 2013; Mento, 2013). Where methodological issues limited Brannon et al. (2008) and Loveless (1974) to assess only the potentials evoked by shorter than standard durations, Chapter 5 investigated potentials evoked by durations shorter and longer than the standard interval. In line with the earlier results, the observed amplitudes were a function of the deviance with the standard, with the N1P2 amplitude forming a V-shaped pattern as it tracked the distance to the standard interval (cf. Tarantino et al., 2010). This symmetric pattern of post-interval components indicates the brain remains sensitive to temporal duration even after standard interval has passed. Recently these results have been replicated in the temporal oddball task in which participants were presented with two oddball durations longer than the standard duration (Mento, Tarantino, Sarlo, & Bisiacchi; under review). As these authors used high-density EEG recordings, they were able to utilize the source reconstruction technique and identify cortical sources of the offset components. The results showed two active sources: the right dorsolateral prefrontal cortex and the SMA. The activity in both structures increases as a function of deviance of temporal oddball. The r-DLPFC has typically been associated with temporal prediction and
monitoring. However, the right Inferior Frontal Gyrus was also involved in the pre-attentive change detection (Tse & Penney, 2008; Tse, Tiun, & Penney, 2006) that suggests a pivotal role of right frontal cortex that depends on task demands. As only one set of probabilities was used in the study by Mento et al. (0.7, 0.3, 0.3, proportions for 1.5, 2.5, and 3s durations, respectively), the lack of condition with modified proportions withhold from clear distinction between the comparison account and the hazard rate account. Nevertheless the study by Mento et al. (under review) further extends the results by Kononowicz and Van Rijn (2014) in that it showed a composition of neural sources that play a role in the comparison process. Of course, it would be of great interest to explore underlying hierarchy and connectivity of these sources as it has been demonstrated in case of Mismatch Negativity component using direct causal modelling (e.g., Garrido, Kilner, Kiebel, Friston, 2008). Such a technique also allows for modelling of deep brain sources (David, Maess, Eckstein, and Frederici, 2011), which could be involved in the generation of prediction error that modulates post-interval components (Kononowicz & Van Rijn, 2014).

Although only little information is available regarding the offset components, the Laplacian-based analysis of the N1P2 amplitudes in Chapter 5, and the results described by Mento et al. suggest that the SMA is involved in the comparison process. Interestingly, a similar V-shaped pattern of neuronal responses, recorded from dopaminergic neurons, has been observed in a single-cell study in monkeys reported by Fiorillo, Newsome, and Schultz (2008). Fiorillo et al. trained monkeys in a conditioning paradigm with a fixed interval between a conditioned stimulus and reward (juice) delivery (Fig. 2A). After some training, and obeying the principles of Pavlovian conditioning, juice was delivered after a variable interval. The authors measured how dopamine neurons in the substantia niagra (SN) and ventral segmental area (VTA) respond to the juice delivery. The response of dopamine neurons followed V-shaped pattern with the lowest spiking rate when a juice drop was delivered at the time of standard interval (Fig. 2C), apparently coding for the prediction error. This V-shaped pattern of dopamine neurons strikingly resembles the N1P2 amplitude modulation reported in Chapter 4. Besides dopaminergic activity in the SN and VTA, the V-shaped pattern has also been found by Mayo and Sommer (2012, see their Figure 2A) who measured spiking responses from monkeys frontal eye fields in the temporal visual discrimination task with durations ranging from 300 to 400ms. Although these authors focussed on the comparison between strength and latency coding in the encoding of temporal duration, it can be clearly seen that a V-shaped pattern is present in some neurons. These studies show that a temporal-prediction error driven V-shaped pattern is present in various brain regions, but as of yet it is not clear whether these patterns in different locations are related to each other.

Future studies should also investigate whether there is any functional link between these new markers of interval timing and CNV. For example, studies should examine how the neural signatures of the comparison process on trial \( n \) may affect other components (e.g., beta power and CNV) on trial \( n+1 \) (also see Durstewitz, 2003).

To summarize, pre- and post-interval activity has rarely been studied as the majority of studies in humans and animals focus on the ramping activity during the
interval. Nevertheless, investigation of pre- and post-interval components provides additional insight in the mechanisms underlying interval timing, and thus to additional support for interval timing theories.

Figure 2. Results of experiment 3 replotted based on Fiorillo, Newsome, & Schultz (2008). A: Experimental design of experiment 3. B: Approximation of neuronal firing over the course of a trial in which juice is present. Orange error bars depict phasic response that is depicted in panel C as bar graph. C: Responses of dopamine neurons as a function of a stimulus-reward interval.
Conclusion

To conclude, the neuroimaging studies presented in this thesis suggest that climbing neural activity does not serve as the temporal accumulator. Hence, the CNA originating from SMA is unlikely to be the accumulator of temporal information and could be involved in some less specific processes. This thesis proposes that the CNA indexes the brain’s excitation in order to prepare for an upcoming event. As CNA is not the source of subjective timing, this thesis proposes that temporal information has to be provided by another brain process possibly, with the cortico-striatal mechanisms proposed by the SBF model as a potential candidate. The SBF model (Matell & Meck, 2004) proposes that timing is derived from coincidence detection between medial spiny neurons and oscillating cortical assemblies that are reset at the onset of the interval to create repeatable patter of activity over multiple time intervals. Another possibility is that timing arises from time-dependent changes in the network state such that timing is defined as a unique trajectory in the multidimensional neural activity space. Future studies should further elucidate which of these mechanisms are the most applicable for interval timing or how they could work in concert to produce our subjective experience the passage of time.
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