Reconfiguration of striatal connectivity for timing and action

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Abstract

The medial cortico-striatal-thalamo-cortical (CSTC) motor circuit is a core system that exerts control over interval timing and action. A common network generates these behaviors possibly owing to cellular coding of temporal and non-temporal information, which in turn promotes reconfiguration of functional connectivity in accord with behavioral goals. At the neuroanatomical level, support for flexible CSTC reconfiguration comes from studies of temporal illusions demonstrating that this system calibrates the experience of time through functional interactions with various context-sensitive brain regions. Revelations that CSTC effective connectivity is pivotal for context-dependent facets of voluntary actions, namely action planning, complement its role in predictive processes such as timing. These observations suggest that the CSTC is positioned to represent high-level information about 'what to do' and 'when to do it' by dynamically reconfiguring effective connectivity as circumstances arise.

Introduction

Research into the neural mechanisms of temporal processing and voluntary action have proceeded independent of one another, even though time is a basic facet of action representation that comes into play when anticipating and guiding the timing of movements. This review seeks to integrate recent findings across these areas by focusing on a core system that exerts control over interval timing and voluntary actions, namely the supplementary and presupplementary motor areas (SMA/preSMA), the striatum, and the thalamus, otherwise referred to as the cortico-striatal-thalamo-cortical (CSTC) system (Figure 1, bottom). We begin by discussing neurophysiological mechanisms by which this system governs interval timing and may also permit reconfiguration of CSTC functional interactions for the control of action. Indeed, CSTC interactions are conditional on the behavioral goal, which is highlighted by the discovery that different neural architectures are specialized for relative and absolute forms of timing. We then consider emerging studies of temporal illusions, which demonstrate that CSTC interactions with various brain regions

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alter perceived duration in a contextually-sensitive manner. This revelation is a powerful illustration of the system's capacity for flexibly calibrating time and by extension, modulating context-dependent facets of voluntary action. Here, we discuss the pivotal role of the CSTC system in planning actions, which complements its role in relative timing.

CSTC system and dopamine neurotransmission in interval timing

A defining quality of purposeful behaviors is time and rhythm, which support the fluency, coordination, and organization of actions into abstract groupings [1]. Timing processes also optimize the prediction of when to act, drawing upon past experiences of temporal regularities in events or responses to them, which seemingly capture attention automatically. There is growing consensus across species that the striatum and dopamine (DA) neurotransmission (Figure 1, top) exert control over interval timing in the range of milliseconds to several seconds ([2–5]; for reviews see [6••,7,8]). This is compatible with impaired timing in basal-ganglia disorders such as Parkinson's disease (PD) [9•,10••,11–13] and prodromal Huntington's disease (prHD) [14,15]. However, psychophysiological features of interval timing, such as the scalar property, emerge through striatal interactions with the cerebral cortex. According to the striatal beat-frequency model, medium spiny neurons of the dorsal striatum sense temporal patterns by serving as coincidence detectors of activity engaged by cortical neurons, which comprise the 'clock signal' ([16]; for reviews see [6••,17•]). One activity pattern is the oscillatory firing patterns of cortical neurons, which are thought to be synchronized to the onset of relevant stimuli via DA release from the substantia nigra pars compacta [18]. There is growing consensus that a key cortical component of interval timing is the medial prefrontal cortex, namely the SMA and preSMA, which complete the medial CSTC motor circuit (Figure 1, bottom). Although SMA function is not well understood, it is routinely engaged during timing [19–25] and may support the accumulation and maintenance of temporal information [21].

Another important finding is that the CSTC system governs relative (e.g., longer of two intervals) rather than absolute (e.g., 500 ms) or implicit forms of timing, in which temporal regularities in events or motor responses can be used to achieve non-temporal goals. For example, when beat rhythms (relative timing) are compared to non-beat rhythms (absolute timing), striatal activity was higher [26] and effective connectivity was stronger between the putamen and SMA [27]. Thus, the CSTC system is pivotal for predicting and generating rhythms. These findings agree with cell recordings in animals showing that temporal tuning in the striatum rescaled when intervals were expanded or contracted [28••]. By contrast, when irregular sequences of clicks were compared to regular sequences, activation was greater in the olivocerebellar system [29].

The prospect of distinct networks for relative and absolute timing is compatible with observations of increased cerebellar activity and effective connectivity in PD during interval timing [10••,30,31•], possibly signifying compensation for CSTC dysfunction. Indeed, temporal and musical cueing therapies for improving gait in PD also improved performance on timing tasks [11,12,32], partly owing to increased metabolism in cerebellar–temporal–parietal regions [33]. The benefits conferred by cueing therapies on movement further suggest that motor disturbances in PD are partly linked to deficient internal timing, possibly

due to CSTC coding of temporal and non-temporal information. In fact, cellular recordings in animals indicate that the SMA and putamen not only display chronotopy during timing, but also represent multiple information streams (e.g., time passed, remaining time for an action, serial order, sensorimotor state of organism) [28••,34,35••,36–39], which may enable the reconfiguration of functional interactions in accord with behavioral goals [40•]. These observations suggest that the CSTC is well placed to represent higher-level information about actions and their timing. Voluntary actions may also rely on the same oscillatory processes as proposed for interval timing [16,17•], yet differ in some measure with respect to the information streams that code features and reconfigure CSTC interactions for goal-directed action [40•].

Context-sensitive interactions of the CSTC calibrate perceived time

The proposal that the CSTC system flexibly alters interactions with various brain centers contingent on the situation is compatible with demonstrations that internal states of an organism, past experiences, and stimulus properties can distort the experience of time. Unraveling the mechanisms by which the CSTC system calibrates perceived duration is important because it also has implications for understanding how this system controls voluntary action, which is also context dependent [41–43]. It has long been known that emotionally aversive, larger magnitude, or intense stimuli are perceived as lasting longer than their physical duration, whereas duration is underestimated when stimuli are repeated, high probability, or non-salient (for a review see [44]). Although the neurobehavioral mechanisms underlying distortions in perceived duration remain debated, there is consensus that attention and arousal can speed up or slow down timing [45–47]. Emerging research also suggests that CSTC regions calibrate time via context-sensitive interactions with various brain centers.

One compelling demonstration of the striatum's role in calibrating time comes from an fMRI study of time dilation in an emotionally arousing situation. Participants judged the duration of aversive-neutral pictures or two neutral pictures, and after imaging memory for the pictures was tested [48•]. Recognition memory was better for aversive pictures that were incorrectly timed (overestimated) than for incorrectly timed neutral pictures. Moreover, activation was greater for incorrectly than correctly timed pictures in the amygdala, striatum, medial frontal cortex, and a region of the ventral attention network (Figure 2), the anterior insula, which is routinely engaged during timing [21,49,50]. Interestingly, better recognition of aversive pictures was correlated with greater insula and putamen activation on incorrectly, but not correctly timed trials. These results suggested that arousal of the ventral attention system by emotionally aversive pictures may accelerate the accumulation of activity into the striatum, which in turn compromises timing accuracy yet improves memory.

Distortions in perceived duration also arise in settings void of emotional undercurrent, wherein temporal information from different senses is commonly paired, namely audition and vision. Auditory signals are perceived as lasting longer than visual signals of the same duration when they are compared together [51•,52], owing to the dominance of audition, which presumably captures and sustains attention during timing more automatically than visual stimuli ([47]; for an alternative interpretation see [53•]). Thus, time is overestimated

(dilated) when the duration of an auditory (A) comparison interval is judged relative to a visual (V) standard interval (VA) and underestimated (compressed) when a V comparison interval is judged relative to an A standard (AV). One study reported that audiovisual timing was mediated by the CSTC, ventral attention (insula), and sensory-association systems (temporal-occipital) (Figure 2) [51•]. Frontal 'cognitive-control' centers (Figure 2) also exhibited greater activation when time was compressed (AV) than dilated (VA), consistent with the greater controlled attention demands of timing visual information, which if not sustained, leads to a loss in pulses from the pacemaker–accumulator mechanism [46]. Converging support for these findings comes from an fMRI study of audiovisual timing in PD [10••]. When timing emphasized controlled attention (AV), time compression was markedly exaggerated in patients relative to control participants, whereas when attention was more easily sustained (VA), time was dilated in both groups, but less so for patients. Importantly, abnormal CSTC and anterior insula effective connectivity in PD differed for the two audiovisual conditions. In the AV condition, effective connectivity of the CSTC and anterior insula was notably weakened in PD with distributed frontal cognitive-control centers and the ventral and dorsal attention networks (Figure 2), consistent with the considerable attentional demands of the condition. In the VA condition, however, effective connectivity of the striatum with frontal cortex and the SMA was stronger in PD relative to controls, possibly signifying compensation when attention to timing was less taxing. Regardless of the condition, effective connectivity of the cerebellum with frontal cortex was stronger in PD relative to controls, suggesting compensation in absolute timing systems [30,31•].

These discoveries are persuasive examples of the CSTC system's capacity for shaping perceived duration by integrating signals from contextually relevant systems involved in cognitive control, attention, emotion and sensory processing, which can also come into play during voluntary action. As such, reconfiguration of CSTC interactions with context-dependent brain networks may be a mechanism by which this system governs 'what to do' and 'when to do' it as a situation arises.

Configuration of CSTC system for action planning

Although it has long been known that voluntary actions are supported by the CSTC system, its specific functional role has received relatively less attention. Nonetheless, there is growing consensus that the CSTC system governs action planning, which is compatible with this system's role in predictive processes such as beat prediction, which depends on a representation of the structure of events to predict and guide behavior [26].

Indirect evidence for the centrality of the CSTC system in action planning comes from neuroimaging studies contrasting movements performed in the presence of sensory information that guides performance (externally guided) with movements performed from memory without external cues (internally generated). Early studies reported greater activation of the CSTC during internally-generated than externally-guided action [42,43], whereas frontoparietal and cerebellar activations were greater during externally-guided action [43]. Importantly, the different avenues for motor control were also distinguished by the type of functional interactions among the same set of brain regions. Stronger interactions

were found amongst the SMA, putamen, and thalamus during internally-generated movement, whereas interactions amongst the cerebellum, premotor cortex, and sensorimotor cortex were stronger during externally-guided movement [54].

Other studies seeking to directly unravel the neural mechanisms of action planning separated activation associated with the premovement period of planning a sequence and the movement period when the action is performed. One study also manipulated sequence complexity [41], which increases planning difficulty. CSTC and premotor cortex activation increased with sequence complexity, more so during the premovement than the movement phase of internally-generated sequences [41]. Notably, only basal ganglia activation increased with sequence complexity during the premovement, but not the movement phase, suggesting a specific role of the striatum in integrating information for action plans. Other studies using similar methods also endorsed a CSTC role in planning [55,56,57•], sometimes jointly with the substantia nigra [55], suggesting dopaminergic gating of motor sequences. Impaired motor planning and an abnormal reliance upon external cues to sequence or initiate actions in PD and prHD [58–62,63•,64,65] provide converging support for CSTC centrality in action planning. More generally, weakened CSTC effective connectivity is observed in PD during voluntary actions [63•] and self-initiated movements [61], whereas strengthened connectivity of the lateral premotor systems [66] or the cerebellar-thalamocortical system is found in PD, especially during externally guided action [67].

Interestingly, the CSTC and the cerebellar systems' respective roles in internally-generated and externally-guided movement parallel their control of relative and absolute timing. One speculation is that action planning exploits relative timing mechanisms, whereas online motor-control engages absolute or implicit timing processes, which predict sensory consequences of actions and rapidly fine tune movement on the basis of an efferent copy of sensorimotor information.

Conclusions

Altogether, interval timing and action planning appear to originate from the CSTC system. However, evidence for flexible, context-dependent CSTC interactions is only beginning to emerge. CSTC connectivity as modulated by timing versus action planning has yet to be studied, but would address basic questions about the nature of this system's interactions with the brain for different behavioral goals. The influence of cognitive demands on connectivity will be especially important as investigations move toward studying more complicated forms of timing (e.g., multiple events) and action planning (e.g., complex actions, larger repertoires of behaviors). These lines of inquiry are highly relevant to unraveling mechanisms of pathological timing and action in basal ganglia disorders, and may provide insight into cognitive-training approaches that target brain networks capable of compensating for neuronal dysfunction.

Acknowledgements

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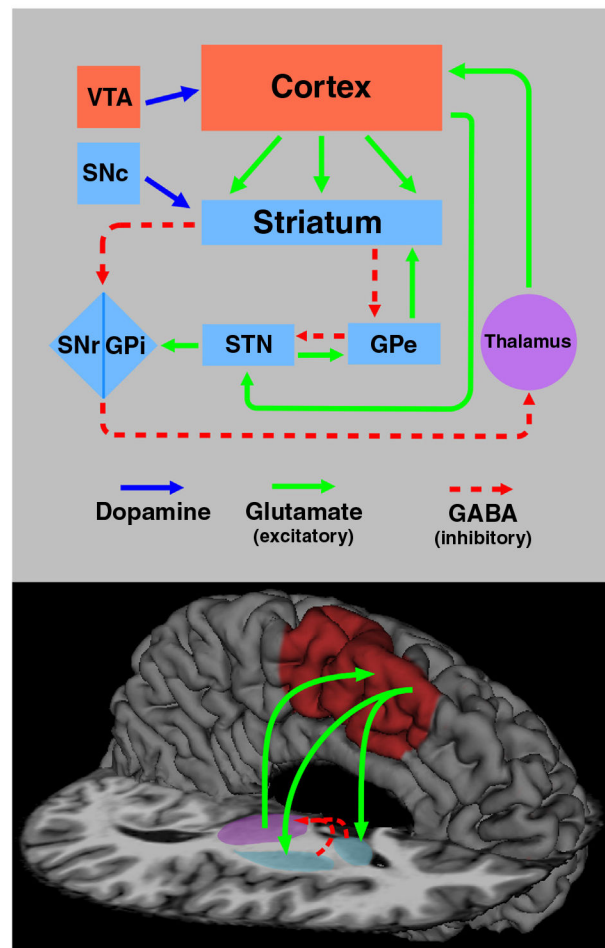
Figure 1.
Neural substrates of interval timing and action planning. (Top) An illustration of cortical-basal ganglia and neurotransmitter systems that are the cornerstone for interval timing and action representation. Elements of basal ganglia and cortical networks are respectively highlighted in light blue and red boxes. Multiple functionally-segregated circuits link the cortex and basal ganglia, which enables the control of timing and actions in a context-sensitive manner. The nigrostriatal dopamine pathway connects the substantia nigra pars compacta (SNc) to the dorsal striatum and is part of the motor circuit. The mesocortical dopamine pathway connects the ventral tegmental area (VTA) to the cortex, particularly the frontal lobes. Excitatory (glutamate) and inhibitory (GABA) projections are designated by green and red dashed arrows, respectively. (Bottom) A core system that governs both interval timing and action planning is the medial corticostriatal thalamo-cortical (CSTC) motor circuit, which consists of the SMA and preSMA (red), the striatum (blue), and the thalamus (purple).
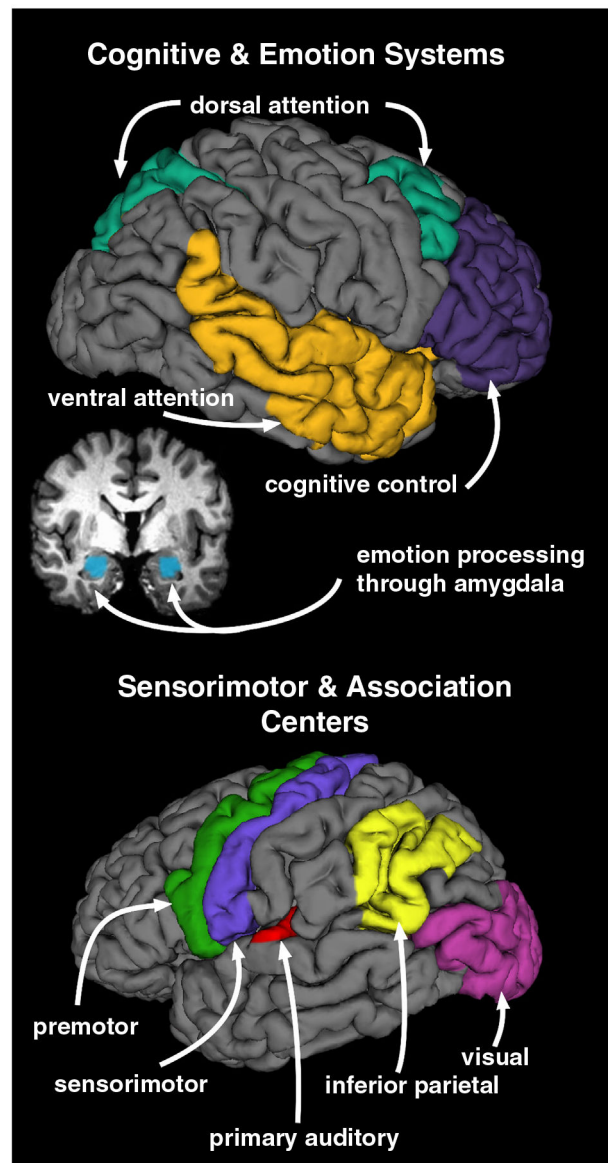
Figure 2.
Brain systems that display context-dependent interactions with the CSTC system. The CSTC
system is thought to shape the experience of time through interactions with other brain
centers that are relevant to a situation. Thus, by extension these functional interactions may
also come into play during action planning. (Top) Cognitive and emotion-based systems
interact with the CSTC system during interval timing in a contextually-sensitive manner.
Lateral and coronal views display cognitive and emotion processing centers known to
exhibit effective connectivity or co-activate with the CSTC system during interval timing.
CSTC functional interactions with of these regions are thought to bring about distortions in
perceived duration. These regions include frontal cognitive-control or executive processing
centers (purple), dorsal (green) and ventral (gold) attention networks, and an emotion-
processing hub, the amygdala (blue; coronal view). (Bottom) Sensorimotor and association
centers also interact with the CSTC system during interval timing and for the purpose of

action planning. These centers include the premotor (green), sensorimotor (blue), inferior parietal (yellow), primary auditory (red), and visual (fuchsia) cortices.