Claustrum, consciousness, and time perception

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Abstract

The claustrum has been proposed as a possible neural candidate for the coordination of conscious experience due to its extensive "connectome". Herein we propose that the claustrum contributes to consciousness by supporting the temporal integration of cortical oscillations in response to multisensory input. A close link between conscious awareness and interval timing is suggested by models of consciousness and conjunctive changes in meta-awareness and timing in multiple contexts and conditions. Using the striatal beat-frequency model of interval timing as a framework, we propose that the claustrum integrates varying frequencies of neural oscillations in different sensory cortices into a coherent pattern that binds different and overlapping temporal percepts into a unitary conscious representation. The proposed coordination of the striatum and claustrum allows for time-based dimensions of multisensory integration and decision-making to be incorporated into consciousness.

Introduction

Consciousness is not a unitary phenomenon, but a class of states that can be viewed as distributed along a continuum of arousal or awareness ranging from none to full awareness [1, 2, 3•]. Conscious awareness varies considerably within an individual across different contexts, such as non-conscious (or minimally-conscious) states as in non-REM sleep to fully conscious states as in normal wakefulness [4]. The identification of the neural correlates of consciousness is both an enduring challenge in consciousness science and the focus of much research although our understanding of how the brain enables conscious states and how shifts in brain states contribute to fluctuations in consciousness remains in its infancy [5]. Emerging evidence from studies of awareness across time, alterations in meta-awareness involving changes in neural synchronization, and clinical populations characterized by distortions in awareness, suggest a close intersection between conscious states and interval timing. Consequently, temporal integration mechanisms have been implicated in the neural substrates of consciousness [6, 7]. Moreover, the primary

neurophysiological correlates of consciousness in these studies has been neural synchronization as a function of alternation between phasic and sustained activity [8, 9•, 10, 11, 12].

In recent years, the claustrum was proposed as a possible neural candidate for the coordination of conscious awareness [13, 14] and to play a key role in integrating diverse sources of neural information during the formation of unified conscious percepts [15, 16]. The interhemispheric connections of the claustrum enable the coordination of bilateral cortical functions by way of its ipsilateral and contralateral connections with prefrontal, premotor, and motor areas. Working from the starting point that subjective time constitutes the "infrastructure of consciousness" [17] we propose that the claustrum plays a crucial role in consciousness by supporting the temporal integration of cortical and thalamic oscillations involved in the multiplexing of sensory input used for interval timing and working memory [18•].

The continuity of experience transduced by temporal integration is one of the defining features, if not the defining feature, of consciousness [19]. Accordingly, a first step in addressing the relevancy of time in consciousness requires a re-evaluation of what is *meant* by "conscious processing" and the control of an internal clock [20•, 21]. On closer examination, a process might be said to be "conscious" in three distinct senses.

(a) one is aware *of* the process

(b) the operation of the process is *accompanied* by awareness (of its *results*) and

(c) awareness *enters into* or *causally influences* the process.

Crick and Koch provided an outline for the scientific study of consciousness [15]. In this framework, the authors proposed that an alternative to tackling the "hard problem" of qualia [22] would be to identify some neural correlate(s) of consciousness in causal terms, that is, "finding a minimal set of neuronal events that gives rise to a specific aspect of a conscious percept". As a consequence, they focused exclusively on neural activity related to a specific sensory modality, i.e. the visual system of primates, leaving unexplored other aspects of consciousness, such as emotion and self-awareness. Although we, in principle, agree with Crick and Koch's perspective, we maintain

that consciousness science should investigate how inputs from different sensory channels can emerge as a complete picture of our ever-changing conscious experience. As a consequence, any specific sensory percept is construed as one input to this emergent principle of coalition. In other forums, this has traditionally been referred to as the 'neural binding' problem [23].

It is easily overlooked that humans share with other animals a remarkable ability to estimate the durations of events and subjectively experience a sense of time passing [24]. It is also tempting to assume that the experience of conscious states, and in particular self-awareness, is dependent upon the ability to perceive duration and to understand the concepts of past, present, and future [25, but see 26] which leads researchers to face the dilemma of whether non-human animals have human-like conscious experience. Although performing a classic timing task such as the peak-interval procedure [27, 28] may not require complete awareness of time passing, more fundamentally our conscious experience may actually be organized by an underlying timing mechanism. Indeed, distinct from physical entities that have multiple dimensions (at least three dimensions in space and one dimension in time in classical physics), time is arguably the only dimension for mental entities (e.g., thought, feeling, sensory perception, etc.), unless they have other dimensions that could only be measured in a phenomenal world [13]. Therefore, it is intriguing to question whether our subjective experiences coalesce mainly because we have a built-in temporal integration process that coordinates different channels of inputs into uniform subjective states. This is particularly important not only because of the "hard problem" of consciousness that has lingered for centuries, but also because timing is disrupted in various mental disorders [29] that can be regarded as "disorders of conscious experience" and thereby may prove valuable in elucidating basic mechanisms and developing treatments. One example is schizophrenia, because schizophrenic patients have a distorted sense of reality and temporal structure [30, 31]. Another example is pathological gambling, because pathological gambling can be directly associated with an altered state of consciousness, dysfunctional risk assessment, and a skewed perception of time and rate of return [32]. The observation that pathological gamblers exhibit reduced gamma

synchronization in paralimbic cortical structures during rest as well as an impairment in task-related changes compared to controls has been associated with a loss of conscious coherence [33]. Behavioral studies suggest that gamblers may be ultra-sensitive to time and experience a delusional high rate of return in various aspects of their lives [34]. Consequently, disrupted optimization of timing abilities and impaired self-awareness may contribute to compulsive gambling behavior [32, 34, 35••].

Consciousness, metacognition and interval timing

By definition, consciousness refers to awareness of one's unique thoughts, feelings and sensations of the environment. A key characteristic is that these experiences are constantly shifting. The ever-shifting stream of thoughts can change dramatically from one moment to the next, but one's experience of it seems smooth and effortless. How does the brain enable such continuity of experience and what are the essential mechanisms for the emergence of conscious experience? Three possible criteria can be derived from 'higher-order' theories of consciousness [36] and 'integrated information theory' [37]:

1. The ability to select one state out of the indefinite possibilities (differentiated information) e.g., differences between a light sensor and a conscious agent.

2. The ability to have awareness of mental representations (metacognition; second-order representations).

3. The ability to tag personal meaning to the state.

It is important to note that there exist fundamental differences between sensitivity (non-conscious) and awareness (conscious): sensitivity relies on the first-order representation in the system, whereas awareness relies on the second-order representation in the system. That is, sensitivity entails the ability to respond in specific ways to certain states of affairs, whereas awareness requires the agent to have the knowledge of the fact that she or he is sensitive to some state of affairs and also cares about a certain state of affairs. For example, a camera doesn't lack consciousness because it's only sensitive to light, but because it has no awareness of being sensitive to light. One

could only make the camera conscious by enabling a second-order mechanism that could coordinate its moments of recording light with its memory of past recordings of light, as well as its own preference for that particular moment of light-sensing and memory traces – this mechanism could obviously be the time-keeping mechanism described above. For such a higher-order timing mechanism to work, each channel of inputs must have its own clock(s) so that these clock phases can be synchronized to form a representation of the present –– "now". The proposal that we present in this review is that the claustrum is critical for the type of temporal integration required by consciousness.

A further link between metacognition and interval timing is suggested by psychological manipulations that alter conscious states and distort time perception as well as by disorders of consciousness. Two such psychological techniques include hypnosis, which involves the administration of a hypnotic induction, involving suggestions for reduced awareness and meta-awareness [38], and meditation, which involves a variety of practices with the intent to foment awareness of mental representations [39]. A hypnotic induction reliably produces a tendency to underestimate time, particularly in highly suggestible individuals [6, 8], who comprise approximately 10-15% of the population [38]. Alongside distortions in time perception, highly suggestible individuals routinely experience states of depersonalization and derealization spontaneously following a hypnotic induction [39]. Although they have not been systematically studied, depersonalization disorder patients are similarly known to experience pronounced disruptions in time perception [39] and drugs that elicit distortions in time perception also induce depersonalization [41]. In contrast, preliminary evidence suggests that meditation training produces a tendency to overestimate intervals [42].

The mechanisms underlying these distortions are not well understood but may lie in atypical metacognition in these populations. A common theme in models of hypnosis is that highly suggestible individuals are characterized by impaired executive monitoring and that the ability to respond to hypnotic suggestions is facilitated by reduced awareness of intentions underlying

responses [38, 43]. Following a hypnotic induction, highly suggestible individuals exhibit reduced medial prefrontal cortex activity [44] as well as reduced frontal-parietal alpha [8] and frontal-central-central beta synchrony [45] relative to low suggestible individuals. These changes implicate default mode, executive attention, and motor networks involved in metacognition, cognitive control, and interval timing [46]. In contrast, there is evidence suggesting that meditators have greater awareness of their intentions to act [39]. Cumulatively, these results suggest that awareness of mental representations is closely intertwined with one's perception of time.

Striatal Beat Frequency (SBF) model of interval timing

In the striatal beat frequency (SBF) model of interval timing [29, 47, 48, 49, 50] duration estimation is based upon the coincidence detection of oscillatory processes in cortico-striatal circuits. The SBF model supposes that at the onset of a "to be timed" signal, populations of cortical (and thalamic) neurons phase reset (and synchronize) and begin oscillating at their endogenous periodicities. Dopamine release from the ventral tegmental area at the onset of the signal is believed to play a part in this resetting function for cortical neurons while also acting as a 'start gun', and dopamine release from the substantia nigra pars compacta at signal onset works in a similar fashion to reset the weights of the synaptic connections in the dorsal striatum [51]. The detection of coincident activation of specific cortical oscillatory patterns is the role of striatal medium spiny neurons (MSNs). The adjustment of cortico-striatal synaptic weights allows the MSNs to discriminate and become 'tuned' to specific patterns of coincident oscillatory activity, thus increasing their likelihood of firing upon similar patterns of cortical activation in the future. This property accounts for the close correspondence between interval timing and working memory performance, which are held to depend on the same neural representation of a specific stimulus [18•]. Given that oscillatory activation repeats itself at regular intervals (its period) and changes in a systematic manner as a function of time (its phase), these cortical oscillatory patterns, when observed across neurons differing in their intrinsic periodicity, can represent time intervals in the seconds-to-minutes range although their neural firing occurs in the milliseconds range. The MSNs are able to detect these

patterns, which bear resemblance to musical chords, by acting as coincidence detectors or 'perceptrons' [52]. Striatal output travels to the thalamus along two pathways: the direct (dopamine D_1 receptor-mediated) and indirect (dopamine D_2 receptor-mediated), then loops back to the cortex and striatum, influencing the rate of oscillatory activity and permitting alterations in clock speed by changing the input to MSNs [53]. Differential activity in the direct and indirect pathways of the basal ganglia may serve to start, stop, or reset the timing process [49]. Consequently, the SBF model has the advantage of being consistent with the known psychophysics, neuropharmacology, and neuroanatomy of interval timing while at the same time making testable predictions regarding the functioning of its components [20•, 48, 51, 54, 55, 56]. A unified timing model that incorporates the SBF model of beat-based timing using cortico-striatal circuits and duration-based models using olivocerebellar circuits is outlined in Figure 2. This model is based on coordinated activity in the core striatal and olivocerebellar networks that are interconnected with each other and the cerebral cortex through multiple synaptic pathways [20•, 57].

Claustrum and consciousness

Crick and Koch described how the claustrum might play a role in integrating separate sensations into the unitary percepts that we experience as consciousness [16]. Smythies and colleagues [13, 14, 58, 59••] subsequently presented a more detailed hypothesis about how such temporal integration might occur based on higher-order temporal synchronization and the neuroanatomy of the claustrum. The claustrum is broadly divided into 3 sub-regions, the anterior-dorsal region connected with somatosensory and motor cortices, a posterior dorsal region connected with the visual cortex, and a ventral area connected to the auditory cortex [60, 61, 62••, 63, 64, 65•]. The claustrum has reciprocally distributed projections to virtually all regions of the cortex (e.g., frontal, premotor, ventral anterior cingulate, ventral temporal, visual, motor, somatosensory, olfactory, and entorhinal cortex), as well as sub-cortical structures (e.g., caudate nucleus, putamen, globus pallidus, and lateral amygdala) that are illustrated in Figure 1. These extensive bilateral and

interclaustral connections support the hypothesis that the claustrum serves as a 'synchrony detector', thereby coordinating information sharing and binding throughout the brain [13, 16]. White et al. [66] have recently reported unanticipated findings relating to the anatomy of connections between the claustrum and the cortex. These include the observation that the projections from non-cingulate cortex to the claustrum are discrete, sparse and mainly directed to the contralateral claustrum while projections from the claustrum to the non-cingulate cortex are discrete, sparse and directed to the ipsolateral cortex. In contrast, the cingulate cortex projects mainly to the contralateral claustrum and the claustrum projects to the ipsolateral cortex as above. The connections between the claustrum and the cingulate, however, are both diffuse and massive with discrete regions in the cingulate cortex projecting to most of the claustrum and vice versa. These anatomical connections suggest that the main output of the claustrum to the motor-control system doesn't go via the sparse direct route, but via the dense route with a relay in the cingulate cortex. This allows the claustrum to play a modulatory role in all the many functions of the cingulate cortex besides controlling motor output and behavior via the premotor cortex. These findings also require an extension of the proposed functions of the claustrum as outlined by Smythies and colleagues [67].

Although other brain areas have extensive interconnections (e.g., amydala, parietal cortex, thalamus), one way in which the claustrum is distinctive is in the proportion of claustral-cortical neurons that use synaptic zinc. Traditionally, Zn+ neurons have been associated with hippocampal mossy fibers and the generation of synchronized oscillations associated with activity-dependent neuroplasticity. The relatively dense zinc-positive (Zn+) terminations in the claustrum suggest the ability to coordinate multisensory processes more effectively given that synaptically released zinc is thought to control a 'window' of postsynaptic excitability without altering firing rates [68, 69].

Cortico-claustral-cortico circuits provide for strong feed forward inhibitory (FFI) processes. An FFI is composed of a group of pre-synaptic neurons that directly excite both glutamaterigic excitatory and GABAergic inhibitory interneurons and provide greater synaptic input to the latter [70]. The post-synaptic neurons are interconnected and circuits that lack inhibition simply relay pre-synaptic activity

to post-synaptic neurons. In contrast, post-synaptic neurons in an FFI are highly sensitive to the relative timing of action potentials, and this allows for the modulation of neural synchrony as transmitted by the pre-synaptic neurons [59••]. Neuromodulators and feedback connections may modulate the temporal sensitivity of such circuits and gate the propagation of synchrony into other layers as well as sub-cortical and cortical areas [58]. The prevalence of strong FFI circuits throughout the brain suggests that synchrony codes in conjunction with time-sensitive cortico-thalamic-basal ganglia (CTBG) circuits are the basis for the temporal integration required for consciousness. In this manner, the claustrum is able to support the full continuum of consciousness through the coordination of CTBG timing circuits in conjunction with cortical-striatal-hippocampal-insular networks, thereby creating a timing-based conscious experience [72, 73••].

This hypothesis also suggests that the claustrum plays an important executive function. Our proposal is that decision-making is mediated by select assemblies of neurons, with synchronized oscillations at different gamma frequencies, that carry integrated sensory information modulated by saliency (reinforcing) mechanisms. These assemblies compete on a winner-take-all basis for access to the output from the claustrum to the prefrontal and premotor cortices. In this way the winner directs the voluntary decision-based behavior of the subject. Exact timing of these events plays a crucial role in the system.

Goll and colleagues [74••] have recently proposed a hypothesis that the claustrum is closely involved in selective attention. They hypothesize that a widespread top-down input from the prefrontal cortex to the claustrum competitively modulates the output from the claustrum to various cortical localities. This allows the claustrum initially to process many different sensory objects simultaneously, and then to allow just one of these at any moment to constitute the center of attention with the inhibition of its competitors. The claustrum is further subject to down-up modulation by unexpected stimuli from sensory cortices that can over-ride the selective attention strategy. The claustrum also has a projection to the motor cortex including the frontal eye fields that promote motor movements, such as eye and neck movements, which modulate the focus of

attention and has been likened to a mechanism for moving the 'spotlight' of attention.

Some recent evidence has cast doubt on the role of the claustrum in consciousness [75]. Combat veterans with penetrating traumatic brain injuries were studied in terms of the effects of claustrum lesions and loss of consciousness on long-term cognitive functions. The extent of claustrum damage was associated with the *duration*, but not the *frequency*, of loss of consciousness. This could be interpreted as indicating that the claustrum plays an important role in regaining consciousness, but not in maintaining cognitive function. In contrast, other researchers have reported that selective bilateral lesions of the claustrum and external capsule resulting from herpes simplex encephalitis and Sugihiritake mushroom poisoning leads to severe encephalopathy with disruptions in consciousness, psychotic symptoms and seizures [62••]. A specific role for the claustrum in auditory scene analysis as reflected by sensitivity to sensory change has also been identified [76]. Cogent to the current hypothesis, Wittmann and colleagues [77] assessed the effect of size and localization of brain lesions on the perception of the temporal order of two acoustic stimuli. Although a moderate association of lesion size and temporal-order threshold was observed among all brain-lesions patients, a clear temporal discrimination deficit was specifically observed in those patients with damage to the claustrum. Unfortunately, no assessment of consciousness was made in this study; hence correlations between temporal processing and consciousness couldn't be performed. Similar types of impairments in temporal order and spatial reversal learning have been observed in rats following lesions of the anterior claustrum [78]. Moreover, the impairments in duration discrimination produced by lesions of the dorsal striatum were magnified as a function of the extent of collateral damage to the claustrum [79].

In support of the role of the claustrum in timing and time perception, a meta-analysis of fMRI studies [80] showed activation of the claustrum during the timing of supra-second durations, particularly in reproduction tasks. Subsequent neuroimaging studies have shown activation of the insula/insular cortex (a region closely related to the claustrum) in a variety of timing tasks [81, 82]. Moreover, Koubeissi et al. [83] recently reported a case study in which the researchers were

apparently able to turn consciousness "on and off" by stimulating a small area of the claustrum/insular cortex.

Conclusions

We endorse the 'attention hypothesis' for claustrum function [74••], which can readily be combined with the SBF model whereby the claustrum serves an executive function for the selection of the stimuli to be processed within the multiplexing system of interval timing and working memory [18•]. In this manner, the claustrum is able to modulate synchronized oscillations from widely distributed cortical regions in order to determine which patterns of spike coincidence-detection should be processed by cortico-striatal-thalamo-cortical timing circuits – either individually (selective attention) or in parallel (divided attention). The anatomical details and attentional functions of this type of time-sharing system have been previously described [74••], but the specific neurophysiological mechanisms remain to be delineated. The basis for this mechanism is suggested by recent evidence indicating the role of competitive synchronized gamma oscillations organized by the Pearson mechanism [59••]. In addition, we propose that the motor output from the claustrum mediates the selection of all voluntary behaviors as well as the movements modulating the focus of attention [67]. Future experimental work addressing the relation between self and time [84] should be designed to test these predictions regarding duration and temporal order discrimination as well as attentional time-sharing and simultaneous temporal processing [85, 86, 87] using optogenetic and designer receptor exclusively activated by designer drug (DREADD) techniques within the claustrum and CTBG [62••, 88, 89, 90]. Such studies should allow for the dissection of beat-based versus interval-based timing [57] within temporal windows defining past, present, and future states of awareness [91, 92, 93] while taking into account the flow of time from temporal sensation to time perception and production in the service of consciousness and the relation between time and self [84, 94, 95, 96, 97••].

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Figure captions.

Figure 1. Input–output connectivity of the claustrum. The architecture of the input–output connectivity of the claustrum is charted in sagittal **(A)** and coronal **(B)** sections of the rodent brain. The primary inputs to the claustrum are from the cortical modalities, which display symmetrical reciprocal connections. Additional inputs come from the prefrontal cortex as well as subcortical inputs from the striatum, thalamus, amygdala, and dorsal raphe. Abbreviations: PrL, prelimbic cortex; ACA, anterior cingulate area; ILA, infralimbic area; MO, motor cortex; SS, somatosensory cortex; ENT, entorhinal area; AI, agranular insular area; PIR, piriform area; PrL, prelimbic area; Fr, frontal cortex; AUD, auditory cortex; VIS, visual cortex; STR, striatum; TH, thalamus; AMG, amygdala; HPC, hippocampus; DR, dorsal raphe. Coronal **(C)** section of the human brain showing the cortico-claustral medial pathway spreading between claustrum and basal ganglia using constrained spherical deconvolution tractography to map white matter fibers. Phylogenetic differences in the organization of the sensory systems of different species makes it difficult to identify homologous areas, consequently these illustrations should be taken as a general outline. Adapted from [62••, 74, 90].

Figure 2. A unified model of interval timing. The striatal network (*blue*) and the olivocerebellar network (*green*) are connected to each other via multiple loops, and with the thalamus, pre-SMA/SMA, and the cerebral cortex. Separate bi-directional circuits connect the claustrum to the cortex and the striatum. Dopaminergic pathways are shown in orange, inhibitory projections in blue, excitatory projections in red, and known anatomical connections in solid lines, respectively. Abbreviations: GPe, globus pallidus external; GPi, globus pallidus internal; IO, inferior olive; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulate; STN, subthalamic nucleus; VTA, ventral tegmental area. Adapted from [20, 57, 97••].
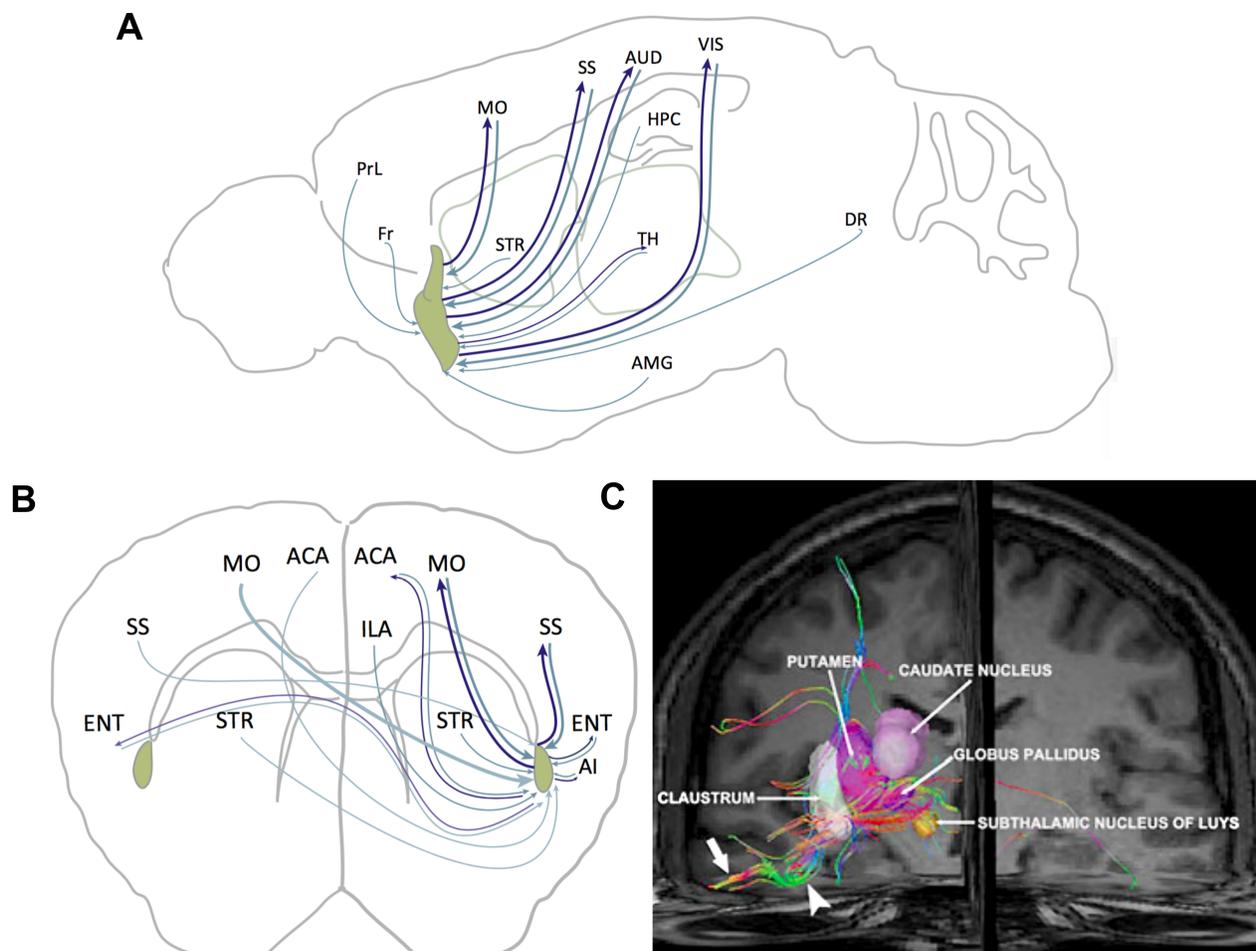
Figure 1.

Figure 2.