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Update article

Monitoring and switching of cortico-basal ganglia loop functions by the thalamo-striatal system

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Abstract

Recent physiological and tract tracing studies revealed tight coupling of the centre médian and parafascicular nuclei (the CM–Pf complex), which are posterior intralaminar nuclei (ILN) of the thalamus, with basal ganglia circuits. These nuclei have previously been classified as part of the ascending reticulo-thalamo-cortical activating system, with studies of single neuron activity and of interruption of neuronal activity suggested that they participate in the processes of sensory event-driven attention and arousal, particularly in the context of unpredicted events or events contrary to predictions. In this article, we propose a hypothetical model that envisions that the CM–Pf complex functions in two different modes depending on the predictability of external events, i.e., one for monitoring 'top-down' biased control through the cortico-basal ganglia loop system for selecting signals for action and cognition and the other for switching from biased control to 'bottom-up' control based on the signals of salient external events. This model provides a new insight into the function of the CM–Pf complex and should lead to a better understanding of this important brain system.

1. Introduction

The centre médian (CM) and parafascicular (Pf) nuclei, together referred to as the CM–Pf complex, are posterior intralaminar nuclei (ILN) of the thalamus that have been classified as part of the ascending reticulo-thalamo-cortical activating system (Moruzzi and Magoun, 1949; Isaacson and Tanaka, 1986; Hu et al., 1989; Steriade et al., 1997). Individual midline and intralaminar nuclei have also been shown to receive specific sets of afferents and to project to specific parts of the striatum and cerebral cortex (Groenewegen and Berendse, 1994). Major projections from the CM–Pf complex are directed to the striatum, while anterior parts of the ILN, i.e., the centralis lateralis (CL) and paracentralis (Pc) seem to participate in corticipetal activation (Paré et al., 1988; Steriade et al., 1997).

The ILN, including the CM–Pf complex, were suggested to convey multimodal sensory stimulus-driven signals to the striatum and to play a major role in behavioural orienting to the origin of a stimulus (Krauthamer, 1979; Grunwerg and Krauthamer, 1992; Coull et al., 2000; Matsumoto et al., 2001; Minamimoto and Kimura, 2002). Support for this theory came from studies that showed that attentional orienting was impaired by lesioning or inactivating the CM–Pf complex (Mancia and Marini, 1995; Minamimoto and Kimura, 2002) or the reticular nucleus of thalamus (Weese et al., 1999). Furthermore, contralateral visual neglect was reported to occur following the lesioning of the ILN in the cat (Orem et al., 1973) and humans (Watson and Heilman, 1979; Watson et al., 1981).

Since a number of regions in the brain, such as the premotor, prefrontal, parietal, and sensory cortices participate in attention and arousal, the specific role played by multimodal information encoded in CM–Pf complex neurons with attentional properties is unclear. This multimodal information is primarily directed to the input region of the basal ganglia, i.e., the striatum, which plays a critical role in cognition and motor function. In this article, we propose a hypothetical model in which the CM–Pf functions in one of two discrete modes depending on the predictability of external events—one that is used for monitoring top-down biased control through the cortico-basal ganglia loops that are used for selecting signals for action and cognition, and the other for switching from top-down to

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bottom-up control based on the signals from salient external events.

2. Tight coupling of the CM–Pf complex with basal ganglia circuits

Large, distinct sets of projections to, and relatively focused projections from, the CM–Pf complex to the basal ganglia and cerebral cortex have been identified. The inputs were shown to originate in the thalamic reticular nucleus (Royce et al., 1991; Steriade et al., 1994), cholinergic and non-cholinergic neurons in the brainstem pedunculopontine tegmental nucleus (PPTN) (Paré et al., 1988; Parent et al., 1988), the superior colliculus (Grunwerg and Krauthamer, 1992; Ichinohe and Shoumura, 1998; Krout et al., 2001), and the midbrain reticular formation (Vertes and Martin, 1988; Royce et al., 1991). In addition to these 'non-specific' inputs, the CM–Pf complex receives 'specific' basal ganglia inputs from the internal segment of the globus pallidus (Kuo and Carpenter, 1973; DeVito and Anderson, 1982; Parent and De Bellefeuille, 1983; Sidibé et al., 1997) and the substantia nigra pars reticulata (de las Heras et al., 1998; Sidibé et al., 2002; Tsumori et al., 2003), as well as from the cerebral cortex (Steriade et al., 1997).

In contrast to its large, distinct sets of inputs, the CM–Pf complex projects relatively focused excitatory signals to the striatum (Nakano et al., 1990; Fenelon et al., 1991; François et al., 1991; Sadikot et al., 1992; Steriade et al., 1997) and subthalamus (Steriade et al., 1997; Orieux et al., 2000; Bacci et al., 2002), though some also project to the cerebral cortices (Steriade et al., 1997; Hatanaka et al., 2003). Fibres that leave the CM predominantly project to the putamen while the Pf projects primarily to the caudate nucleus and nucleus accumbens (Sadikot et al., 1992). The thalamo-striatal projection innervates cholinergic and parvalbumin-containing interneurons as well as projection neurons (Lapper and Bolam, 1992; Sidibé and Smith, 1999; Matsumoto et al., 2001). Dopaminergic modulation of this thalamo-striatal pathway may not be essential since the thalamic nerve terminals that synapse on the shaft of proximal dendrite of spiny projection neurons in the striatum and the boutons of dopaminergic fibres do not converge on the same postsynaptic structures. This is in contrast to the cortico-striatal fibre terminals and boutons of dopaminergic fibres which converge and synapse on the dendritic spines of striatal projection neurons (Smith and Bolam, 1990; Smith et al., 1994). Thus, the thalamo-striatal system appears to have the potential to influence synaptic integration of striatal projection neurons directly, as well as indirectly through interneurons in a manner that is less able to be influenced by dopaminergic neurons.

3. Salient sensory events activate CM–Pf neurons

In only a few studies have investigators recorded the activity of ILN neurons; their results showed that these neurons respond briskly to multimodal sensory stimuli of a visual, auditory, and somatosensory nature (Krauthamer, 1979; Grunwerg and Krauthamer, 1992; Krauthamer et al., 1992). Neurons in the primate CL and Pc thalamic nuclei receive large amounts of contralateral visual receptive field information and were found to be insensitive to stimulus size, shape, and brightness but responsive to changes in the visual scene (Schlag and Schlag-Rey, 1984).

Recently, Matsumoto and others who examined single neuron responses in the primate CM–Pf complex to visual, auditory, and tactile stimuli on the arm and shoulder (Matsumoto et al., 2001), identified the presence of two types of neurons—one that displayed short latency facilitation (SLF) that was located primarily in the Pf and another that displayed long latency facilitation (LLF) that was located mainly in the CM. More than two-thirds of these neurons were multimodal and exhibited dominant responses to auditory stimuli. When the same stimulus occurred repeatedly, the neuronal response to the stimulus gradually decreased suggesting that these cells play a role in attentional processing in which novel, unpredictable stimuli are involved (Matsumoto et al., 2001). Involvement of the CM–Pf complex in attentional control of action was investigated by using the cued-target detection task, a conventional attention paradigm in which a visual trigger stimulus appeared either 80% of the trials at the same spatial location as the preceding warning signal (valid condition) or 20% of the trials at an opposite location (invalid condition) (Minamimoto and Kimura, 2002). Reaction times in the valid condition were found to be shorter than those in the invalid condition. The validity effect, i.e., the difference between the reaction times in the two conditions, has been suggested to reflect covert attention on the location of the warning stimulus (Posner, 1980; Bowman et al., 1993). SLF-type neurons showed strong activation when the warning stimulus appeared in the contralateral visual field. Fig. 1 shows the average response of SLF neurons in response to a warning signal and to valid and invalid targets. Inactivation of the CM–Pf complex by the local infusion of muscimol, a GABA$_A$ receptor agonist, abolished the validity effect.

The ILN and midbrain reticular formation were found to be specifically activated in human subjects when they transitioned from a relaxed awake state to the performance of an attention-demanding reaction time task (Kinomura et al., 1996). The reticular nucleus of the thalamus, which exerts strong inhibitory control over both specific sensory relay nuclei and the ILN (Steriade et al., 1997), was shown to be activated during the presentation of attended stimuli, as determined by the increased presence of Fos-positive neurons (McAlonan et al., 2000).

These lines of experimental evidence suggest that the ILN is critically involved in the processes of attention and arousal. On the other hand, it remains unclear how the processes of attention and arousal in the ILN contribute to action mechanisms. LLF neurons in the CM, but not SLF neurons in the Pf, exhibit activations in relation to arm

movements in the cued-target detection task (Minamimoto and Kimura, 2002). Although the sensory responses of the SLF neurons on the whole were not strongly dependent on whether the stimuli were associated with a reward or not, there was a tendency for the SLF neurons to show larger responses to stimuli that were not associated with a reward (Matsumoto et al., 2001). This finding is in contrast to the reported properties of neurons in the striatum with preferences for reward-associated stimuli (Hikosaka et al., 1989; Aosaki et al., 1994b; Hollerman et al., 1998). Nevertheless, the responsiveness of striatal neurons to reward-associated stimuli appears to critically depend on inputs originating in the CM–Pf complex, since inactivation of the neuronal activity of the CM–Pf complex by the local infusion of muscimol almost completely abolished the responses of striatal neurons to reward-associated stimuli (Matsumoto et al., 2001). Furthermore, SLF neurons showed greater responses to invalid targets which appeared on the opposite side relative to the warning signal than to valid targets that appeared in the same location as the warning signal (Fig. 1). While paying attention to the location of the warning signal allowed monkeys to respond with shorter reaction times to valid targets which appeared 80% of the trials, in the invalid condition, monkeys needed to shift their attention from the location of the warning signal to the invalid target, the latter of which appeared 20% of the trials. In light of these findings, it seems plausible that critical aspects of the activation of SLF neurons may reflect the switching from attentionally biased top-down control of behavioural responses to a valid target to sensory-driven control of the behavioural reaction to such a target. It is possible that the remarkable ability of CM–Pf neurons to specifically switch to sensory-driven control

plays an indispensable role in counterbalancing the potent top-down control of this process through the cortico-basal ganglia loop system. On the other hand, the magnitude of the responses to both valid and invalid targets appears to be closely related to the probability of occurrence of these stimuli. In other words, the responses are larger when the predictability of the stimulus is low, while they are smaller when the stimulus is fairly predictable. This may, in part, explain why the responses of SLF and LLF neurons to a click noise without reward were larger than those to a click noise that was followed by a reward. In the click-with-reward condition, monkeys received their reward *as expected*, whereas in the click-without-reward condition, the monkeys may have expected a reward that never came, even though they understood that the click would not be accompanied by a reward. This hypothesis was recently supported by the observation of a much stronger activation of LLF neurons after the appearance of one of two possible visual signals that required an action to be performed without any reward than after one that was followed by a reward (Minamimoto et al., 2003).

Taken together, the characteristic properties of neuronal activity suggest that the CM–Pf complex participates in the switching from top-down biased control to sensory-driven control of actions in the context of unpredictable or contra-predictable events, as well as in the processes of sensory event-driven attention and arousal.

4. Monitoring and switching of top-down biased control functions of cortico-basal ganglia loops through the thalamo-striatal system

As described above, the CM and Pf receive signals from the internal segment of the globus pallidus and from the substantia nigra pars reticulata, respectively (Sidibé et al., 1997, 2002). They also receive 'non-specific' signals that originate in the reticular nucleus of the thalamus, the superior colliculus, the PPTN, and the midbrain reticular formation. These nuclei (CM–Pf) then give major projections to the striatum and minor ones to the cerebral cortices. The output signals from the basal ganglia are fed back to the striatum by way of this 'internal loop' in parallel with the basal ganglia-thalamo-cortical 'external' loops. Figure 2 shows a simplified model of this proposed circuit. Fibres from the CM–Pf complex innervate projection neurons and interneurons in the striatum including cholinergic interneurons and parvalbumin-containing interneurons (Lapper and Bolam, 1992; Sidibé and Smith, 1999; Matsumoto et al., 2001). Neuronal signals mediating specific actions or cognition which are processed in the cerebral cortical areas converge on the neural circuits in the striatum (top-down signals), with reward-, motivation-, and attention-related information originating from the nigrostriate dopamine system, the limbic system, and the thalamus. Expectation of reward strongly enhances action- and cognition-related top-down signals (Kimura et al., 1984; Hikosaka et al., 1989; Aosaki
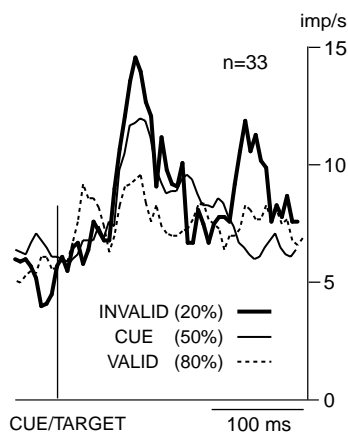

Fig. 1. Superimposed average responses of SLF-type neurons to a warning signal (CUE) and valid (VALID) and invalid (INVALID) targets that appeared in the contralateral visual field. The activity of 33 SLF-type neurons was centered at the onset of each stimulus (vertical line). The probability of occurrence of the cue either in the ipsilateral or contralateral visual field (thin solid curve) was 50%. The probabilities of occurrence of either valid (interrupted curve) or invalid (thick solid curve) targets in the contralateral visual field were 80 and 20%, respectively. Modified from Fig. 5 in Minamimoto and Kimura (2002).
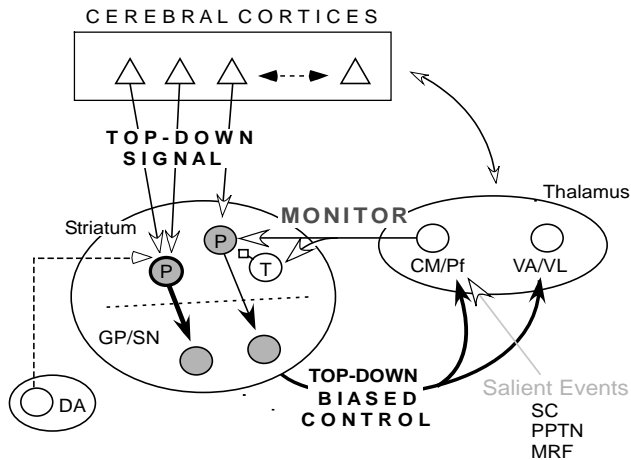
Fig. 2. A hypothetical model illustrating the role of the thalamo-striatal system in monitoring biased control function of cortico-basal ganglia loops. Open and filled arrows indicate the excitatory and inhibitory projections, respectively. Thick and thin lines with arrowhead in the basal ganglia indicate activated and less activated groups of neurons. Filled arrows with broken lines in the cerebral cortex signify arrays of pyramidal neurons projecting to the subcortical structures. The circles with the letter P and T indicate groups of projection neurons and interneurons, respectively. SC: superior colliculus; PPTN: pedunculopontine tegmental nucleus; MRF: midbrain reticular formation; VA/VL: ventro-anterior and ventro-lateral nuclear group; GP/SN: globus pallidus and substantia nigra; DA: midbrain dopamine-containing neurons.
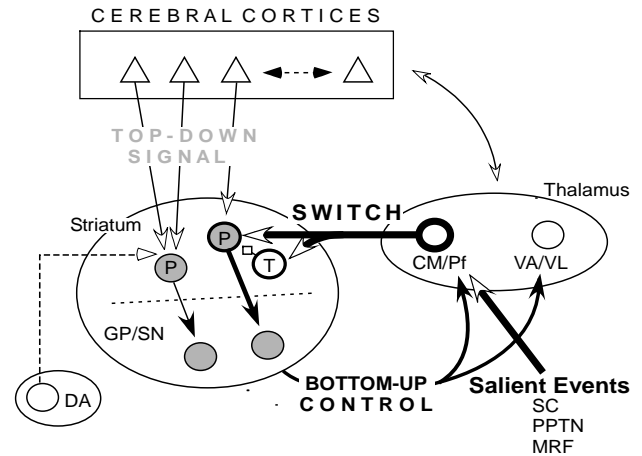

Fig. 3. A hypothetical model illustrating the role of the thalamo-striatal system in switching the control function of the cortico-basal ganglia loops in response to salient events. Thick arrows attached to circles represent the activation of CM/Pf neurons by the salient event.

et al., 1994a; Kawagoe et al., 1998; Hassani et al., 2001; Cromwell and Schultz, 2003). The enhancement of action- and cognition-related signals in the striatum by the expectation of reward would bias the processing toward a goal (biased processing) that would be mediated by nigrostriatal dopaminergic inputs as well as inputs from the limbic system.

Activation of a population of striatal neurons by top-down signals would allow the striatum to enhance and suppress particular sets of action- and cognition-related signals through the cortico-basal ganglia loops in terms of the well-known direct and indirect pathways (biased control) (Alexander and Crutcher, 1990; Kimura, 1995; Mink, 1996; Boussaoud and Kermadi, 1997; Fukai and Tanaka, 1997; Graybiel, 1998; Hikosaka et al., 2000). Thus, the cortico-basal ganglia external loops seem to work as a top-down 'biased control' system in favour of a selected set of signals that effect action and cognition at particular context. For the selection of neural signals to work optimally, ongoing feedback of selected information to the striatum, where specific cortical and modulatory signals merge, appears to be essential. The CM–Pf complex must play a central role in this 'monitoring' function while it, at the same time, receives one of its major inputs from the output stations of the basal ganglia (Fig. 2).

When a salient external event occurs, particularly in a behavioural context in which the event is not predictable or is contrary to what is expected, the event strongly activates CM–Pf neurons. Strong activation of CM–Pf neurons that

have diverging projections to the striatum has potent direct and indirect effects on striatal neuronal activity. Thus, thalamo-striatal projections conveying bottom-up signals related to salient external events modify the pattern of activity of striatal neurons overall. Changes in the activity pattern in the striatum result in cancellation of biased control of the cortico-basal ganglia loop system, and lead to the switch to bottom-up control based on external events. Figure 3 schematically depicts how the external and internal loop systems work by changing their mode from monitoring to switching. Candidate nuclei that might be the source of the signals in the CM–Pf complex relating to salient external events are the superior colliculus, PPTN, reticular nucleus of thalamus, and midbrain reticular formation.

Since the magnitude of SLF-type neuronal responses to valid and invalid targets was inversely proportional to the predictability of the occurrence of the target stimuli (Fig. 1), the proposed monitoring and switching of cortico-basal ganglia loop function may represent the extremes of a single basic mechanism driven by the predictability of events. Prominent activity of CM–Pf neurons is a phasic activation or suppression related to sensory stimuli and body movement, whereas its tonic activation has not been observed during expectation of a valid target in the cued-target detection task, or during expectation of a reward in the click-with-reward task. Thus, the monitoring and switching functions of the thalamo-striatal system appear to be most effectively driven by the occurrence of external events.

5. Conclusions/perspectives

Although we are making important strides in our understanding of the electrophysiological and anatomical bases of the neuronal circuits involving the CM–Pf complex of the thalamus, its function has not been clearly elucidated as yet,

except for the knowledge that it is involved in the processes of attention and arousal. In this article, we hypothesized that the CM–Pf complex receives both specific signals from the basal ganglia and non-specific signals related to the occurrence of salient external events. According to this model, these non-specific signals are used to trigger attention and arousal, and are then projected primarily to the striatum. This circuit design allows the CM–Pf complex to function in two different modes depending on the predictability of external events—one for monitoring top-down biased control through the cortico-basal ganglia loop system for selecting signals for action and cognition, and the other for switching from top-down biased control to bottom-up control based on signals of salient external events that are not predictable or occur contrary to expectation. Although this model does not address the roles of every circuit within the CM–Pf complex including reciprocal connections that it makes with the cerebral cortices and its projections to the subthalamus, it does provide new insight into the function of the posterior intralaminar nuclei.

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