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# Hippocampal Influences on Movements, Sensory, and Language Processing: A Role in Cognitive Control?

*Douglas D. Burman*

## Abstract

Beyond its established role in declarative memory function, the hippocampus has been implicated in varied roles in sensory processing and cognition, particularly those requiring temporal or spatial context. Disentangling its known role in memory from other cognitive functions can be challenging, as memory is directly or indirectly involved in most conscious activities, including tasks that underlie most experimental investigations. Recent work from this lab has examined the directional influence from the hippocampus on cortical areas involved in task performance, including tasks requiring movements, sensory processing, or language judgments. The hippocampus shows preferential connectivity with relevant cortical areas, typically the region critically involved in task performance, raising the possibility that the hippocampus plays a role in cognitive control. Minimal criteria for a role in cognitive control are proposed, and hippocampal connectivity with sensorimotor cortex during a non-mnemonic motor task is shown to meet this standard. Future directions for exploration are discussed.

**Keywords:** hippocampus, cortex, connectivity, PPI, cognitive control, sensorimotor, language

## 1. Introduction

Since its earliest description in 1587, many different functions have been ascribed to the hippocampus, each based on the available techniques and prevailing understanding of brain function. The earliest hypotheses were based on its observed anatomical connections. The hippocampus was first believed to be olfactory, based on erroneous observations suggesting direct olfactory input [1]. Olfactory input to the hippocampus is in fact indirect; except for a role in odorous memories, olfaction is no longer believed to be the hippocampus' primary function.

By the early twentieth century, a role of the brain in emotional and cognitive states had been well-established, and procedures were developed to better trace brain pathways and identify brain lesions. The hippocampus was identified as one structure within the "limbic lobe". Including the entire hippocampal formation, cingulate gyrus, and associated areas, Papez theorized this region to be involved in the expression of emotional behaviors [2, 3]. Support for this idea was seen in the

experiments of Klüver and Bucy, who reported that resection of the medial temporal lobe (including the hippocampal formation and nearby amygdaloid complex) had extreme effects on emotional behaviors [4–6].

In the 1950s, the spontaneous activity of the hippocampus was noted to bear a consistent relationship to various states of consciousness [7], generating several hypotheses about high-level cognitive functions. These ideas were largely dismissed, as researchers had demonstrated that lower mammals could still function (albeit with deficits) after the hippocampus was experimentally removed [8]. Anatomical studies further refined our knowledge of hippocampal connections across the brain. After several stages of processing, information from every sensory modality funnel into the hippocampus via the entorhinal cortex, with multiple senses sometimes combined; the hippocampus indirectly projects to the entire cerebral cortex, mostly via the subiculum [9].

When Scoville and Milner surgically resected a patient's hippocampus in an attempt to relieve epileptic seizures, the patient was unable to form new episodic and declarative memories (i.e., those that can be verbalized) [10]. This finding firmly established a role for the hippocampus in these types of learning and memory, eventually replacing the prevailing inhibition theory of the hippocampus. The inhibition theory had been based on observations of hyperactivity and difficulty learning to inhibit responses following hippocampal damage [11, 12].

An additional theory of hippocampal function was developed in 1971 with O'Keefe's discovery of hippocampal place cells in rats [13]. The intensity of these cells' activity depended on the animal's location within a baited maze. Extensive study was undertaken to identify which environmental cues were used by the animal to recognize its spatial position, and whether activity of the place cells showed spatially selectivity when the animals were placed in a different environment [14, 15]. Navigational problems were observed following hippocampal lesions [16, 17]. Whether the mnemonic and spatial properties are functionally distinct or different facets of the same overarching function was a matter of debate, however, which continues to this day [18–21].

Through most of the twentieth century, theories of hippocampal function relied on evidence from lesion and anatomical studies, plus recordings of electrical activity. The advent of neuroimaging methodologies, particularly functional magnetic resonance imaging (fMRI), allowed hippocampal function to be studied non-invasively in humans. This technique detects regional changes in oxygenated blood resulting from increased neuronal activity, providing the means to identify brain areas based on their functional activity. With the advent of fMRI, investigators could verify in humans the patterns of functional activity observed in non-human animals, adding more complex tasks to further elucidate functional properties.

Early neuroimaging studies examined mean changes in neural activity that differentiated between blocks of time where different tasks were performed, tasks that differed in their cognitive requirements (e.g., memory). Soon, methods were enhanced to identify neural activity during individual trials [22]. Consistent with its theorized mnemonic function, regional increases in hippocampal activity were observed during learning and recall; furthermore, greater activity was observed during those learning trials where a stimulus was presented that was later recalled successfully [23, 24]. Similarly, hippocampal activity during virtual navigation experiments could be correlated with spatial cues [25–27], consistent with its proposed function as a cognitive map. Thus, the two prevalent theories of hippocampal function were both supported. Additional studies described new properties, such as sensitivity to the temporal duration or spatial relationships [28–30], and a role in scene perception and reconstruction [31]. Some interpret these properties as contextual elements required for memory recall [19, 28, 32]; others suggest a more

fundamental perceptual role in identifying changes in the environment, which may consequently be incorporated into memories [33, 34]. Differences between these viewpoints are often nuanced. As more information about hippocampal activity has accrued, other roles for the hippocampus have also been suggested, including a role in conscious perception [35–37] and cognitive control [38–40].

The traditional “activation” analysis of fMRI data is patterned on traditional methods for analyzing electrical activity from localized regions of the brain. It assumes all information in a neuron’s electrical activity is carried through its frequency of discharge, yet additional information is carried in the hippocampal temporal pattern of activity [41–43]. Cognitive functions also require interactions between neural structures. With the development of connectivity analysis from fMRI data early this century, influences between brain regions could be inferred based on the temporal pattern of neural activity. Early connectivity studies used *functional connectivity*, any of several statistical methods that examines correlations in neural activity between brain regions. Although useful for broadly identifying connections and identifying their abnormalities, the direction of influence in these studies cannot be known with certainty; two regions with correlated activity, for example, might both be influenced from a third region. Methods were soon developed to analyze *effective connectivity*, the influence of one brain region over another.

This chapter will focus on the influence of the hippocampus across a variety of cognitive domains; as such, effective connectivity studies will be emphasized, with particular attention to those that use *psychophysiological interactions* (PPI). This form of effective connectivity analysis reveals task-specific influences between regions. Results show a pattern whereby the hippocampus consistently influences activity in cortical areas involved in task performance, including tasks requiring movements, sensory processing, language judgments, and memory. Careful consideration of results and the cognitive requirements of these tasks suggests hippocampal connectivity could play a role in cognitive control, perhaps in parallel with the role of prefrontal cortex in translating thoughts into action.

## 2. Task-specific connectivity of the hippocampus

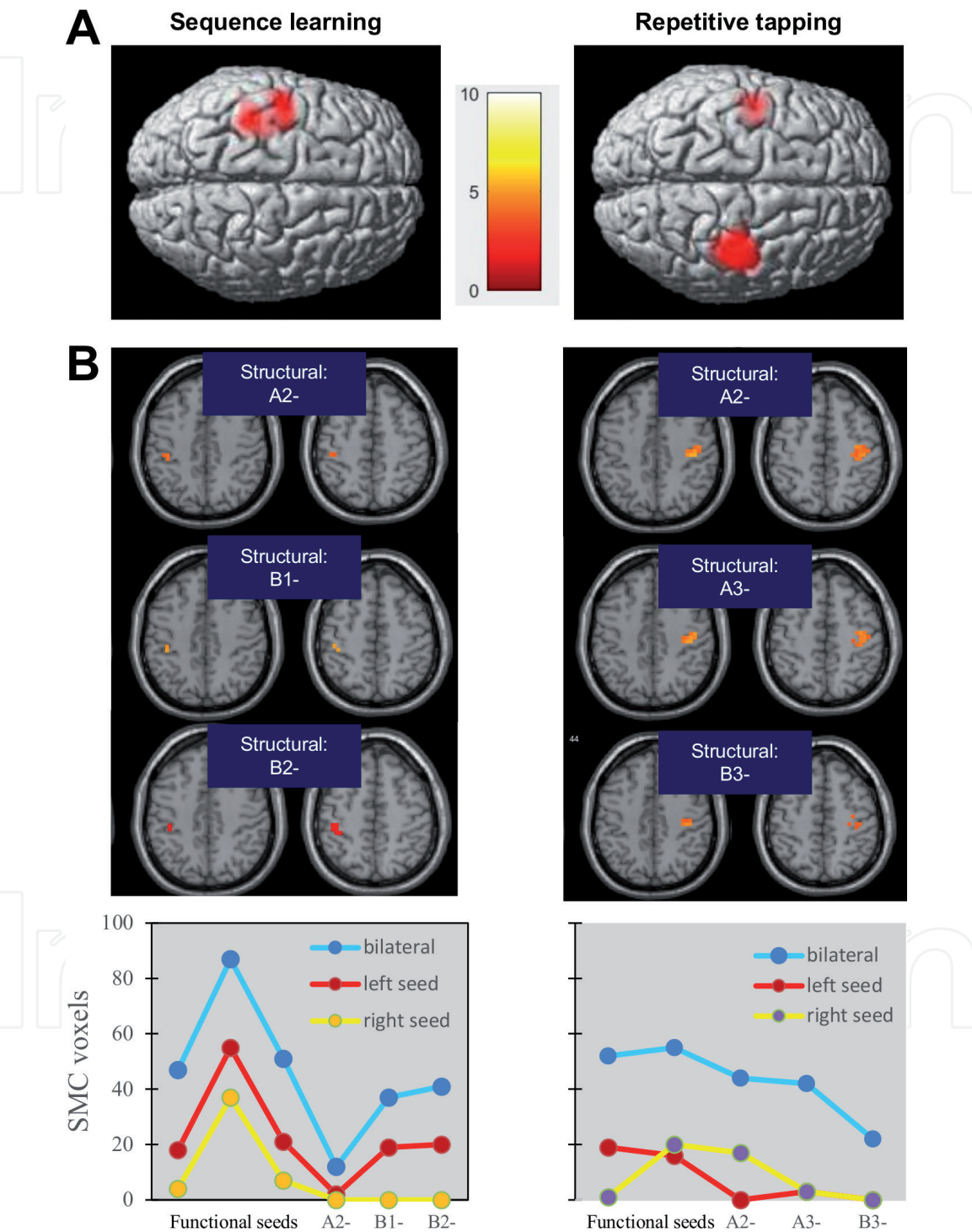
### 2.1 Connectivity with sensorimotor regions during movement tasks

Known hippocampal properties of memory or navigation are not required by common daily movements, such as walking or even “automatic driving” behaviors, so few human studies have examined hippocampal connectivity with motor regions. Initially, those that did examined hippocampal connectivity during sequence learning [44–46], where subjects learn an unfamiliar pattern of finger movements. Hippocampal connectivity was observed with the striatum, suggesting a mnemonic-motor interaction [46], perhaps culminating in striatal-associated movements derived from habits [47, 48].

Hippocampal connectivity with sensorimotor cortex (SMC) was recently studied with PPI during two paced motor tasks, only one of which involved motor learning [49]. For both tasks, subjects were instructed to listen to a 2 Hz metronome for 2 s before initiating movements, then tap the appropriate finger in synchrony with the taps from a metronome. Subjects quickly anticipated the timing of the taps, moving shortly before the sound; thus, cognitive awareness of the expected timing informed motor behavior. During the sequence learning task, the temporal precision and variability of right-handed finger movements improved with repetition; no such learning effects were observed in the repetitive tapping task.



Sensorimotor cortical activation during these tasks (**Figure 1A**) was consistent with previous studies. The sequence learning task was performed with the right hand only, evoking focal activation in left sensorimotor cortex, both in pre- and postcentral gyrus; repetitive tapping was performed with both hands, evoking bilateral sensorimotor activation. Although positive connectivity during sequence



**Figure 1.** Sensorimotor activation during performance of motor tasks. (A) Group analysis revealed unilateral activation in left sensorimotor cortex during performance of the unimanual sequence learning task and bilateral activation during the bimanual repetitive tapping task. (B) Inverse connectivity was generated from three structural seeds in both tasks, evident in the left sensorimotor cortex during sequential learning and the right sensorimotor cortex during repetitive tapping. The extent of connectivity was larger using combined (“bilateral”) activity from corresponding regions of the left and right hippocampus (bottom). Images are shown in the neurological format (left side of axial images represents left side of brain); structural and functional seeds refer to the method of selecting hippocampal seed regions for connectivity analysis, as described elsewhere [49].

learning was also observed from localized hippocampal regions, inverse (negative) connectivity was more prevalent. During sequence learning, inverse connectivity from central and central-medial regions of the left hippocampus was observed in left SMC (**Figure 1B**, left); the volume of connectivity was slightly improved when examining joint connectivity from the hippocampus in both hemispheres. Inverse connectivity from anterior middle and lateral regions of the hippocampus was observed during repetitive tapping in the right SMC, most evident examining joint connectivity from the hippocampus in both hemispheres (**Figure 1B**, right).

During both tasks, hippocampal connectivity selectively targeted the hand representation within SMC, overlapping the region activated by the task.

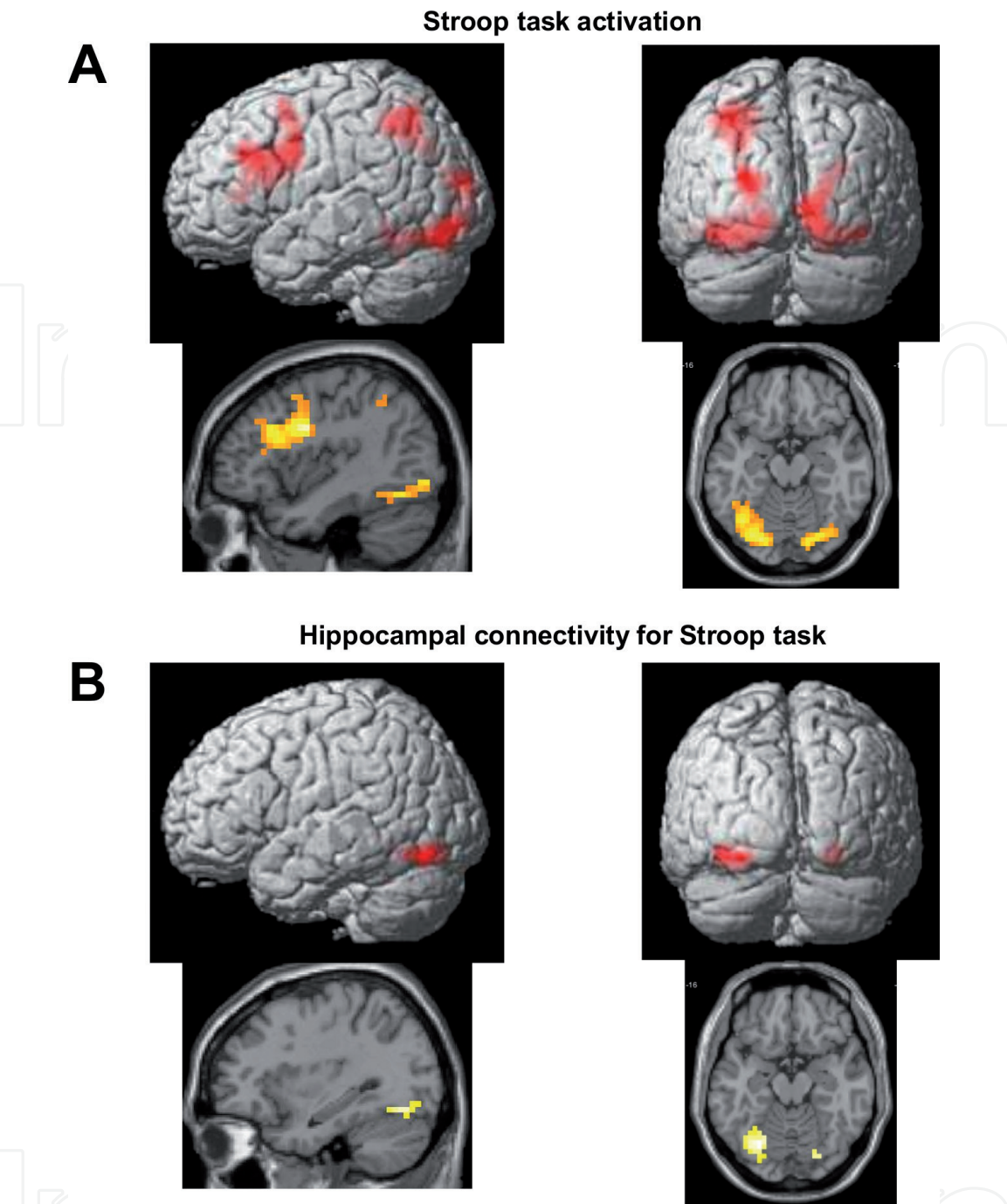
## 2.2 Connectivity with sensory regions during sensory tasks

Sensory information passes into the brain passively through bottom-up processes, but can be enhanced or filtered through top-down processes [50–53]. Top-down processes modify neural responses based on expectations or attentional processes.

Hippocampal influences on cortical processes were examined on tasks that enhanced sensory activation. The Stroop task requires particular attention to colors. On separate trials, words that name colors and cross symbols were presented in colored inks. The word meaning may or may not represent the same color as the ink in which it is written, but the correct behavioral response depends on the ink color. Due to interference from the automatic recognition of the word meaning, subjects require extra time to respond on word trials, especially on mismatch trials; to respond correctly, they must attend to the stimulus color while suppressing the behavioral response suggested by the word meaning. Activation by colored words (vs. colored crosses) was observed in the left inferior frontal gyrus and ventrolateral visual cortex (see **Figure 2A**). Within the activated region, a ventrolateral visual cortex specialized for color [54, 55] showed inverse connectivity from the hippocampus (**Figure 2B**). Despite activation in the left inferior frontal gyrus, an area involved in language function, no hippocampal connectivity was observed there.

Images and sounds that evoke a strong emotional response evoke strong activation in sensory cortices. **Figure 3** shows activation and connectivity associated with a task where subjects were instructed to pay attention to music and images, allowing an emotional response to what they viewed. Pictures were presented from a national database where thousands of subjects had rated images for the intensity and sign of their affective response [56]; harsh dissonant music accompanied negative images, upbeat classical music accompanied positive images, and bland jazz music accompanied neutral images, interspersed between positive and negative images. **Figure 3** shows brain activity evoked by negative stimuli. **Figure 3A** shows bilateral activation in visual cortex along the calcarine sulcus, plus auditory association cortex within the superior temporal gyrus; a similar pattern of activation was observed for positive stimuli (not shown). Hippocampal connectivity was not observed in visual cortex, whereas inverse connectivity was observed bilaterally in the activated region of the superior temporal gyrus (**Figure 3B**).

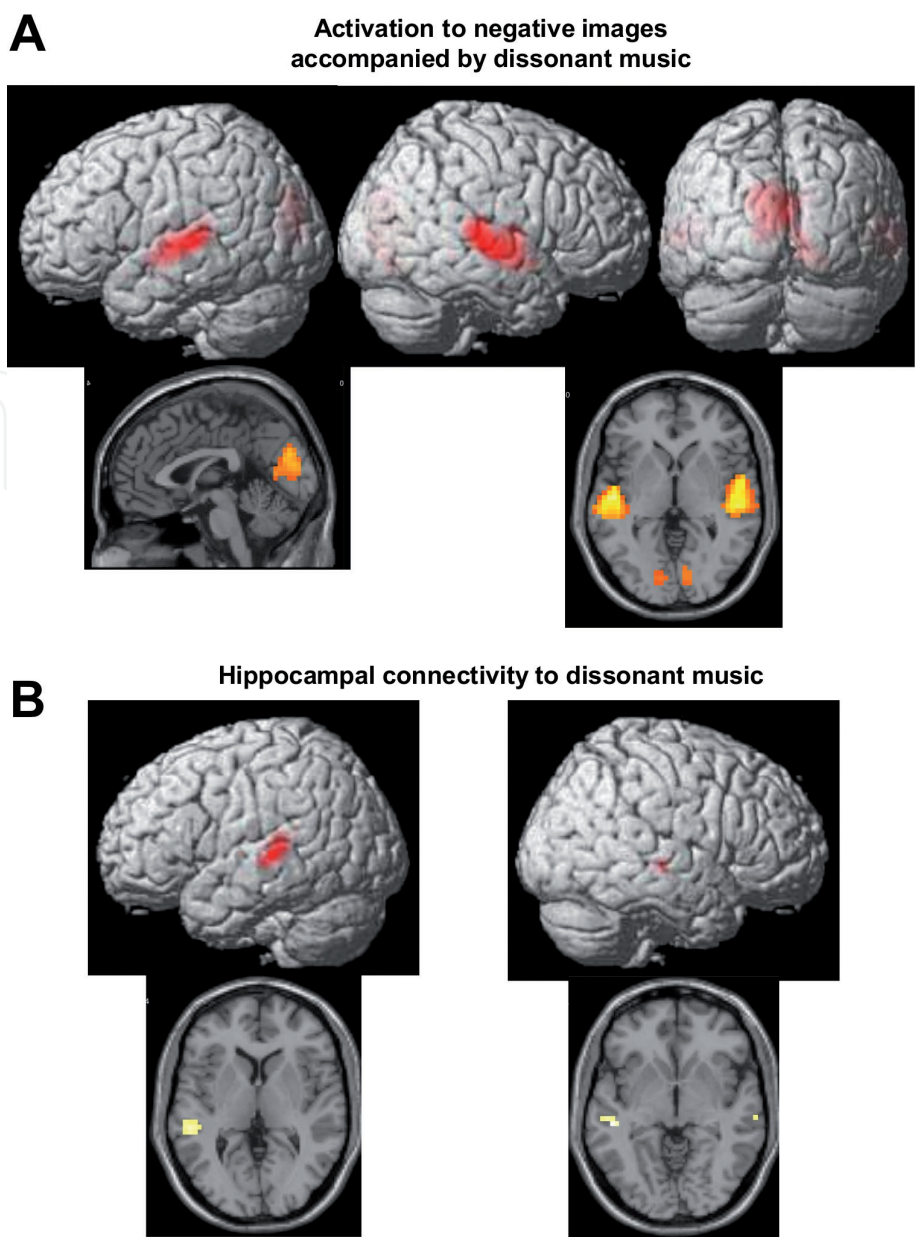
Tactile brain activation was tested by rubbing the arms of thirty-five patients with brain tumors evaluated during pre-operative planning. Patients were instructed to attend to the spatial pattern of tactile stimuli, which were applied bilaterally; analysis was carried out separately for those patients with tactile impairments on the left vs. right sides. Bilateral activation was generated in the postcentral gyrus, weaker in the sensory cortex contralateral to the sensory deficit (not shown). Hippocampal connectivity was absent.



**Figure 2.** Activation and hippocampal connectivity during performance of Stroop task. (A) Activation was observed in the left inferior frontal gyrus (a language area), the left inferior parietal lobe, and bilateral occipital cortex, extending into the fusiform gyrus (visual areas). (B) Inverse connectivity from bilateral seeds in the center of the hippocampus was observed in fusiform regions associated with color processing.

As illustrated above, hippocampal connectivity was never observed in a primary sensory region, but was observed in activated regions of sensory association cortex (for example, the activated color association cortex during the Stroop task and auditory association cortex during dissonant music). This pattern of results has functional implications. Patterns of visual cortex activity are constrained by attentional processes and cognitive expectations [57], and the hippocampal mechanism of pattern completion reflects cognitive expectations [58]. Visual responses in the hippocampus are retinotopic, suggesting their joint function in sensations and memory [59]. Visual and auditory areas specialized for language also receive hippocampal input (as shown in the next section). This pattern of results suggests consistent hippocampal cognitive input to sensory areas that extract features relevant to task performance.





**Figure 3.**  
*Activation and hippocampal connectivity during presentation of multisensory emotionally-charged stimuli. (A) Activation was observed bilaterally in the occipital cortex along the calcarine gyrus and the superior temporal gyrus. Emotionally-charged photographic images accompanied by dissonant music were contrasted with neutral images of furniture, faces, and scenery. (B) Hippocampal connectivity was limited to auditory association cortex within the superior temporal gyrus.*

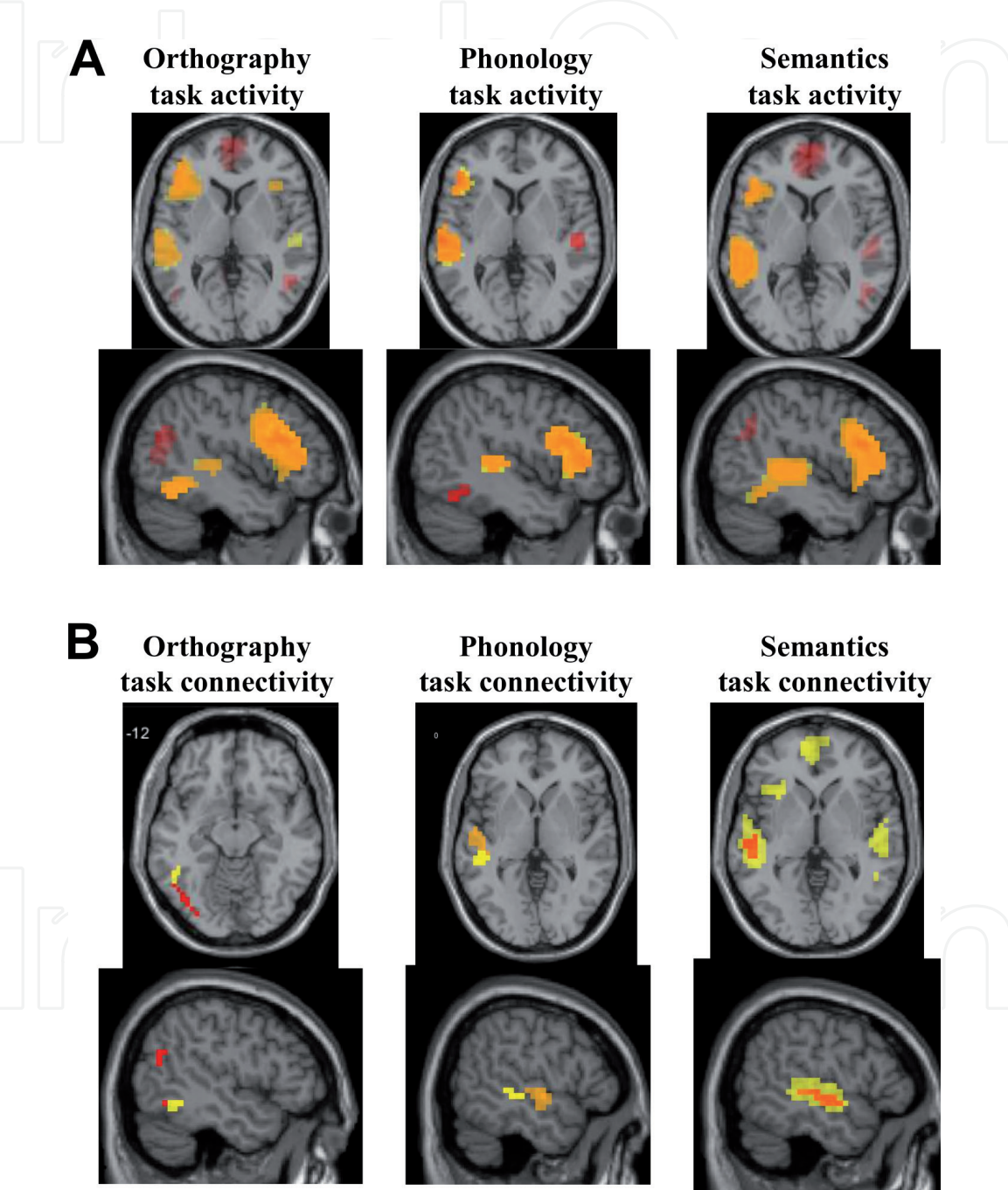
2.3 Connectivity with language regions during language tasks

The language network consists of interconnected brain regions that vary in linguistic properties. The left inferior frontal gyrus (Broca’s area) is typically active during all language tasks, although subregions have been identified with various linguistic functions [60, 61]. Occipital and temporal regions are specialized for processing specific linguistic components [62–67]. The default mode network typically shows decreased activity during language judgment tasks, yet the magnitude of its activation and connectivity with language areas can be correlated with performance accuracy [68, 69].

Representative activity during three language tasks is shown in **Figure 4**. **Figure 4A** shows results from both a t-test analysis (representing positive activation, yellow) and an anova F-test (red); overlap appears in orange. The t-test analysis shows the traditional language network, including the left inferior frontal



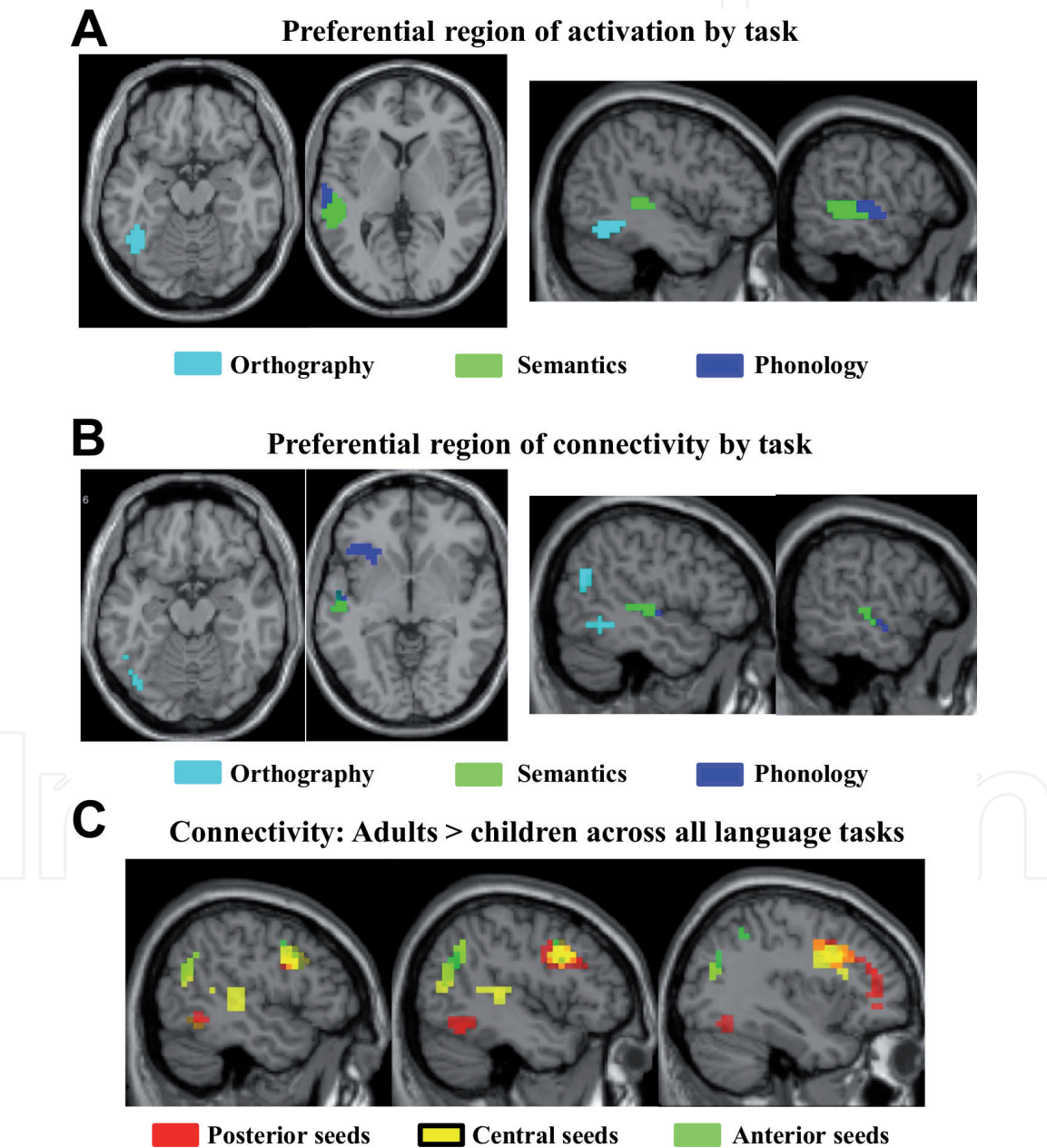
gyrus, middle and adjacent superior temporal gyrus, and the fusiform gyrus. The F-test analysis additionally shows deactivation in the default mode network, including the precuneus, angular gyrus, and ventromedial prefrontal cortex. Regions with hippocampal connectivity during the auditory version of these tasks is shown in **Figure 4B**, both for adults (yellow) and children (red). In the orthography task, *inverse* connectivity was observed for children in the left fusiform gyrus and the posterior default mode network; all other regions reflect *positive* connectivity. A larger area of connectivity was observed in adults for phonology



**Figure 4.** Activation and hippocampal connectivity during language tasks. (A) Activation during language tasks was evaluated both with an F-test (red) and t-test (yellow). Areas identified from the t-test are traditionally associated with language activation, including the left inferior frontal gyrus, middle/superior temporal gyrus, and fusiform gyrus; the F-test additionally demonstrated areas in the default mode network (precuneus, angular gyrus, and ventromedial prefrontal cortex). (B) Hippocampal connectivity varied across different language tasks. During the orthography task, hippocampal connectivity in the fusiform gyrus was more anterior in children than adults, who also showed connectivity in the angular gyrus. Hippocampal connectivity in the phonology and semantic tasks overlapped in the temporal gyrus, extending further posterior during semantics; the semantics task additionally showed connectivity in the left inferior frontal gyrus and ventromedial prefrontal cortex.

and semantic tasks, encompassing the area of connectivity observed in children. In addition, adults showed connectivity in the left insula/inferior frontal gyrus (Broca's area) in the semantics task, as well as ventromedial prefrontal cortex of the default mode network.

These three language tasks varied only in the linguistic judgment required for accurate performance [70, 71]. Three words were presented sequentially; the required response depended on the rule designated for that task (the third word must be spelled the same, rhyme, or be related in meaning to either of the two previous words). Hippocampal activity likely reflected its memory for the first two words, consistent with its mnemonic function, yet its connectivity with language areas depended on the task requirements. The three language tasks preferentially activated different areas in the language network (**Figure 5A**): fusiform gyrus



**Figure 5.** Language task selectivity and developmental changes in hippocampal connectivity. (A) Task-preferential activation was observed in the left fusiform gyrus (orthography), posterior middle/superior temporal gyrus (semantics), and adjacent superior temporal gyrus (phonology). (B) Hippocampal connectivity showed the same task-dependent pattern. (C) Developmental increases in hippocampal connectivity were observed in most language areas (left fusiform, posterior middle/superior temporal gyrus, inferior frontal gyrus), plus part of the default mode network (precuneus, angular gyrus). Different regions of the hippocampus showed developmental increases with different cortical areas.



for orthography, superior temporal gyrus for phonology, and posterior middle temporal gyrus for semantics. These same areas showed task-specific connectivity from the hippocampus (**Figure 5B**). Language deficits are associated with abnormal activity or connections in these areas [72, 73]; thus, hippocampal connectivity altered the activity in those language areas necessary for performing the task.

Hippocampal connectivity with language areas increased through adulthood, with different hippocampal regions showing developmental increases in connectivity with different cortical areas (**Figure 5C**). Areas with increased connectivity included the fusiform and posterior middle temporal regions (associated with spelling and semantics, respectively), but also the inferior frontal gyrus and parts of the default mode network. Developmental changes have also been observed within the language network, both in activation [71, 74–76] and connectivity [77–80]. Developmental changes have been tied to changes in language skills [81, 82]. Developmental changes in hippocampal connectivity may reflect cognitive changes associated with these language skills.

## **2.4 Connectivity with prefrontal regions during memory tasks**

Different types of memory are often differentiated by interactions between different brain regions. Many memories are believed to involve the hippocampus, either during memory formation, the search for a specific memory (“construction” for autobiographical memories), its elaboration during recall, or updating (“integrating”) memories to incorporate new content.

In autobiographical memories, posterior hippocampal regions interact with visual perceptual areas [83, 84]; during the construction of these memories and imagined future events, anterior hippocampal regions show increased connectivity with prefrontal regions [83]. New information inconsistent with a previous schema changes hippocampal-prefrontal connectivity [85]. Successful integration of recalled information in an inference task results in enhanced hippocampal theta power, plus coherence in medial prefrontal cortex [86], suggesting a directional flow of information from the hippocampus to prefrontal areas. During a working memory task, hippocampal activity precedes frontal activity during successful trials [86], reflecting successful retrieval and suggesting a directional flow of information from the hippocampus to prefrontal cortex. In combined EEG-fMRI recordings, recollection-specific theta-alpha (4–13 Hz) effects are correlated with increases in hippocampal connectivity with the PFC and the striatum, areas that have been linked repeatedly to retrieval success [87, 88].

Information also flows in the reverse direction. Ventromedial prefrontal cortex drives the hippocampus during the generation and processing of mismatch signals; the hippocampus then integrates this information into a new schema, modifying existing memories [89]. Elaboration of emotional autobiographical memories generates connectivity from ventromedial prefrontal cortex to the hippocampus, with greater connectivity generated during highly emotionally arousing events than those with neutral or positive affect [83]. Prefrontal feedback may thus reinforce the strength of hippocampal activity based on emotional content, explaining why emotionally-charged events are more likely to be remembered [90, 91]. Bidirectional interactions between the hippocampus and medial prefrontal cortex also play a role in working, episodic, and spatial memory [92, 93], with dysfunction in these pathways likely contributing to psychiatric disorders [94, 95]. The pattern of information flow suggests that the context of ongoing experience (the schema) is required to retrieve relevant memories, allowing patterns of neural activity from the original event to be recreated in sensory association cortices [96, 97].



In summary, the flow of information between the hippocampus and prefrontal cortex is bidirectional during memory-related tasks: the hippocampus provides contextual information when novel stimuli or patterns appear, with feedback from the prefrontal cortex resetting the contextual schema in perceptual areas that provide input to the hippocampus.

### **3. Implications for cognitive control**

#### **3.1 Hippocampal properties are consistent with a role in cognitive control during volitional movements**

Cognitive control has variously been defined as a psychological construct for the coordination of thoughts and actions under conditions of uncertainty [98], the collective processes that organize different thoughts and memories, allowing the separation of currently relevant and irrelevant information [40], brain processes involved in regulating behavior according to internal goals or plans [38], and the ability to coordinate multiple streams of information to prevent confusion and select appropriate behavioral responses, especially when presented with competing alternatives [39]. Cognitive control processes allow us to efficiently process information and generate appropriate responses.

The essence of cognitive control is that neural processes involved in cognitive (psychological) processes act upon those regions of the brain needed to translate our thoughts into action. In this sense, “action” includes processes involved in making decisions, accessing memories, attentional control, response inhibition, and mental computations – i.e., any process that can potentially result in changes in behavior due to ongoing mental activity. Early explorations used tasks that unambiguously require cognition, such as:

- the Wisconsin card sorting task. A rule has to be identified to select the correct card for a reward, then the rule changes.
- the Stroop task. The subject’s response must be based on ink color, ignoring the meaning of presented words that refer to a different color.
- the  $n$ -back task. Letters are presented sequentially, and the subject indicates whether the currently-presented letter matches the letter appearing  $n$ -stimuli previously.

Neural activity that correlates with these task behaviors is observed in prefrontal cortex [99–102], and prefrontal lesions in animals [103, 104] or humans [105] impair task performance. Neurological disorders associated with impaired frontal function, such as schizophrenia, also show impairments on these tasks [106]. The prefrontal cortex exerts top-down influences on sensory areas by functioning as a filtering mechanism that biases bottom-up sensory information toward the optimal response for a given context [107, 108]. This feedback loop may also be involved in memory recall, since the act of remembering evokes activity in the same sensory areas as the original event [96, 97]. The accumulated evidence supports a role of the prefrontal cortex in cognitive control.

Nonetheless, not all aspects of complex cognition benefit from prefrontal regulation, and the prefrontal cortex is not the sole source of cognitive control [109–111]. Indeed, the role for the prefrontal cortex in some functions may be limited. Prefrontal influence on activity in the primary motor cortex is indirect via dorsal

premotor cortex when learning to perform sequential finger movements, and absent during repetitive movements [112–114]. However, repetitive finger movements paced by a metronome do reflect cognitive control, as movements soon anticipate the auditory cue [49]. Under these conditions, the hippocampus provides connectivity selectively to the sensorimotor cortex hand representation, as shown in **Figure 1**.

An unequivocal set of criteria for a role in cognitive control has never been established, most studies relying on correlations between cognitive task performance and neural activity. In proposing minimal criteria for the cognitive control of movements [38], Burman noted an analogy between the skeletal movement system and the frontal eye field (FEF), which plays a critical role in volitional eye movements [115, 116]. Modifiable by cognitive influences, FEF cells only have three response properties, providing the basis for his proposed criteria:

1. Neural activity must be tied to a cognitive/volitional state of consciousness.
2. Cognitive influences must be selective for the time period required for task performance (*temporal selectivity*).
3. Cognitive influences must be selective for the spatial region to be acted upon (*spatial selectivity*).

Hippocampal connectivity with sensorimotor cortex during the repetitive tapping task arguably meets these criteria. Topographical connectivity maps were identified from single-voxel functional seeds that differentiated between movements of adjacent fingers [38]. Using the finger representations identified from an earlier study [117], the intensity of connectivity from each functional seed was then compared statistically across time periods for movement of each finger. The criteria for cognitive control were met:

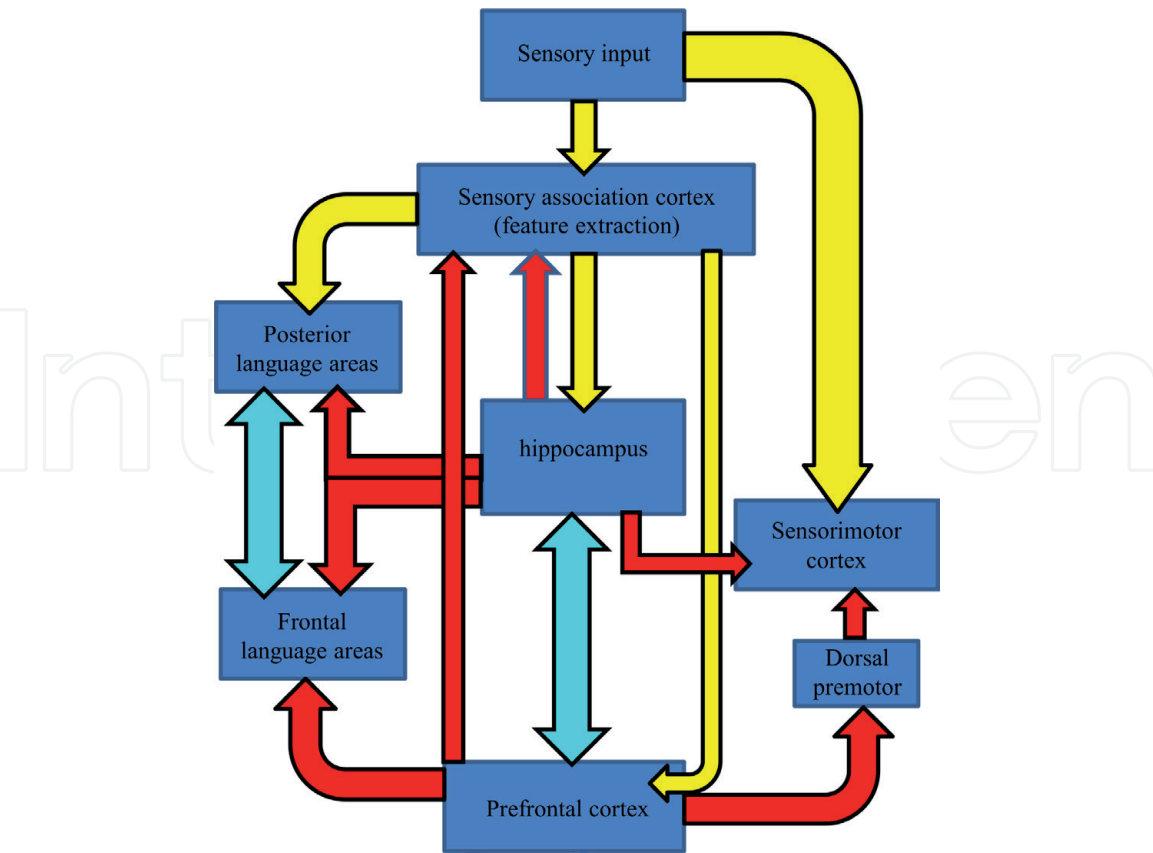
1. The repetitive tapping task involved a *volitional state of consciousness*. The timing of movements resulted from a cognitive schema, as movements anticipated the auditory cue in this task, whereas the hippocampus is unresponsive during implicit learning of movements [118].
2. At each finger representation, maximal connectivity was observed during the time period when the represented finger was moving (*temporal selectivity*). Connectivity tapered during the time period when the adjacent finger moved, with residual activity likely resulting from coupled movements between adjacent fingers.
3. Throughout the task, maximal connectivity was observed at the representation of the finger that was currently moving (*spatial selectivity*). With the fingers and response pad at a fixed location, movement of each finger represented movement in a specific region in space.

The extent to which these results can be generalized is limited, as the spatial area covered by finger movements was restricted, only one temporal pattern of movements was tested, and only finger movements were involved. Nonetheless, known hippocampal properties are consistent with these conclusions: hippocampal function is associated with conscious states such as declarative memories, and the hippocampus is sensitive to the timing of events as well as their spatial properties. Exploring a wider range of spatial regions involved in physical manipulation, as well as varied durations of movements, could more fully delineate the extent of its cognitive control over volitional movements.

### 3.2 Evidence for cognitive control suggested by prefrontal and hippocampal connectivity studies

**Figure 6** summarizes cortical connections between areas involved in sensory, language, memory, and motor functions. Sensory input from primary sensory cortices passes to association cortex for feature extraction (yellow arrows), then to higher centers involved in language, memory formation and cognition. The higher centers have bidirectional connections (blue arrows); in addition, the hippocampus and prefrontal cortex modify activity in sensory, language, and motor areas (red arrows). As described below, the red arrows represent candidates for cognitive control.

Cognitive control requires influence from a higher center to modify neural activity in those areas required to perform a task. The prefrontal cortex and hippocampus [40] have both been suggested to play such a role, and both have connections appropriate for a role in cognitive control over sensory input, language, and memory (as shown in **Figure 6**). Connectivity from prefrontal cortex to motor areas is indirect and limited to sequential movement learning tasks; otherwise, there is little in the pattern of connectivity to differentiate between these candidates. The hippocampus and prefrontal cortex show strong interactions, suggesting they may often work jointly to exert cognitive control. Such redundancy would have an evolutionary advantage, since damage to either area by itself will be less crippling. As shown in **Figure 6**, hippocampal effects on sensory areas may also be indirectly mediated through prefrontal cortex. This could explain a number of curious findings, such as why the hippocampus is needed for memory formation (to provide contextual information to prefrontal cortex) but not for memory recall (when prefrontal cortex provides memory recall by reactivating sensory areas involved in sensory



**Figure 6.** Summary diagram of cortical connections. Sensory pathways are colored yellow, modulatory feedback pathways red, and bidirectional connections blue. Red pathways in this summary originate from prefrontal cortex and the hippocampus, which are both likely to play a role in cognitive control, informed by their mutual connections and feedback.



perception). Such redundancy can also account for residual cognitive abilities during neurological disorders that disrupt function in either region.

A recent study compared functional connectivity during tasks and the resting state condition, the latter representing the intrinsic architecture of the brain [119]. Small but consistent changes were observed across dozens of task states, suggesting both task-specific and task-general network changes. Appearing within the resting state network, the hippocampus (but not prefrontal cortex) accounted for most variance in connectivity across all tasks. This finding suggests that the hippocampus, unique from prefrontal cortex, plays a primary role in regulating task behavior.

### **3.3 Testing for cognitive control in the hippocampus and prefrontal cortex**

Regardless of the brain region studied, the same criteria can be applied to establish a role in cognitive control. It was previously noted that early studies used tasks that unambiguously required cognition to perform, such as the Stroop and n-back tasks; prefrontal cortex was implicated because response properties correlated with task performance. This approach addresses the first of the three criteria proposed above: the neural activity is tied to a cognitive or volitional state of consciousness. For the hippocampus, the need to relate hippocampal activity to a cognitive or volitional state may not initially be apparent due to its association with declarative memory, yet hippocampal activity has also been reported during the formation of implicit memories [120–122]. Until we know the functional role of hippocampal activity during implicit learning conditions (decision-making? context? association pairings?), we cannot assume that hippocampal activity necessarily reflects a volitional state of consciousness. Behaviors acquired through hippocampus from repeated stimulus–response associations, for example, require little thought and may ultimately be mediated by the cerebellum and striatum [48, 123–125].

Involvement in cognitive processes does not in itself indicate a role in cognitive control. The left inferior frontal gyrus (Broca's area) was activated by words in the Stroop task, for example, yet the behavioral response suggested by the meaning of conflicting words had to be suppressed for accurate performance. To play a role in cognitive control, brain regions involved in cognition must act upon brain areas required to achieve the goal of a task. Effective connectivity tools provide a method to study such effects, particularly useful when demonstrable effects are task-specific. (This is the advantage of the PPI technique, which is both directional and task-specific).

Such a task-specific influence must be relevant to task performance. This is the purpose of the temporal- and spatial-selectivity criteria suggested above: task performance is always delimited in time, and typically involve perceptual stimuli or volitional movements appearing within a spatial environment. Cognitive processes such as emotional associations may not be invariably linked to a concrete stimulus, yet the provocative stimulus in an experiment can still be spatially delimited. Any additional constraints imposed by a task should also be reflected in a signal for cognitive control.

A role in cognitive control can be confirmed when loss of the control signal results in the inability to perform the task. As noted above, however, the behavioral deficit will not be complete unless signals are removed from all areas involved, which may include both the hippocampus and prefrontal cortex.

## **4. Conclusions**

The hippocampus provides task-specific influences on sensory, motor, language, and mnemonic areas of the brain. Detailed analysis in sensorimotor regions during

motor tasks showed a pattern of connectivity consistent with the requirements for cognitive control; connectivity patterns across tasks suggest a joint role for the hippocampus and prefrontal cortex. Criteria and suggestions for further evaluation of cognitive control from both regions are considered.

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## Author details

Douglas D. Burman  
NorthShore University HealthSystem, Evanston, IL, USA

\*Address all correspondence to: [dburman2@northshore.org](mailto:dburman2@northshore.org)

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