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Neural Basis of the Perception and Estimation of Time

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Keywords

temporal processing, interval tuning, medial premotor cortex, cortico-thalamic-basal ganglia circuit, striatal beat-frequency model

Abstract

Understanding how sensory and motor processes are temporally integrated to control behavior in the hundredths of milliseconds-to-minutes range is a fascinating problem given that the basic electrophysiological properties of neurons operate on a millisecond timescale. Single-unit recording studies in monkeys have identified localized timing circuits, whereas neuropsychological studies of humans who have damage to the basal ganglia have indicated that core structures, such as the cortico-thalamic-basal ganglia circuit, play an important role in timing and time perception. Taken together, these data suggest that a core timing mechanism interacts with context-dependent areas. This idea of a temporal hub with a distributed network is used to investigate the abstract properties of interval tuning as well as temporal illusions and intersensory timing. We conclude by proposing that the interconnections built into this core timing mechanism are designed to provide a form of degeneracy as protection against injury, disease, or age-related decline.

Contents

INTRODUCTION

Timing is everything. The flow of information through time structures how information is perceived, experienced, and remembered. Throughout normal development we gradually acquire a sense of duration and rhythm that is basic to many facets of behavior such as speaking, driving a car, dancing to or playing music, and performing physical activities (Allman et al. 2012, Meck 2003). Yet there is no specific biological system that senses time as there are for sight, hearing, and taste. As such, there has been an explosion of research into the neural underpinnings of timing. Initially, a driving force behind many studies was scalar timing theory, which defined sources and forms of timing variability that were derived from clock, memory, and decision processes (Gibbon et al. 1984). However, as an understanding of the neurobiological bases of timing developed, so did a neurophysiological model of timing (Matell & Meck 2004), which captured the intrinsic interactive nature of interval-timing circuits as well as Weber's law and the scalar property of interval timing (Brannon et al. 2008, Cheng & Meck 2007, Gu et al. 2013, Meck & Malapani 2004).

This article reviews recent progress toward elucidating the neural mechanisms of interval timing, wherein durations in the range of hundreds of milliseconds to multi-seconds are perceived, estimated, or reproduced. We begin by discussing advances in psychophysics and in cell-ensemble recording that address the fundamental debate about whether explicit timing is governed by a common system or by distributed context-dependent networks. Next, we review current research into the functional significance of neuroanatomical systems that govern interval timing. We then consider emerging investigations into brain mechanisms underlying distortions in temporal resolution, which emanate from intersensory timing or factors that produce illusions of time. This body of research indicates that interval timing emerges from interactions of a core timing center with distributed brain regions. To this end, the striatal-beat frequency model of interval timing (Matell & Meck 2004) is discussed, which captures the psychophysiological and neuroanatomical properties of timing networks.

EVIDENCE FAVORING A COMMON TIMING MECHANISM

The psychophysics of the perception and estimation of time started in the late nineteenth

century (Fraisse 1984) and evolved as many timing tasks and species were studied to test the boundaries of categorical scaling (Penney et al. 2008) and the existence of one or multiple clocks (Buhusi & Meck 2009b). One central finding was that the variability of interval timing is proportional to the duration of the interval used. This scalar property implies that the standard deviation of the quantified intervals increases proportionally with the average of the intervals and follows Weber's law. Weber's law is given as $SD(T) = kT$, where k is a constant corresponding to the Weber fraction. The coefficients of variation (σ/μ) or the Weber fractions show similar values in the range of hundreds of milliseconds in a variety of tasks, sensory modalities, and species, suggesting a common timing mechanism for this, and perhaps other, time scales (Gibbon et al. 1997). The conceptual framework behind this hypothesis proposes that the temporal resources of a common internal clock are shared in a variety of timing tasks, thereby producing similar temporal variance (**Figure 1*a***).

Another major finding was that the overall variability in a timing task can be dissociated into time-dependent (e.g., clock) and time-independent (e.g., motor) sources (Repp 2005). Different quantitative and paradigmatic strategies were used to distinguish components of performance variability. The slope method, for instance, uses a generalized form of Weber's law, wherein investigators compute a linear regression between the variability and the squared interval duration. The resulting slope corresponds to the time-dependent component, whereas the intercept corresponds to the time-independent processes. Slopes of interval discrimination and synchronization-continuation tapping tasks are similar for a range of intervals from 325 to 550 ms (Ivry & Hazeltine 1995), supporting the view of a common clock in a variety of contexts (**Figure 2*a***). Moreover, temporal variability among an individual's performance correlates between different explicit timing tasks, including self-paced tapping tasks using the finger, foot, and heel (Keele et al. 1985), tapping and phasic figure drawing (Zelaznik et al. 2002), and duration-discrimination and tapping tasks (Keele et al. 1985). This correlation implies that participants who are good timers in one behavioral context are also good timers in another, again in support of a common timing mechanism.

The study of perceptual learning and generalization to other behaviors and modalities has provided important insights into the neural underpinnings of temporal processing (**Figure 1*b***). For example, intensive duration-discrimination learning can generalize across untrained auditory frequencies (Karmarkar & Buonomano 2003), sensory modalities, and stimulus locations (Nagarajan et al. 1998), and even from sensory to motor-timing tasks (Meegan et al. 2000). However, these studies found no reliable generalization toward untrained durations, which concurs with a study of duration-production learning that reported a smooth decrease in generalization as the untrained interval deviated from the trained duration and suggested the existence of neural circuits that are tuned to specific durations (Bartolo & Merchant 2009). Overall, these findings support the notion of a common or a partially overlapping distributed timing mechanism, but they also introduce the concept of duration-specific circuits. Of course, these two features are not mutually exclusive when a large neural network is considered (Karmarkar & Buonomano 2007, Matell & Meck 2004).

EVIDENCE FAVORING A UBIQUITOUS TIMING ABILITY OF CORTICAL NETWORKS

Other studies support the hypothesis that timing is an inherent computational ability of every cortical circuit and that it can be performed locally (**Figure 2*b***). This notion, based on network simulations, implies that cortical networks can tell time during perception tasks as a result of time-dependent changes in synaptic and cellular properties, which influence the population response to sensory events in a history-dependent manner (Karmakar & Buonomano

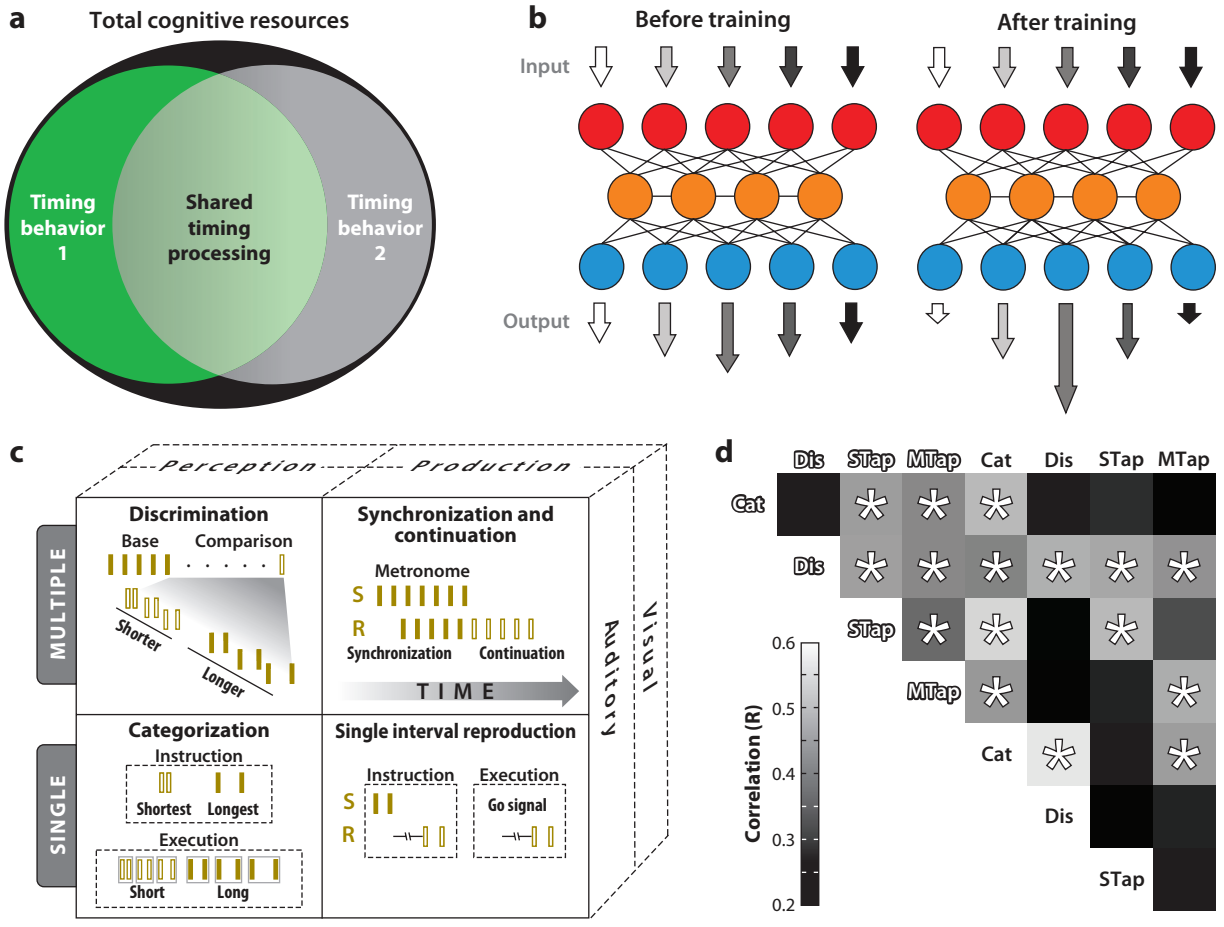

Figure 1

Psychophysical tools to study the neural underpinnings of interval timing using a black-box approach. (*a*) The hypothesis in some experimental psychology studies is that because some cognitive resources are shared across timing tasks there should be a common timing mechanism. (*b*) The characterization of the generalization properties of specific overlearned timing tasks across modalities, stimulation sites and properties, interval durations, and timing contexts; also has been used to test the existence of a common or multiple interval clocks. (*c*) Timing tasks. Four timing tasks, performed with auditory or visual interval markers, were used to evaluate the influence of three factors on timing performance: visual versus auditory modality, single versus multiple intervals, and perception versus production of the intervals. (*d*) Correlation matrix showing the Pearson R value in a grayscale matrix (*inset*, *bottom left*) for all possible pairwise task comparisons. Asterisks indicate significant correlations ($P < 0.05$) between specific pairs of tasks. Open and closed fonts correspond to tasks with auditory and visual markers, respectively. Abbreviations: Dis, discrimination; Cat, categorization; STap, single interval reproduction; MTap, synchronization and continuation task. Adapted from Merchant et al. 2008c.

2007). In contrast, motor timing is thought to depend on the activity of cortical recurrent networks with strong internal connections capable of self-sustained activity (Buonomano & Laje 2010). Chronic stimulation in cortical slices produces changes in the temporal structure of the cell activity that reflect the durations used during training (Johnson et al. 2010). Hence, this in vitro experimental evidence suggests that recurrent cortical circuits have inherent timing ability in the hundreds of milliseconds.

Psychophysical experiments also suggest that sensory timing is local. For example, the apparent duration of a visual stimulus can

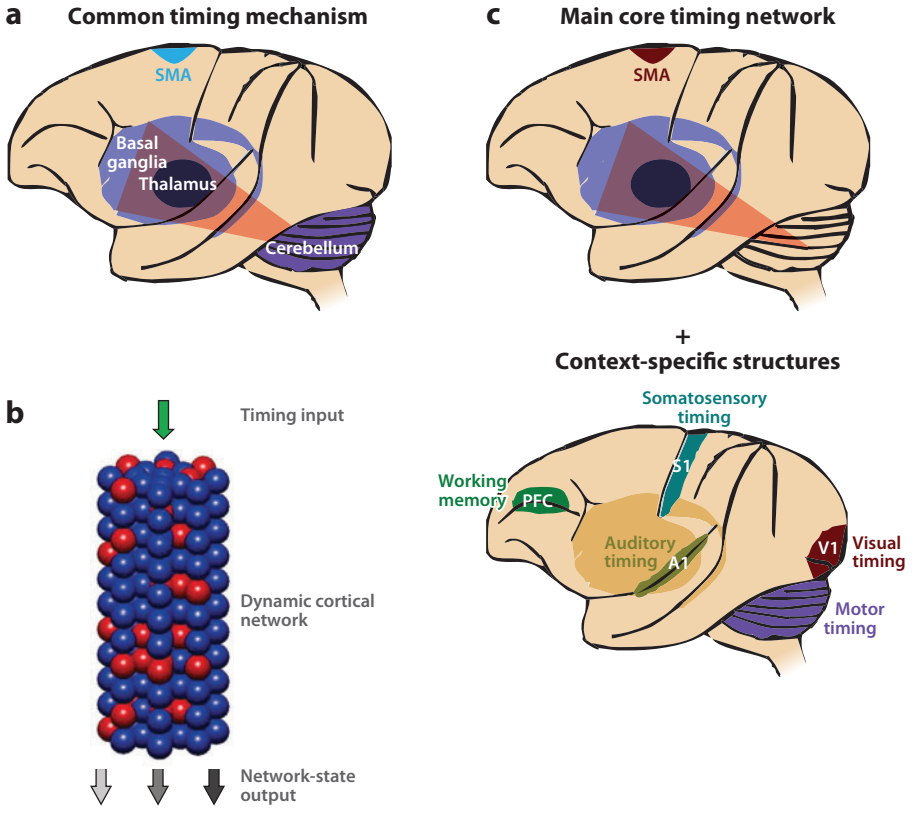

Figure 2

Three possible timing mechanisms. (*a*) Common timing mechanism. Psychophysical and lesion studies have suggested the existence of a dedicated timing mechanism that depends on one neural structure such as the cerebellum or the basal ganglia and that is engaged in temporal processing in a wide range of timing behaviors. However, fMRI studies have suggested that this general timing mechanism is distributed and depends on the activation of a large network including the supplementary motor area (SMA), the parietal and prefrontal cortices, as well as the basal ganglia and the cerebellum. (*b*) Ubiquitous timing. Modeling and cell-culture recordings have suggested that timing is an intrinsic property of cortical network dynamics and therefore that there is no dedicated neural circuit for temporal integration. (*c*) Partially shared timing mechanism. This model proposes that temporal estimation depends on the interaction of multiple areas, including regions that are consistently involved in temporal processing across timing context and that conform the main core timing network and areas that are activated in a context-dependent fashion. The main core timing network consists of the SMA and the basal ganglia. The interaction between the two sets of structures gives the specific temporal performance in a task. The red triangles correspond to the dopaminergic system innervating the basal ganglia.

be modified in a local region of the visual field by adapting to oscillatory motion or flicker, which suggests a spatially localized temporal mechanism for time perception of visual events (Burr et al. 2007, Johnston et al. 2006). Furthermore, learning to discriminate temporal modulation rates is accompanied not only by a specific learning transfer to duration discrimination, but also by an increase in the amplitude of the early auditory evoked responses to trained stimuli (van Wassenhove & Nagarajan 2007). These studies emphasize the concept of timing as a local, context-dependent process.

CTBG: cortico-thalamic-basal ganglia

MPC: medial premotor areas

SMA: supplementary motor area

AN INTERMEDIATE HYPOTHESIS: A MAIN CORE TIMING MECHANISM INTERACTS WITH CONTEXT-DEPENDENT AREAS

Other research suggests that a hybrid model may better account for temporal performance variability in different contexts. Merchant and colleagues (2008c) conducted a multidimensional analysis of performance variability on four timing tasks that differed in sensorimotor processing, the number of durations, and the modality of the stimuli that defined the intervals (**Figure 1*c***). Though variability increased linearly as a function of duration in all tasks, compliance with the scalar property was accompanied by a strong effect of the nontemporal variables on temporal accuracy (Merchant et al. 2008b,c). Intersubject analyses comparing performance variability between pairs of tasks revealed a complex set of correlations between many, but not all, tasks, irrespective of stimulus modality (**Figure 1*d***). These results can be interpreted neither as evidence for multiple context-dependent timing mechanisms, nor as evidence for a common timing mechanism. Rather, in accordance with neuroimaging research described below, the findings suggest a partially distributed timing mechanism, integrated by core structures such as the cortico-thalamic-basal ganglia (CTBG) circuit and areas that are selectively engaged by different behavioral contexts (Buhusi & Meck 2005, Coull et al. 2011) (**Figure 2*c***). Task-dependent areas may interact with the core timing system to produce the characteristic pattern of performance variability in a specific timing paradigm and the pattern of intertask correlations depicted in **Figure 1*d***.

NEUROPHYSIOLOGICAL BASIS OF TIME ESTIMATION: RAMPING ACTIVITY IN THE CORE TIMING CIRCUIT

Cell activity changes associated with temporal processing in behaving monkeys are found in the cerebellum (Perrett 1998), basal ganglia (Jin et al. 2009), thalamus (Tanaka 2007), posterior parietal cortex (Leon & Shadlen 2003), prefrontal cortex (Brody et al. 2003; Genovesio et al. 2006, 2009; Oshio et al. 2008), dorsal premotor cortex (Lucchetti & Bon 2001), motor cortex (Lebedev et al. 2008), and medial premotor areas (MPC), namely the supplementary (SMA) and presupplementary motor areas (preSMA) (Mita et al. 2009). These areas form different circuits that are linked to sensorimotor processing via the skeletomotor or oculomotor effector systems. Most studies report climbing activity during a variety of timing tasks. Therefore, the increase or decrease in instantaneous activity with the passage of time is a property present in many cortical and subcortical areas that may be involved in different aspects of temporal processing in the hundreds of milliseconds range.

Recently, the activity of MPC cells was recorded during a synchronization-continuation tapping task (SCT) that includes basic sensorimotor components of rhythmic behaviors (Zarco et al. 2009) (**Figure 1*c***). Different types of neurons exhibit ramping activity before or after the button press in the SCT (Merchant et al. 2011). A large group of cells shows ramps before movement onset that are similar across produced durations and the sequential structure of the task and are considered motor ramps (Perez et al. 2013) (**Figure 3*a***). Another cell population exhibits an increase in ramp duration but a decrease in slope as a function of the monkey's produced duration, reaching a particular discharge magnitude at a specific time before the button press. These cells are called relative-timing cells because their ramping profile appears to signal how much time is left to trigger the button press (**Figure 3*b***). Another group of cells shows a consistent increase followed by a decrease in their instantaneous discharge rate when the neural activity was aligned to the previous button press. In these absolute-timing cells, the duration of the up-down profile of activation increases as a function of the produced interval (**Figure 3*c***), whereas in the time-accumulator cells we see

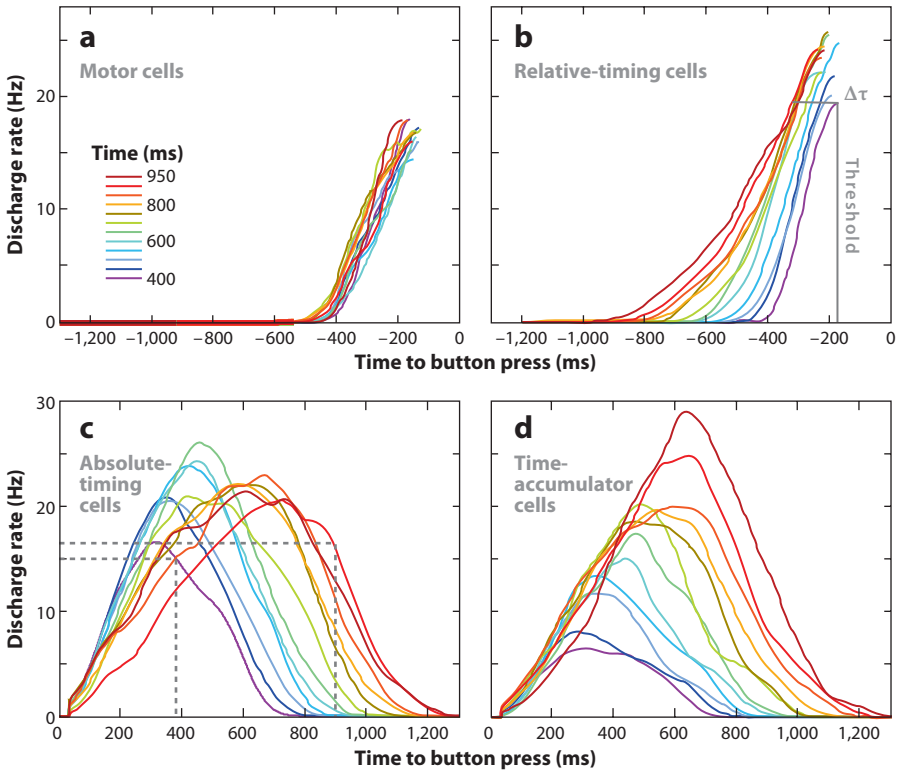

Figure 3

Ramp population functions for motor (*a*) and relative-timing (*b*) cells aligned to the next button press. Ramp population functions for absolute-timing (*c*) and time-accumulator (*d*) cells aligned to the previous button press. The color code in the inset of panel *a* corresponds to the duration of the produced intervals during the synchronization-continuation tapping task (SCT). The ramp population functions are equal to the total magnitude of individual ramps over time. Adapted from Merchant et al. 2011.

an additional increase in the magnitude of the ramps' peak (**Figure 3*d***). Therefore, these cells could be representing the passage of time since the previous movement, using two different encoding strategies: one functioning as an accumulator of elapsed time where the peak magnitude is directly associated with the time passed, and another where the duration of the activation period is encoding the length of the time passed since the previous movement. The noisy character of ramping activity implies that whatever is reading this temporal information downstream cannot be relying on single cells to quantify the passage of time or to produce accurately timed movements. Therefore, a population code is suggested for encoding elapsed time, by which the reading network adds the magnitudes of a population of individual ramps over time, resulting in a ramp population function (Merchant et al. 2011) (**Figure 3**).

The rhythmic structure of the SCT may impose the need to predict when to trigger the next tap to generate an interval, but also to quantify the time passed from the previous movement to have a cohesive mechanism to generate repetitive tapping behavior. Indeed, the cells encoding elapsed (absolute-timing) and remaining time (relative-timing) interacted during the repetitive phases of the SCT, supporting the proposed rhythmical timing mechanism (Merchant et al. 2011).

The ubiquitous increases or decreases in cell discharge rate as a function of time across different timing tasks and areas of the core CTBG timing circuit suggest that ramping activity is a fundamental element of the timing mechanism. Key characteristics of ramping activity are its instantaneous nature and the fact that it normally peaks at the time of an anticipated motor response. Although the absolute-timing and the time-accumulator cells (**Figure 3*c*,*d***) are encoding elapsed time since the previous motor event, ramping cells are engrained in the temporal construction of motor intentions and actions (Merchant et al. 2004). This integration is crucial because interval-timing tasks require a response to express a perceptual decision or produce a timed response. Therefore, the ramping activity may be part of the temporal apparatus that gaits the motor responses. However, more abstract tasks such as interval tuning may represent the more cognitive aspects of temporal processing that can be dissociated from the motor response and the corresponding ramping activity.

INTERVAL TUNING: AN ABSTRACT SIGNAL OF TEMPORAL COGNITION

Investigators have observed a graded modulation in the cell discharge rate as a function of event duration during the SCT in MPC. **Figure 4*a*,*c*** shows the activation profile of a cell in the preSMA of a monkey performing this task. The neuron shows a larger discharge rate for the longest durations, with a preferred interval around 900 ms (**Figure 4*e***). In fact, a large population of MPC cells is tuned to different signal durations during the SCT, with a distribution of preferred durations that covers all intervals in the hundreds of milliseconds. These observations suggest that the MPC contains a representation of event duration, where different populations of duration-tuned cells are activated depending on the duration of the produced interval (Merchant et al. 2012b). Most of these cells also showed selectivity to the sequential organization of the task, a property that has been described in sequential motor tasks in MPC (Tanji 2001). The cell in **Figure 4*a*,*c*** also shows an increase in activity during the last produced interval of the task's continuation phase. Again, at the cell-population level, all the possible preferred ordinal sequences were covered. These findings support the proposal that MPC can multiplex event duration with the number of elements in a sequence during rhythmic tapping (Merchant et al. 2013).

Researchers have evaluated the existence of a common timing mechanism or a set of context-dependent neural clocks on interval-selective cells, comparing their tuning properties during the execution of two tasks: the SCT and a single duration reproduction task (SIRT) (**Figure 1*c***) (Merchant et al. 2013). A large group of neurons showed similar preferred durations in both timing contexts. **Figure 4*a–d*** shows that the cell that is tuned to long durations during the SCT is similarly tuned during the SIRT. Furthermore, the tuning curves for the cells in the SCT and the SIRT are similar for auditory and visual markers (**Figure 4*e***). These findings confirm that MPC is part of a core timing circuit and suggest that interval tuning can be used to represent the duration of intervals in different timing tasks. Additional experiments are needed to determine whether tuning to event duration is an emergent property of MPC cells that depends on the local integration of graded inputs or occurs throughout the CTBG circuit (Matell et al. 2003, 2011). In summary, cell tuning is an encoding mechanism used by the cerebral cortex to represent different sensory, motor, and cognitive features, including event duration (Merchant et al. 2012). This signal must be integrated as a population code, in which the cells can vote in favor of their preferred duration to establish the interval for rhythmic tapping (Merchant et al. 2013).

NEUROANATOMICAL AND NEUROCHEMICAL SYSTEMS FOR INTERVAL TIMING

Turning to neuroanatomical and neurochemical levels of analysis, investigations in humans

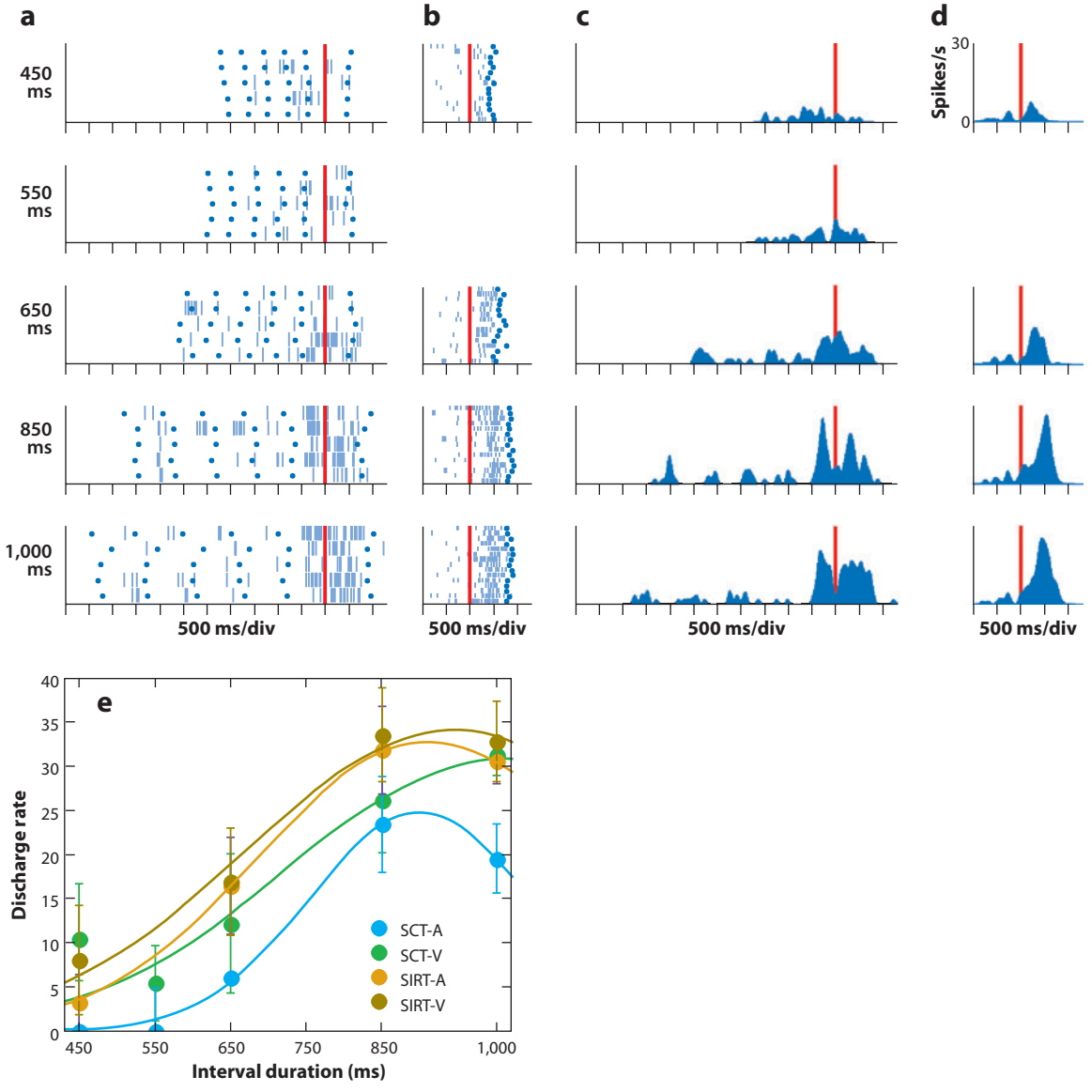

Figure 4

Interval tuning across tasks and sensory modalities. Responses of an interval-tuned cell with a long preferred interval across different temporal contexts. (*a*) Raster histograms (*blue*) aligned (*red line*) to the third tap of the continuation phase during the synchronization-continuation tapping task (SCT) in the visual condition. (*b*) Raster histograms (*blue*) aligned (*red line*) to the first tapping movement during the single duration reproduction task (SIRT) in the auditory condition. (*c*, *d*) Average spike-density functions of the responses shown in panels *a* and *b*, respectively. (*e*) Tuning functions for the same cell, where the mean (± SEM) of the discharge rate is plotted as a function of the target interval duration. The continuous lines correspond to the significant Gaussian fittings: SCT, visual SCT, auditory SIRT, visual SIRT.

DEGENERACY AND THE NEURAL REPRESENTATION OF TIME

Lewis & Meck (2012) have recently proposed a form of degeneracy in timing systems that parallels the degeneracy observed in many other aspects of brain function, as well as in the genetic code and immune systems (Mason 2010, Price & Friston 2002). Degeneracy is a type of functional compensation that is distinct from redundancy in that structurally different mechanisms are involved in degeneracy, whereas multiple copies of identical mechanisms are the basis for redundancy. The fundamental importance of timing to all perception and action necessitates degeneracy and may explain the ease with which timing can be performed by a range of different neural architectures (Wiener et al. 2011b). Degeneracy also allows for predictions about timing hierarchies and the sources and forms of variability in timing as a function of manipulations such as rTMS and reversible pharmacological treatments (Jahanshahi et al. 2010a,b; Teki et al. 2012). The applicability of this line of thought to time perception should be obvious: It is very difficult to abolish time perception completely, especially as a result of focal, unilateral brain lesions where, in addition to degeneracy, redundancy from the opposite hemisphere likely contributes to recovery (Aparicio et al. 2005; Coslett et al. 2010; Meck et al. 1984, 2013; Yin & Troger 2011).

and other animals emphasize the centrality of the striatum and dopamine (DA) neurotransmission in explicit timing (Agostino et al. 2011; Balci et al. 2013; Cheng et al. 2007; Coull et al. 2011, 2012; Gu et al. 2011; Hinton & Meck 1997, 2004; Höhn et al. 2011; Jones & Jahanshahi 2011; Lake & Meck 2012; Meck 1996, 2006a,b; Pleil et al. 2011). These findings are compatible with reports of timing dysfunction in disorders of the basal ganglia, including Parkinson's disease (PD) (Gu et al. 2013; Harrington et al. 1998b, 2011b; Jones et al. 2008; Koch et al. 2004, 2008; Meck & Benson 2002; Smith et al. 2007) and prodromal Huntington's disease (HD) (Paulsen et al. 2004, Rowe et al. 2010, Zimbelman et al. 2007). However, investigators have observed exceptions notably in PD, which has been studied the most extensively. For example, normal performance was reported on a test of motor timing (Spencer & Ivry 2005) and on several different tests of time perception (Wearden et al. 2008). The reasons for this variation are unclear but may be due to the insensitivity of tasks when temporal discriminations are easy and/or when feedback is frequently provided (Wearden et al. 2008). Another important consideration is that timing deficits in PD correlate with disease severity (Artieda et al. 1992). Numerous studies have tested early-stage PD patients, who, despite considerable DA cell loss, may have the capacity to compensate for cognitive difficulties. The cerebellum may be one compensatory route (Kotz & Schwartze 2011, Yu et al. 2007), possibly because it predicts and finely tunes behavioral states on the basis of an efferent copy of sensory and motor information. Cortical systems may support compensatory processing in PD, as well. These issues of degeneracy aside (see sidebar, Degeneracy and the Neural Representation of Time), the finding that subgroups of PD patients do and do not exhibit timing disturbances (Merchant et al. 2008a) resonates with the considerable heterogeneity in the disease's clinical symptoms, their day-to-day fluctuations, and individual differences in response to DA therapy.

Neurodegenerative disorders eventually alter cortical functioning, which may be another source of timing disturbances in PD and prodromal HD. Indeed, damage to the right hemisphere of the prefrontal (dorsolateral prefrontal and premotor) and the inferior parietal cortices disrupts time perception (Harrington et al. 1998b). Moreover, in patients with right but not left hemisphere damage, elevated temporal discrimination thresholds correlated with a weakened ability to reorient attention but did not correlate with deficits in pitch discrimination. This finding suggests that frontoparietal systems may govern attention and working memory, which interact with timekeeping processes (Lustig et al. 2005). Unfortunately, systematic investigations into cortical regions that are essential for timing in humans have been hampered by difficulties in obtaining sufficient samples of patients with focal damage, particularly to some brain regions now thought to be critical.

DA: dopamine

PD: Parkinson's disease

The advent of functional magnetic resonance imaging (fMRI) has been a welcome development to the study of timing. To date, most of this research has been conducted in healthy adults and has focused on regional activation patterns that are associated with various timing tasks. Research shows fairly good consensus that, apart from the basal ganglia, the SMA, an element of the CTBG (**Figure 2*c***), is routinely engaged during interval timing (Coull et al. 2011; Harrington et al. 2004, 2010; Meck et al. 2008; Wiener et al. 2010c). Carefully conducted meta-analyses further suggest that the rostral SMA, namely preSMA, may be more engaged by perceptually based timing within the suprasecond range, whereas caudal SMA may be more engaged by sensorimotor-based timing within the subsecond range (Schwartze et al. 2012). However, mounting evidence indicates that timing is governed by more distributed neural networks that are recruited depending on the behavioral context and stage of learning (Allman et al. 2012, MacDonald et al. 2012). Consequently, the major challenge has been to unravel their functional significance.

FUNCTIONAL SIGNIFICANCE OF BRAIN CIRCUITS THAT GOVERN INTERVAL TIMING

Temporal processing unavoidably engages a host of cognitive and sensorimotor processes that activate multiple brain regions. For this reason, it has been difficult in functional imaging to distinguish core-timing systems from those that support other interacting processes. One approach to the dilemma is to exploit the temporal resolution of event-related fMRI by linking the acquisition of brain images across time to different components of a task that are assumed to engage certain processes. The ordinal-comparison procedure commonly used to study time perception involves two steps: encoding an anchor or standard duration (encoding phase), followed by encoding a comparison interval and judging whether it is longer or shorter than the standard (decision phase) as illustrated in **Figure 5*a*** (Gu & Meck 2011, Harrington et al. 2004). A hypothetical hemodynamic response function associated with each of the phases is illustrated in **Figure 5*b***. One assumption is that activation in core-timing systems should be seen while encoding the standard and the comparison intervals. Activation in systems that support executive or decisional processes may be more apparent when comparing the two intervals during the decision phase when a judgment is made. To control for the engagement of cognitive and low-level sensorimotor processes, the time course of activation is compared with control tasks that contain the same stimuli but require different decisions. If auditory signals are timed, tasks that control for processing involved in perceptual decision making (pitch perception) or low-level sensorimotor processes (sensorimotor control tasks) may be used (**Figure 5*a***). An early fMRI study sought to distinguish timing-related brain activation using these methods (Rao et al. 2001). In the time-perception task, a 1,200-ms standard interval was compared with four shorter and longer intervals that were ±5% increments of the standard. For pitch perception, a 700-Hz standard tone was compared with 4 higher or lower comparison pitches. The results showed that caudate and putamen activation evolved early in association with standard-interval encoding and was sustained during the trial's decision phase. Activation of the right parietal cortex also began at the onset of the standard interval, possibly owing to its role in attention. In contrast, cerebellar activation unfolded later, just before and during movement execution, suggesting that it did not govern interval encoding. Subsequent studies using this general approach also linked striatal activation to interval timing (Coull et al. 2008, 2011; Harrington et al. 2004).

At the same time, independent empirical work (Lewis et al. 2004) and theoretical developments (Hazy et al. 2006) implicate the striatum in working memory. Owing to the short delays between the encoding and the decision phases of the time-perception tasks in earlier studies (Coull et al. 2008, Harrington et al. 2004, Rao et al. 2001), brain systems

fMRI: functional magnetic resonance imaging

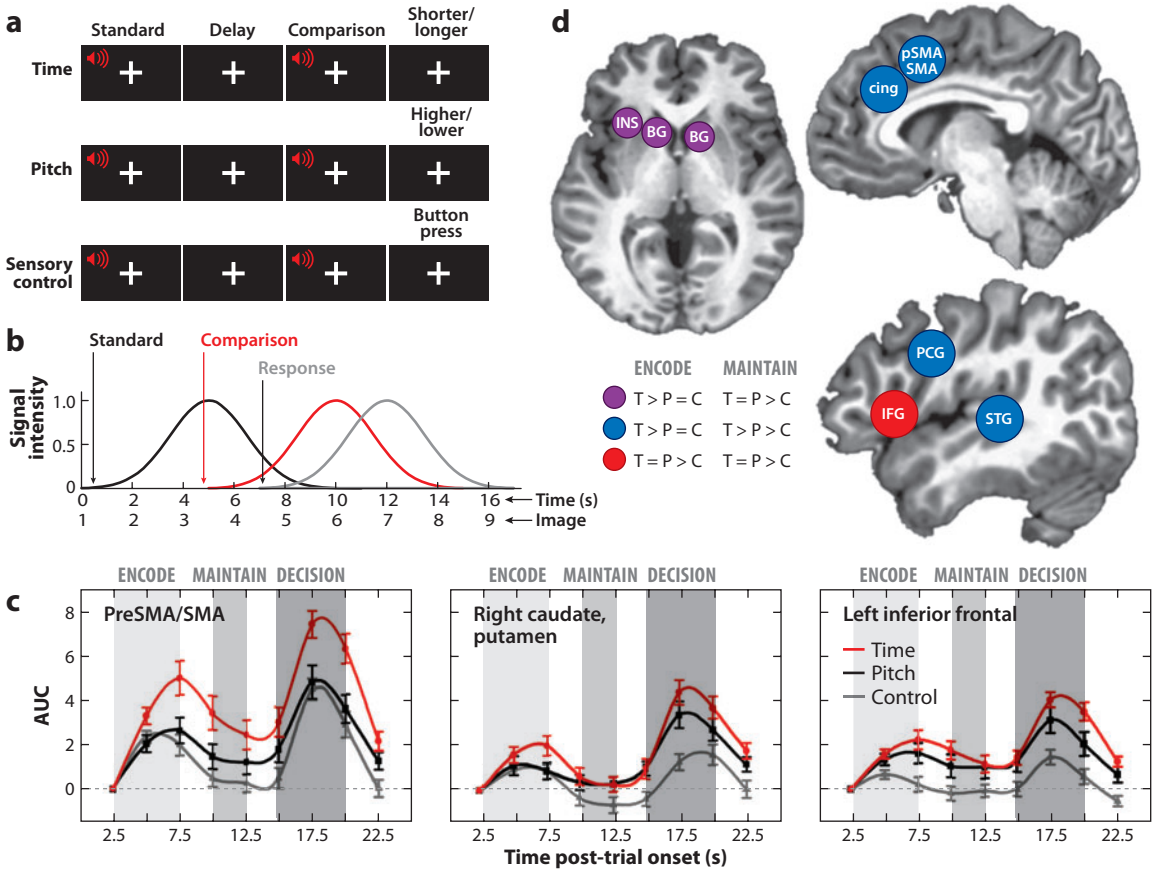

Figure 5

Functional significance of brain circuits that govern interval timing. (*a*) Illustration of the trial events in time-perception and control tasks. In the time-perception task, a standard and a comparison interval are successively presented and separated by a delay, which varies across studies. In the example, intervals are designated by tones. To control for brain activation related to cognitive and low-level sensorimotor processing, activation is compared with tasks composed of the same trial events but with different processing requirements. In the pitch perception task, the frequency of the two tones is discriminated. In the sensory control task, a button press is made following the presentation of the tones. A fixation cross remains on the screen during imaging. (*b*) The three hypothetical time-course functions illustrate the expected hemodynamic response associated with encoding the standard interval (*black*), encoding the comparison interval (*red*), and making a response (*gray*). Arrows leading from each event designate their onset. The hemodynamic response peaks 4 to 6 s after event onset. An image of the entire brain is acquired every 2 s. (*c*) Time course of activation (area under the curve; AUC) for the time-perception (*red*), pitch perception (*black*), and control (*gray*) tasks in representative regions (adapted from Harrington et al. 2010). Gray boxes on the *x* axis denote the epochs used to calculate AUC for a trial's encode, maintain, and decision phases. (*d*) Illustration of regional activation patterns for a trial's encode and maintain phases in the time (T), pitch (P), and control (C) tasks (Harrington et al. 2010). Activation in purple regions was related to interval encoding ($T > P = C$ for encode; $T = P > C$ for maintain). Activation in blue regions was related to accumulation and maintenance of sensory time codes ($T > P = C$ for encode and maintain). Activation in the red region was related to inhibitory control ($T = P > C$ for encode and maintain). For all regions except the IFG, activation was greater for the time than for the pitch and control tasks in the decision phase. Abbreviations: BG, basal ganglia; cing, anterior cingulate; IFG, inferior frontal gyrus; INS, anterior insula; PCG, precentral gyrus; preSMA, presupplementary motor area; SMA, supplementary motor area; STG, superior temporal gyrus.

involved in the maintenance of temporal information could not be ascertained. To address this issue, Harrington et al. (2010) inserted 10-s and 12.5-s delays between the standard and comparison interval, thereby permitting a better separation of activation associated with a trial's encoding, maintenance, and decision periods, as illustrated in **Figure 5*c***. Pairwise subtractions of brain activation during time discrimination (T), pitch discrimination (P), and the sensorimotor control (C) tasks were conducted for each period. Task difficulty did not differ between the time and the pitch tasks. The fMRI results showed that the striatum's pattern of timing-related activation during the different epochs could be distinguished from that found for most other brain regions. Striatal (bilateral caudate and putamen) activation was greater for the timing task than for the two control tasks (T > P = C) during encoding but did not differ between the time and pitch tasks (T = P > C) during maintenance (**Figure 5*c,d***). Thus, timing-related activity was specific to interval encoding, consistent with the positive correlation of striatal activation and timing proficiency noted during this same period (Coull et al. 2008, Harrington et al. 2004). This result also concurs with the view that passive maintenance of working memory is controlled via recurrent excitation of the prefrontal cortex and sensory neurons, and active maintenance over longer periods involves recurrent thalamocortical activity (Hazy et al. 2006). The only other region exhibiting the same activation pattern as did the striatum was the anterior insula. This region is situated to integrate processing from disparate domains (e.g., interoception, emotion, and cognition), including time (Kosillo & Smith 2010; Wittmann et al. 2010a,b), via its dense interconnections with most association centers and the basal ganglia. Moreover, anterior insula connectivity with frontal cognitive-control centers suggests that it also assists in the perceptual analysis of sensory information (Eckert et al. 2009). In contrast, preSMA/SMA, precentral, and superior temporal activation was greatest for the timing task (T > P = C) during both encoding and maintenance periods (**Figure 5*c,d***). This finding suggests that the preSMA and SMA modulate nontemporal aspects of processing, consistent with reports that timing-related activation is lost in the face of more difficult control tasks (Livesey et al. 2007). One prospect is that the SMA and association areas support accumulation and maintenance of sensory information, which is more demanding for interval timing. Another important finding was that activation of the inferior frontal gyrus did not differ between the time and pitch tasks during all three periods of the trial, although it was greater than in the control condition (T = P > C) (**Figure 5*c,d***). The inferior frontal gyrus is an inhibitory control center with fiber tracts to preSMA. This pathway may be a route to control the accumulation of sensory information into preSMA. Last, during the trial's decision phase, activation in almost all regions including the striatum was greater during the timing task (T > P > C), perhaps signifying the more significant integration demands of duration than pitch processing. In addition, timing-related activation of the cerebellum and a classic frontoparietal executive network did not emerge until the decision phase (T > P > C). The latter finding supports the positive correlation of frontoparietal region activity with time-discrimination difficulty (Harrington et al. 2004).

Taken together, interval timing was governed by distributed brain networks that flexibly altered activation, depending on task demands. Although some have argued that much brain activation during temporal processing relates to cognitive or sensory processes, timing emerges from the communication among brain regions rather than from processing in a single region. The use of control tasks can identify regional activity that is more dominant during timing; however, sensory and cognitive centers that are vital for interval timing can be overlooked. For example, using the subtractive method has led some to conclude that the inferior parietal cortex is not a key element of interval encoding (Coull et al. 2008, Harrington et al. 2010, Livesey et al. 2007). Yet applying

repetitive transcranial magnetic stimulation (rTMS) to the supramarginal gyrus of the right hemisphere dilated perceived duration owing to its effect on interval encoding (Wiener et al. 2010a, 2012). This result indicates that the right supramarginal gyrus is a critical element of the neural circuitry that encodes time, which corroborates the detrimental effect of right parietal damage on time perception (Harrington et al. 1998b). Furthermore, as we begin to explore how the brain construes time under circumstances that alter the resolution of perceived duration, interactions among larger-scale brain networks will likely be considerably important.

ILLUSIONS OF TIME

An area of research that has potential to enrich our understanding of timing networks concerns illusions of time, which are important because they reveal how the brain normally organizes and interprets information depending on internal states, past experiences, or properties of stimuli. Psychophysical studies have long reported that the experience of time is not isomorphic to physical time, but rather depends on many factors. For example, emotionally aversive events are perceived as lasting longer than their physical duration (Cheng et al. 2008a, Droit-Volet & Meck 2007). Larger magnitude, more complex, or intense stimuli also expand perceived duration, whereas repeated, high-probability, and nonsalient stimuli compress time (Eagleman 2008, van Wassenhove et al. 2008). The mechanisms of temporal illusions continue to be debated, but the consensus indicates that attention and arousal are key factors. In pacemaker-counter models, attention and arousal are thought to speed up or slow down timing by closing or opening a switch that allows pulses generated from a "clock" to be accumulated and counted (Buhusi & Meck 2009a, Ulrich et al. 2006). For instance, heightened levels of physiological arousal induced by psychologically negative sounds expand subjective duration (Mella et al. 2011). Reducing the level of attention devoted to timing compresses perceived duration and attenuates activation in the CTBG timing-related circuit, but also in the frontal, temporal, and parietal cortices (Coull et al. 2004, 2011).

Despite this impressive body of work, little is understood about brain mechanisms that bring about temporal illusions. Emerging neuroimaging research suggests that the mechanisms may be partially context dependent. One fMRI study investigated the neural mechanisms of time dilation produced by a looming visual stimulus (Wittmann et al. 2010b), which captures attention possibly because it signals a potential intrinsic threat to organisms. Participants viewed a series of five discs; all but the fourth disc, which was a looming or receding disc, were static, and participants judged whether the fourth stimulus was longer or shorter than the others. Relative to the receding control condition, activation was greater in rostral-medial frontal areas and medial-posterior cortices, including the posterior cingulate. These areas are tightly interconnected with the limbic system, which governs a variety of functions including emotion and motivation processing. The results were attributed to the arousing effect of looming signals, which have an inherently emotional component.

Another study investigated mechanisms of time dilation produced by emotionally aversive stimuli (Dirnberger et al. 2012). Participants judged which of two pictures was displayed for a longer or shorter amount of time. Perceived duration was dilated when one of the pictures was aversive (aversive-neutral) relative to a control condition, in which both pictures were neutral. On a subsequent recognition test, overestimation of time was associated with better memory of a picture, indicating that time dilation enhanced memory encoding. A region-of-interest analysis revealed that activation of rostral-medial frontal areas (superior frontal, preSMA/SMA) and lateral inferior frontal cortex was greater for aversive-neutral than control pairs. Brain activation was further distinguished by the accuracy of time discriminations, whereby right amygdala, anterior insula, and putamen activation was greater on trials in which time was overestimated than on correct

trials. Thus, when time was dilated, the limbic system (amygdala) and tightly interconnected regions, notably the anterior insula and medial frontal cortex, were more engaged. Taken together, both studies suggest that time dilation via stimuli that have an emotionally threatening connotation is partly brought about by heightened activity in elements of the limbic system and interconnecting medial cortical areas.

Temporal distortions also emerge in contexts that have no emotional overtone, such as the illusion that auditory signals are perceived as lasting longer than visual signals of the same physical duration when they are compared. A recent fMRI study sought to investigate the neural basis of the illusion (Harrington et al. 2011a), which is of interest because it may elucidate how synchrony is maintained across the senses. The audiovisual effect on perceived duration has been attributed to a pacemaker-accumulator system that runs faster for auditory than for visual signals, possibly owing to an attentional switch that permits a faster accumulation of pulses (Lustig & Meck 2011). In this study, participants judged whether an auditory (A) or visual (V) comparison interval was longer or shorter than a standard interval, which was either of the same or a different modality (**Figure 6*a***). Time was dilated relative to all other conditions when the duration of an A comparison interval was judged relative to a V standard (V-A), and time was compressed when the duration of a V comparison interval was judged relative to an A standard (A-V) (**Figure 6*b***). Regional analyses of brain activation showed that audiovisual distortions were governed by frontal cognitive-control centers (preSMA, middle/inferior frontal), where activation was greater when time was compressed, and higher association centers (superior temporal cortex, posterior insula, middle occipital cortex), where the level of activation was driven by the modality of the comparison interval (**Figure 6*c***). Although this study identified regional activation differences between time dilation and compression, timing emerges from communication among brain networks, to which conventional regional analyses of activation are insensitive. As such, the effective connectivity of these regions was examined to determine if the strength of their interactions with other brain regions differed between the time dilation and compression conditions. Effective connectivity was not found for frontal cortical areas, possibly because, as supramodal control centers, they flexibly direct attention and executive resources, though more so when time discriminations are demanding (A-V). Rather, connectivity of bilateral association areas with frontoparietal and temporal cortices and the striatum was typically stronger when perceived duration was dilated than when compressed (**Figure 6*d***). This result may be due to the salience of auditory signals in the context of timing (Repp & Penel 2002). This attention-based explanation would cause "clock pulses" to accumulate faster (pacemaker/accumulator models) or perhaps increase cortico-cortical oscillatory frequencies (Allman & Meck 2012), thereby producing an overestimation of time for auditory signals. Altogether, the finding reveals a basic principal of functional organization that produces distortions in the experience of time.

Notably, regional activation of the striatum did not differ between the time dilation and compression conditions (Harrington et al. 2011a). Although this result suggests that the integration of cortical oscillatory states by the striatum may not be faster for auditory than for visual signals, it leaves open the question of whether the strength of striatal connectivity is modulated by time dilation and compression (Matell & Meck 2004, N'Diaye et al. 2004). This area of inquiry is important for future research because measures of brain connectivity can be more sensitive to effects of psychological variables than are conventional regional analyses of activation. Indeed, it appears that the striatum may influence time dilation in emotionally aversive contexts (Dirnberger et al. 2012).

INTERSENSORY TIMING

The synthesis of temporal information across the senses is essential for perception and

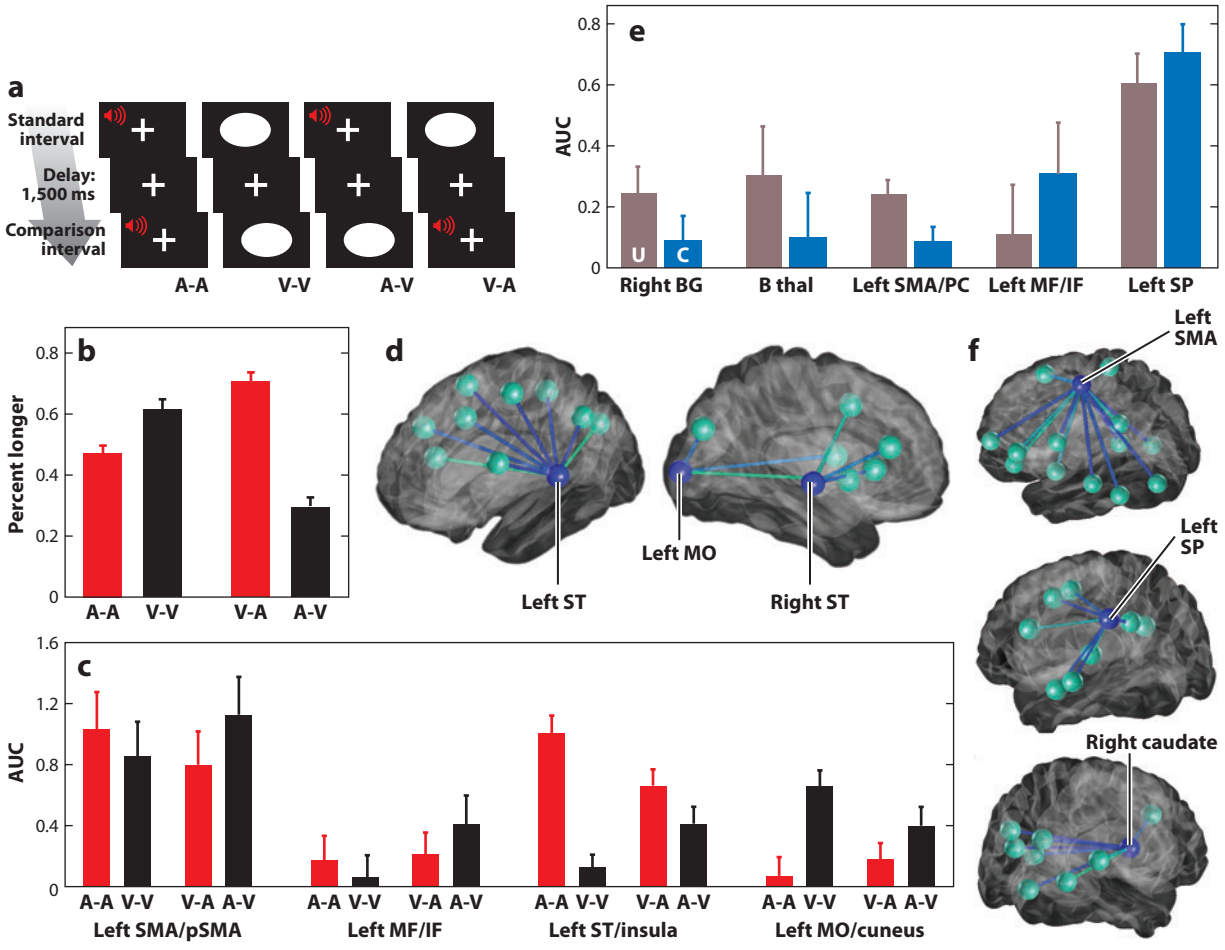

Figure 6

Brain networks that govern distortions in time and intersensory timing. The content contained in this figure is adapted from Harrington et al. (2011a). (*a*) Trial events for four conditions of a time-perception task. Pairs of auditory (A) and visual (V) stimuli were successively presented. The standard interval and comparison interval were of the same modality in the unimodal conditions (A-A, V-V) and were different in the cross-modal conditions (A-V, V-A). The four standard durations (1467, 1540, 1620, and 1710 ms) were each paired with three shorter and three longer comparison durations that were ±7% increments of each standard interval. A fixation cross remained on the screen during imaging. (*b*) Mean percent longer responses. Relative to all other conditions, time was significantly dilated for the V-A condition and compressed for the A-V condition. (*c*, *d*) Results from analysis of time dilation and compression effects on brain activity. (*c*) Mean area under the curve (AUC) in representative regions showing an interaction of comparison interval modality × timing condition (unimodal versus cross-modal). Horizontal bars denote significant differences between conditions. (*d*) Connectivity map of the left and right superior temporal cortex and left middle occipital cortex with representative regions. Effective connectivity of the bilateral superior temporal cortex and insula and the left middle occipital cortex was typically stronger for the time dilation than for the compression condition. (*e*, *f*) Results from analyses of brain systems that govern intersensory timing. (*e*) Mean AUC in representative regions showing differences in activation between unimodal and cross-modal timing. (*f*) Connectivity maps of left SMA, left superior parietal cortex, and right caudate with representative regions. Effective connectivity for all regions was stronger for cross-modal than for unimodal timing. Abbreviations: BG, basal ganglia (caudate, putamen); IF, inferior frontal; MF, middle frontal; MO, middle occipital cortex; PC, precentral cortex; preSMA, presupplementary motor area; SMA, supplementary motor area; SP, superior parietal; ST, superior temporal; Thal, thalamus.

cognition, yet little is understood about how the brain maintains temporal synchrony among modalities. The striatum may be central to governing intersensory timing because it is involved in multisensory integration (Nagy et al. 2006) and is thought to integrate cortical oscillatory activity that comprises the clock signal (Coull et al. 2011). These proposals agree with a report that the bilateral striatum and also the thalamus and SMA exhibit greater activation during unimodal as compared with cross-modal timing (Harrington et al. 2011a) (**Figure 6*e***). The result was not compatible with an attention-switching model of striatal function (van Schouwenburg et al. 2010), which would predict greater activation in the cross-modal than in the unimodal condition. The activation pattern may develop if intersensory integration of time codes is less stable or noisier relative to intrasensory timing. By comparison, activation of a classic frontoparietal working-memory network was greater for cross-modal than for unimodal timing, likely because of greater attention and executive demands of intersensory timing. The effective connectivity of these regions was then examined to determine if the strength of their interactions with other brain regions differed between the timing conditions. All regions showed stronger connectivity for cross-modal than for unimodal timing, perhaps owing to the more effortful demands of multimodal temporal integration. **Figure 6*f*** illustrates that caudate, SMA, and superior parietal connectivity was stronger with frontal cognitive-control centers, association centers, visual areas, and a memory system (precuneus, posterior cingulate, parahippocampus). Thus, the synthesis of audiovisual time codes in core timing and attention networks involves interactions with extensive brain networks.

STRIATAL BEAT-FREQUENCY MODEL OF INTERVAL TIMING

The inherent interactive nature of timing networks revealed by the above studies is embodied by the striatal beat-frequency (SBF) model of interval timing (Allman & Meck 2012, Matell & Meck 2004, Oprisan & Buhusi 2011, van Rijn et al. 2011). The SBF model uses medium spiny neurons located in the dorsal striatum, which is typically thought to be involved in decision making and executive function. Each spiny neuron receives ~30,000 inputs from cortical neurons, and it is this level of convergence (many to one) that allows the medium spiny neurons to serve as coincidence detectors of activity patterns engaged in by the cortical neurons. One easily detectable activity pattern is the oscillatory firing pattern of cortical neurons that is typically synchronized to the onset of relevant stimuli by DA release from the substantia nigra pars compacta (Jahanshahi et al. 2006). Given this initial synchronization (i.e., temporary alignment of the downbeat of neural firing), the subsequent evolution of neural firing will reflect the inherent rhythmical structure of each neuron's tendency to fire as well as random drift or desynchronization of firing among individual neurons. Despite the variability in this pattern of neural firing, which grows as a function of the time since the initial synchronization, the medium spiny neurons can still detect different patterns of neural firing on the basis of the high degree of redundancy in the system due to the convergence of 30,000 inputs. This coincident detection involves the ability of medium spiny neurons to sense temporal patterns of simultaneous activity across their spatially arranged receptive fields. Individual synapses within these receptive fields are trained to detect and respond to specific patterns of oscillatory input on the basis of previous experience and the influence of long-term potentiation and depression—two well-known neurobiological mechanisms for the encoding of event durations (Matell & Meck 2000, 2004).

Each time period from milliseconds to seconds or minutes to hours will be reflected by different patterns of neural activity that can be repeatedly reproduced as long as the initial synchronization retains its efficacy and the pattern is not reset or interrupted by subsequent stimulus onsets affecting that particular set of detectors. Multiple durations can be timed simultaneously by assuming multiple detectors

SBF: striatal beat-frequency (model)

or timers (i.e., spiny neurons) within the striatum that display chronotopy, a preference for particular ranges of durations. The readout of such a timing system is provided by frontal cortex monitoring of the firing activity of this chronotopically arranged time line—thereby completing the CTBG circuit. In this respect, the SBF model is an important advancement because of its veracity at both behavioral and physiological levels. Previous timing models either provided a good description of timing behaviors, but contained components that were inconsistent with the properties of the brain structures involved, or were neurobiologically feasible, but made inaccurate behavioral predictions. The computational version of the SBF model as described by Matell & Meck (2004) is constructed such that its mechanisms are consistent with neural regions thought to be involved in timing (e.g., frontal cortex and striatum), and its output is consistent with physiological recordings and behavioral results from interval-timing experiments (Matell et al. 2003, 2011; Meck et al. 2012). Indeed, striatal neurons fire in a peak-shaped manner centered on the target duration, following the predictions of the SBF model. Critically, the SBF model reproduces the scalar property, the hallmark of interval timing (Gibbon et al. 1984, 1997; Van Rijn et al. 2013). Preservation of this scalar property is critical for experimental manipulations thought to influence the timing system per se (i.e., deviations are considered diagnostic of effects on other systems that influence behavior). In the SBF model, the scalar property occurs because of variability in the firing patterns of striatal neurons and because cortical activity is assumed to be oscillatory, such that firing patterns at the harmonics (i.e., 1/2, 2/3, etc.) are similar but not identical to those occurring at the target duration. Teki et al. (2012) recently proposed a unified model of interval timing based on coordinated activity in the core striatal and ancillary olivocerebellar networks that takes advantage of the interconnections between these networks and the cerebral cortex. Timing in this model posits a type of degeneracy (Lewis & Meck 2012) that involves the initiation and maintenance of timing by beat-based striatal activation that is adjusted by olivocerebellar mechanisms that can substitute for the striatal timing system as a function of neural deactivation if needed (Allman & Meck 2012, Jahanshahi et al. 2010a) and/or by genetic modifications of neurotransmitter/receptor function (Liao & Cheng 2005, Sysoeva et al. 2010, Wiener et al. 2011a) and aging (Balci et al. 2009; Cheng et al. 2008b, 2011a).

CONCLUSIONS

Recent research concurs with modern neurophysiological models whereby the capacity to perceive and estimate time is thought to emerge from interactions of a core CTBG timing circuit with brain regions that provide signals needed to time events (Allman & Meck 2012, Lustig & Meck 2005). Important advances from cell recordings further indicate that elements of the CTBG not only display chronotopy, but also represent organizational features of the context that permits more abstract timing behaviors (Merchant et al. 2011). At the neuroanatomical level, basal ganglia and SMA functioning were dissociated by differential activity that was respectively linked to fluctuations in the task's interval timing and working-memory demands (Harrington et al. 2010). Thus, elements of the CTBG timing circuit display different context-dependent activation dynamics that warrant further inquiry. The functional significance of networks engaged by timing will also be advanced by studies of how the brain construes time in situations that influence the resolution of perceived duration. Emerging research indicates that temporal distortions produced by emotionally charged events or stimuli that capture attention are partly brought about by activity in emotion or association networks (Dirnberger et al. 2012, Cheng et al. 2011b, Harrington et al. 2011a, Wittmann et al. 2010b). Although the role of the striatum remains debated in these studies, temporal distortions that emanate from intersensory timing are driven by the CTBG circuit. Likewise, degeneracy in timing

revealed by disease (Jahanshahi et al. 2010a) and individual differences in the expression of neurotransmitter function (Sysoeva et al. 2010, Wiener et al. 2011a) also hold promise for uncovering neurophysiological mechanisms of timing networks. More generally, it is important for future research to study brain connectivity, which more fully characterizes the communication of timing circuits with other brain networks (Cheng et al. 2011b; Harrington et al. 2011a,b; MacDonald & Meck 2004).

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