Hippocampal connectivity with sensorimotor cortex during volitional finger movements.

II. Spatial and temporal selectivity

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short title: Spatio-temporal properties of hippocampal-sensorimotor connectivity

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Abstract

Cognitive control refers to brain processes involved in regulating behavior according to internal goals or plans. This study examines whether hippocampal connectivity with sensorimotor cortex during paced movements shows a pattern of spatial and temporal selectivity required for cognitive control. Functional magnetic resonance imaging activity was recorded from thirteen right-handed subjects during a paced, non-mnemonic (repetitive tapping) motor task. Connectivity was examined from psychophysiological interactions in hippocampal activity during two analyses: the first identified motor interactions relative to rest, whereas the second identified differential motor activity between adjacent fingers. Connectivity was observed in both pre- and postcentral gyrus, but only postcentral connectivity was topographical, coincident with finger representations identified in a previous study. Differences in the magnitude of connectivity were observed between finger representations, representing spatial selectivity for the target of movements; the postcentral representation of the moving finger invariably showed greater connectivity than adjacent fingers. Furthermore, the magnitude of connectivity within a pre- or postcentral finger representation was largest when its finger moved, representing temporal selectivity for movement. While the hippocampus is known to be sensitive to spatial and temporal features of the environment, consistent with its role in learning and memory, the pattern of spatial and temporal selectivity of hippocampal connectivity observed in this study occurred during volitional movements in the absence of motor learning or recall. Spatial and temporal selectivity of connectivity during volitional movements meets the criteria for cognitive control adapted from oculomotor studies, suggesting a role for the hippocampus in motor control.

Introduction

To move purposefully, one or more signals within our brain direct the motor system to carry out the intended movement. This is the essence of *cognitive control*, the process by which goals or plans influence behavior. Although various regions of prefrontal cortex have been broadly implicated in cognitive control (1-5), the source of cognitive influence on the motor system is still subject to speculation.

Requirements for cognitive control of movements have been demonstrated in oculomotor studies, particularly those investigating the neural basis of reading (6-8) and other purposive eye movements (9-11). Such studies emphasize three components: 1) neural activity evident during conditions that require cognition; 2) spatial specificity, reflecting the spatial goal of the eye movement (i.e., target location); and 3) temporal specificity, which determines when the movement occurs.

The frontal eye field (FEF) is involved specifically in voluntary saccades, both in human and non-human primates (11, 12). Recording activity from nerve cells is generally avoided in humans, but FEF neurons in non-human primates reflect all three of these properties (13). These three properties are also evident from deficits following FEF lesions; for example, impairments in the accuracy and latency for a variety of volitional, but not reflexive eye movements are observed in both humans (11, 14-20) and non-human primates (21-24). In humans, lesions of the FEF and parietal eye field (PEF) differentially affect the selection of saccade targets and their timing (25); in monkeys, lesions of either area produce modest impairments in the accuracy and initiation of saccades, whereas combined lesions produce profound impairments (26). These studies demonstrate that the FEF, singly or in combination with PEF, is critically involved in the

62 generation of volitional eye movements, providing the timing of purposive eye movements and
63 their target location.

64 Analogous to the FEF in the oculomotor system (27), the primary motor cortex is necessary for
65 volitional movements of individual fingers (28, 29), with short fiber tracts that connect
66 postcentral with precentral regions of sensorimotor cortex providing sensory feedback required
67 for accurate performance (30). Neural activity in the FEF and sensorimotor cortex (SMC) both
68 reflect cognitive input. FEF properties that reflect cognitive input includes activity that predicts
69 two sequential saccades (31-33), target selection (34-37), covert attention (38-42), and changes
70 during learning (27, 43). Similarly, cognitive input to SMC is evident from neural changes
71 during motor learning, both in its response properties (44-49) and changes in connectivity (50-
72 52). Although cognitive input to both areas can be inferred, direct evidence for the source (or
73 sources) of this input is sparse. Indirect evidence from neural properties and lesion effects has
74 implicated the supplementary eye field (SEF) (53, 54), basal ganglia (55), and dorsolateral
75 prefrontal cortex (56) in the cognitive control of eye movements, and the basal ganglia (57),
76 cingulate (58), and prefrontal cortex (1, 59-63) for the cognitive control of skeletomuscular
77 movements.

78 From this, it is tempting to speculate that the prefrontal cortex regulates finger movements. The
79 prefrontal cortex has traditionally been associated with cognitive control, yet its connectivity to
80 the SMC is indirect via the dorsal premotor cortex (2, 64, 65). Prefrontal areas are functionally
81 coupled to premotor areas when learning movement sequences but not during repetitive tapping
82 (66, 67), suggesting prefrontal cortex may be involved in cognitive control when learning
83 complex movement sequences but not during simple movements. In its role, premotor cortex is
84 analogous to the SEF (27), which is specialized for learning eye movement sequences (27, 68-

85 70) and resolving conflicts between potential saccade targets (71, 72). Because prefrontal
86 connectivity to FEF and SMC is indirect and limited to complex movements, cognitive control of
87 simpler movements mediated specifically through FEF and SMC may arise from a different
88 source. Thus, a relationship between neural activity and task complexity is unlikely when
89 studying cognitive control in SMC, even though such a relationship has been used effectively to
90 study cognitive control elsewhere (4, 73, 74).

91 The control of finger movements is more complex than eye movements for at least two reasons.
92 First, the spatial reference for finger movements is different. Whereas eye movements are
93 encoded from the current position of the eyes within the orbit (retinocentric space), finger
94 movements are based upon the current position of the body (body-centered space); thus, the
95 combination of finger muscles required to achieve a goal differs with different body positions.
96 Second, the load on eye muscles is constant, whereas muscles moving the fingers may require
97 different forces when moving objects of different resistance. When a task requires the initiation
98 of finger movements from a set position with minimal load, however, requirements for cognitive
99 control are the same as for eye movements: the neural mechanism must be active during
100 volitional movements that require *cognition*, while specifying the timing and goal of the
101 movement. The goal under these conditions reflects the body part that moves (e.g., hand or
102 finger), requiring *cortical specificity* for neural activity within the SMC hand representation.

103 Whereas Part I of this study examined hippocampal-SMC connectivity within the framework of
104 volitional movements, part II considers whether this connectivity shows spatial and temporal
105 selectivity, necessary to specify which finger moves and when. Connectivity associated with
106 movements of individual fingers is shown to be organized topographically, with connectivity in
107 the representation of the moving finger greater than for adjacent fingers (spatial selectivity);

furthermore, connectivity within each finger representation is greatest when the finger moves, falling when movement stops (temporal selectivity). Combined with Part I, hippocampal-SMC connectivity thus fulfills the three conditions of selectivity required for cognitive control. After considering alternative interpretations, we conclude that hippocampal connectivity is consistent with cognitive control of motor function, and describe experiments that could further elucidate this functionality.

Materials and methods

Subjects

Thirteen right-handed adults from the Chicago metropolitan area participated in the study (ages 24–59, mean=42.3, five females). The nature of experimental procedures were explained to each subject before obtaining written consent; consent procedures complied with the Code of Ethics set forth in the Declaration of Helsinki, and were approved by the Institutional Review Board at the NorthShore University HealthSystem / Research Institute. Consented subjects had no history of the following: a previous concussion, psychiatric illness, learning disability, attention deficit disorder, abnormal physical or cognitive development that would affect educational performance, central neurological disease (or structural pathology), or neurosurgical intervention.

Immediately prior to their fMRI tests, subjects were trained on one cycle of each experimental task.

Experimental tasks

130 The tasks were described in detail in part I. Briefly, the visual/motor task used in this study
131 comprised 6 cycles of a specified sequence of visual and motor conditions. Motor conditions
132 were preceded by an instruction screen, accompanied by a metronome ticking at 2 beats per
133 second. During the sequence learning task, subjects rehearsed a remembered sequence of button
134 presses, tapping in synchrony with the metronome; this was followed by a visual condition,
135 which required fixation at the center without finger movements while a circular checkerboard
136 flashed at 4Hz. The instruction screen for repetitive tapping followed. For repetitive tapping,
137 subjects repeatedly tapped the same finger on both hands, corresponding to the button identified
138 on-screen; the index finger ('F1') tapped first, and the finger increased incrementally every 4s
139 (eight taps). After tapping movements from all four fingers (F1-F4 during time periods T1-T4,
140 respectively), the visual condition was repeated. Connectivity analysis in this report focused on
141 repetitive tapping.
142

143 # MRI data acquisition

144 Images were acquired using a 12-channel head coil in a 3 Tesla Siemens scanner (Verio). Visual
145 stimuli projected onto a screen (Avotec Silent Vision) were viewed via a mirror attached to the
146 head coil, and behavioral responses were recorded by Eprime [Psychology Software Tools, Inc.]
147 from an optical response box (Current Designs, Philadelphia, PA). Blood-oxygen level
148 dependent (BOLD) functional images were acquired using the echo planar imaging (EPI)
149 method, using the following parameters: time of echo (TE) = 25ms, flip angle = 90°, matrix size
150 = 64 x 64, field of view = 22cm, slice thickness = 3mm, number of slices = 32; time of repetition
151 (TR) = 2000ms. The number of repetitions for the visual/motor condition was 182. A structural
152 T1 weighted 3D image (TR = 1600ms, TE = 3.46ms, flip angle = 9°, matrix size = 256 x 256,

153 field of view = 22cm, slice thickness = 1mm, number of slices = 144) was acquired in the same
154 orientation as the functional images.
155

156 fMRI data processing

157 Data was analyzed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm), using procedures
158 described in Part I. Briefly, images were spatially aligned to the first volume to correct for small
159 movements, sinc interpolation minimized timing-errors between slices, and functional images
160 were coregistered to the anatomical image and normalized to the T1 Montreal Neurological
161 Institute (MNI) template, then smoothed with a 10mm isotropic Gaussian kernel. During
162 analysis, conditions of interest were specified for sequence learning, visual, and each of the four
163 fingers moving during the repetitive tapping block; global normalization scaled the mean
164 intensity of each brain volume to a common value to correct for whole brain differences over
165 time.

166 Global conjunctive analysis of both motor conditions generated a bilateral activation map for
167 hand movements, used as the ROI for connectivity analysis.
168

169 Psychophysiological interactions (PPI)

170 Preprocessing

171 Connectivity analysis was carried out using psychophysiological interactions (75), modified to
172 account for individual variability in connectivity (76). As descried in Part I, alternate voxels
173 were sampled from the left (13) and right hippocampus (13) of the normalized brain, as delimited
174 by the aal atlas in the WFU PickAtlas toolbox (http://fmri.wfubmc.edu/software/PickAtlas).

175 Two sets of connectivity analyses were employed, differing only in the interaction term used to
176 identify task-specific activity. In the first analysis, an interaction term specified a greater effect
177 of seed activity during movement of a single finger than during the visual condition; this
178 identified the effect of movement relative to rest (e.g., F1>rest). In the second analysis, the
179 interaction term specified a greater effect of seed activity during movement of one in a pair of
180 adjacent fingers (e.g., F1>F2 or F2>F1); this identified preferential activity for one finger. After
181 adjustments for regional differences in timing, a regression analysis identified the magnitude of
182 the BOLD signal in SMC that was correlated with the PPI interaction term.

183 Seed selection

184 Two approaches were used to select seeds. The first approach was "structural"; the hippocampus
185 was divided into 8 regions from posterior to anterior, with connectivity evaluated for each region
186 (position-1 through position-8). The second approach was empirical or "functional"; the
187 hippocampal voxel generating the greatest connectivity anywhere within SMC during a task was
188 selected as a seed. Regardless of the method for selection, a voxel seed was selected from both
189 the left and right hippocampus, and a conjunction (global) analysis was used to characterize
190 connectivity.

191 Finger topography and spatio/temporal selectivity

192 The topographical arrangement of connectivity associated with individual finger movements was
193 examined during both sets of analysis, exemplified by F1>rest and F1>F2. In the first analysis,
194 the region of connectivity was plotted for each finger. In the second, the region of connectivity
195 for each finger was restricted to the area of overlap between PPI maps for a specified finger; for
196 example, connectivity for F2 was visualized as the overlap in connectivity between F2>F1 and

197 F2>F3.

198 Although differing in voxel resolution, the topographical arrangement of connectivity during
199 these analyses overlapped the finger topography identified in a previous study, which used a
200 variant of our paced repetitive tapping task to identify finger representations through differential
201 activation (77). (See Fig S1 for this comparison.) To investigate patterns of spatial and temporal
202 selectivity, the voxels constituting pre- and postcentral finger representations F1 through F3 from
203 the previous study were identified, and the beta estimate for the magnitude of connectivity was
204 recorded for each voxel.

205 During a specified time period, statistics were derived from voxel-wise comparisons with the
206 mean connectivity in the representation of the moving finger. To minimize confounds due to
207 variations in the baseline, the magnitude of connectivity for the moving finger was operationally
208 defined as the difference in connectivity during movement and the connectivity extremum when
209 the finger was stationery; the magnitude of connectivity for all other fingers (or time periods)
210 was expressed as a percentage change from this. A separate analysis was run for each time
211 period.

212 *Spatial selectivity* compared the magnitude of connectivity between two finger representations
213 during a single time period. Two-tailed paired t-tests identified differences in connectivity
214 between pairs of finger representations; differences between the moving finger and adjacent
215 fingers were particularly relevant. The paired t-test identified patterns of differences between
216 finger representations observed across individuals.

217 *Temporal selectivity* evaluated whether the magnitude of connectivity within each finger
218 representation differed across time periods; it was evaluated separately for each finger
219 representation. Two-tailed paired t-tests identified voxel-wise changes in connectivity between

each pair of time periods; differences in connectivity from the time period when the represented finger was moving were particularly relevant.

Results

Topography of Connectivity

The extent and topography of hippocampal connectivity with SMC derived from interactions between movements of a single finger and rest are shown in Fig 1 (see also Table 1). Functional seed-1 and seed-2 both generated connectivity in left SMC, with seed-2 generating more intense, bilateral connectivity; the expected time course of activity for later fingers was delayed (Fig 1A). By superimposing connectivity maps from each finger, a topographical distribution was evident (Fig 1B). Postcentral connectivity for F4 extended further dorsal than F2 and F1, evident in both the left postcentral gyrus for functional seed-1 (see sagittal section) and bilaterally for functional seed-2 (see coronal sections).

Fig 1. Connectivity and topography for individual fingers. (A) Peak activity predicted for connectivity from the left (solid colored line) and right hippocampal seeds (dashed colored line) were progressively delayed for F1 through F4; the timing predicted for fMRI activation is provided for comparison (black dotted line). Except for F3, connectivity associated with individual finger movements was limited to the left SMC for functional seed-1, but bilateral for functional seed-2. (B) A topography was evident from connectivity in the left postcentral gyrus for seed-1 and bilaterally for seed-2; connectivity for F4 was dorsolateral to the SMC region of connectivity for F2.

Table 1. Finger-specific connectivity in left SMC.

Finger/task interaction	Hemisphere (SMC)	Region	Cluster size	Z-score (peak)	Peak Coordinates
Funct-1 seed					

F1 > visual	left	pre/post	42	3.90	(-34,-24,54)
F2 > visual	left	pre/post	42	3.77	(-34,-24,54)
F3 > visual	left	pre post	62	3.93 3.58	(-34,-20,58) (-38,-36,62)
	right	pre post	29 8	5.06 3.80	(34,-12,62) (38,-36,58)
F4 > visual	left	pre/post	46	3.55	(-34,-24,54)
	right	pre	7	3.24	(42,-12,62)
Funct-2 seed					
F1 > visual	left	pre post pre	102	3.70 3.66 3.17	(-34,-16,54) (-34,-32,62) (-50,-8,42)
	right	pre post	154	4.68 3.97	(34,-16,58) (38,-36,58)
F2 > visual	left	pre post pre	110	3.70 3.66 3.17	(-34,-36,58) (-30,-20,54) (-50,-24,46)
	right	pre post post	166	5.14 4.80 4.41	(34,-16,62) (48,-24,50) (38,-36,58)
F3 > visual	left	pre post post	124	4.11 4.10 3.88	(-34,-16,58) (-38,-36,62) (-46,-24,42)

	right	pre	166	5.48	(34,-16,62)
		post		5.15	(50,-24,54)
		post		4.50	(34,-40,54)
F4 > visual	left	post	154	4.37	(-38,-32,58)
		pre		4.31	(-34,-16,58)
		post		3.64	(-50,-8,42)
	right	post	167	5.53	(46,-20,54)
		pre		5.53	(38,-16,58)
		post		4.24	(38,-40,58)

Connectivity clusters in the left SMC from movement of individual fingers, surviving an intensity threshold of p=0.05 with a family-wise error correction.

Fig 2 shows connectivity derived from hippocampal interactions in activity between movements of adjacent fingers (see also Table 2). Arising from differences in the timing of neural activity (Fig 2A, compare left and right columns), the area of cortical connectivity depended on the pair of adjacent fingers used for analysis; connectivity only partially overlapped across pairings with one finger in common (second row for F2 and third row for F3). Regions of overlap designated connectivity for an individual finger. Connectivity showed a similar topographical organization in the right postcentral gyrus (Fig 2B) as shown previously for the left (Fig 1B).

Fig 2. Connectivity and topography identified from psychophysiological interactions between movements of adjacent fingers. (A) The brain location of connectivity and its timing depended on the finger pairing; e.g., the interaction between F2 and F1 shown in the second row arose earlier than the interaction between F2 and F3, and the spatial extent of their connectivity differed. To better define topography, connectivity for F2 was identified from their overlap. (B) Connectivity was organized topographically, from F4 (blue, located dorsal) to F2 (red, intermediate) to F1 (yellow, ventral). For simplicity, connectivity for F3 is not shown.

245

246 **Table 2. Location of finger-specific connectivity in right SMC.**

Finger/task interaction	Hemisphere (SMC)	Region	Cluster size	Z-score (peak)	Peak Coordinates
F1>F2	right	precentral postcentral	9 18	4.36 4.05	(38,-12,66) (38,-32,50)
F2>F1	right	postcentral postcentral precentral	22	5.05	(50,-24,50) (38,-32,62) (50,-16,46)
F2>F3	right	postcentral postcentral	22	4.41 4.21	(42,-28,54) (34,-32,58)
F3>F2	right	postcentral precentral precentral	58	5.11 5.03 4.69	(50,-24,54) (34,-12,66) (46,-16,50)
F3>F4	right	precentral postcentral precentral	58	4.01 3.61 3.59	(34,-16,66) (50,-24,54) (38,-16,46)
F4>F3	right	precentral postcentral precentral	71	4.44 4.08 4.07	(50,-12,46) (42,-28,58) (38,-12,58)

247 Connectivity clusters in the right SMC from movement of individual fingers, surviving an intensity
248 threshold of p=0.05 with a family-wise error correction.

249

250 ## Spatial / temporal interactions within SMC finger representations

251 One or more voxels within each finger representation showed significant connectivity during
252 each time period; spatial and temporal selectivity were identified from differences in the
253 magnitude of connectivity across representations or time periods.

254 Fig 3 examines spatial and temporal selectivity. Fig 3A illustrates spatial selectivity in the left
255 SMC during the time period for each finger movement, based on the magnitude of connectivity
256 derived from seed-1 interactions between finger movements and rest. Typically, differences
257 >10-20% in connectivity between finger representations were significant (tabulated in Table S1).
258 Differences were invariably observed in connectivity between the postcentral representation of
259 the moving finger and the adjacent finger; differences were also observed during T2 between
260 precentral representations of F2 and adjacent fingers. Connectivity with the postcentral SMC
261 representation of the finger *adjacent* to the moving finger (e.g., F2 during T1) could also differ
262 significantly from the representation of the finger twice removed from movement (in this

Fig 3. Spatial and temporal selectivity of SMC connectivity. (A) Spatial selectivity in left SMC reflected differences in the magnitude of connectivity between finger representations within a time period; except for F2, spatial selectivity was limited to postcentral gyrus. On each timeline, the highlighted period shows when a finger was moving; the colored arcs represent connectivity for those finger representations with elevated connectivity that includes the specified time period (yellow=F1, red=F2, green=F3). (B) Although connectivity in the right postcentral gyrus was identified from seed interactions between movements of adjacent fingers, spatial selectivity was similar to that observed in the left SMC. (C) Temporal selectivity in SMC connectivity reflected significant differences in the magnitude of a single finger representation's connectivity across time periods; systematic differences were not observed between pre- and postcentral gyrus. Connectivity in each finger's representation significantly differed during time periods when the finger was not moving.

Significant differences ($p<0.05$) are italicized in bold type, with marginally significant results ($p<0.10$) shown in plain type.

example, F3), suggesting connectivity is also elevated in the representation of the adjacent finger.

Fig 3B illustrates spatial selectivity in the right SMC for each time period, based on the magnitude of connectivity derived from seed-2 interactions between movements of adjacent fingers. Results were similar to those observed in the left SMC, except no connectivity was observed in precentral SMC.

Fig 3C examines temporal selectivity. In each row, the thickened segment highlights the time period serving as the statistical baseline for comparison. Within a finger representation, the magnitude of connectivity was elevated during the time period when the finger was moving, differing significantly from adjacent time periods. Connectivity during an adjacent time period could also be elevated, although modestly, adding a sequential time period without finger movements where differences were observed.

The magnitude of connectivity between and within individual finger representations shows both spatial and temporal selectivity, as summarized in Tables S1 and S2.

Discussion

In two analyses, the topography of hippocampal connectivity with SMC was found to be consistent with that previously demonstrated from fMRI activation (77). The magnitude of connectivity within these finger representations demonstrated both spatial selectivity (differences between finger representations during movement of a single finger) and temporal selectivity (differences across time periods within a finger representation). Because these movements were under volitional control, as demonstrated in Part I, these patterns of connectivity fulfill the

requirements for cognitive control adapted from oculomotor studies. The hippocampus thus augments the role of prefrontal cortex in the cognitive control of volitional finger movements, which is reportedly limited to complex sequences of movements.

Topography of finger representations

Activation studies have shown overlapping activation between nearby fingers, with representations for later fingers (e.g., F4) located dorsal to earlier fingers (77-82). The topographic organization of connectivity associated with individual finger movements followed this pattern in the postcentral gyrus of both hemispheres; no topography was apparent in the precentral gyrus, although precentral connectivity was observed.

Spatial selectivity

Spatial selectivity identified differences in the magnitude of connectivity between finger representations during a time period when a single finger moved. Selectivity was observed during each time period; the magnitude of connectivity was greatest for the moving finger, dropping significantly in the adjacent postcentral finger representation. Elevated connectivity could spill over into an adjacent finger representation, however; significant differences in connectivity were observed during T1, for example, between the representations for F2 and F3, as well as between F1 and F2. A similar spillover effect has been observed for fMRI activation during finger movements, where movement-related activation extends into the representation of adjacent fingers (78-82), perhaps reflecting the fact that adjacent fingers do not move independently

Spatial selectivity was observed bilaterally in postcentral finger representations.

Temporal selectivity within the finger representations

Temporal selectivity identified differences in the magnitude of connectivity at a specific finger representation across time periods. At each finger representation, maximal connectivity occurred when the finger was moving, with reduced connectivity during other time periods. Similar to the spillover into an adjacent finger representation observed for spatial selectivity, however, elevated connectivity could spill over into an adjacent time period.

Temporal selectivity did not differentiate between pre- and postcentral finger representations.

Hippocampal properties are consistent with cognitive control

As noted in the introduction, three features are essential for a role in cognitive control: 1) selective presence during tasks under volitional control; 2) spatial selectivity, reflecting actions directed to specific target locations; and 3) temporal selectivity, reflecting the timing of action. Neural activity consistent with these criteria has previously been reported for the hippocampus.

The hippocampus is selectively active during movements requiring cognitive control. Because the hippocampus is preferentially involved in conscious memories and environmental interactions (83, 84), studies of hippocampal interactions with the motor system have traditionally been focused on its role in explicit learning and memory consolidation. Hippocampal connectivity with the striatum increases during explicit motor learning and consolidation (85-87); consolidation after rehearsal is further reflected through increased motor activation following sleep in both the primary motor area and the hippocampus (85, 88).

329 Hippocampal connectivity to SMC occurs during paced repetitive tapping movements as well as
330 sequence learning; subjects' anticipatory responses indicate volitional control of these
331 movements (see Part I of this study). These findings demonstrate hippocampal involvement in
332 movements and motor learning under explicit cognitive control; by contrast, the hippocampus is
333 inactive during implicit learning of motor sequences (89).

334 The second requirement for cognitive control is spatial selectivity. The hippocampus is sensitive
335 to spatial location and navigation, with spatial functioning localized to the posterior
336 hippocampus (90, 91), including space cells that encode a spatial map (92-96). Because the
337 spatial location of the hand on the response pad was fixed in the current study, the spatial
338 location of a button press corresponded to a SMC finger representation, and posterior structural
339 seeds generated connectivity restricted to the SMC hand representation (see Part I).
340 Furthermore, spatial selectivity was observed between finger representations, as the magnitude
341 of connectivity dropped with distance from the representation of the finger currently moving.
342 Thus, spatial properties of the hippocampus provided the selectivity in motor response required
343 for cognitive control.

344 The third requirement for cognitive control is temporal selectivity. The hippocampus responds
345 differentially to sequences of events that differ in order (97-100), and to the intervals between
346 stimuli within a sequence (101-103). Cognitive awareness of the temporal intervals between
347 metronome beats provided the basis for anticipatory behavioral responses in the current study.
348 Furthermore, temporal selectivity was observed within each finger representation, such that
349 connectivity was greatest when the represented finger was moving.

350 Connectivity with SMC during motor tasks is thus consistent with known hippocampal
351 properties and meets the three criteria for the cognitive control of movements. This does not

352 preclude an additional role in cognitive control of SMC from other areas. Prefrontal cortex has
353 been suggested to play an indirect role through its connectivity with dorsal premotor cortex (2),
354 although functional coupling of prefrontal with premotor areas is limited to movement sequences
355 (66). During paced repetitive tapping, however, hippocampal connectivity provides the best
356 explanation for the cognitive control of SMC.
357

358 Cognitive control vs. other theories of hippocampal function

359 There is currently no consensus about the functional significance of the spatial and temporal
360 properties of the hippocampus. Some have suggested the hippocampus has cognitive functions
361 beyond its traditional roles (104-106), whereas others suggest its diverse properties merely
362 reflect the varied components of episodic and long-term declarative memory (92, 93, 107).
363 Although hippocampal connectivity with SMC meets the requirements for cognitive control,
364 could the results be better explained through its other known functions?

365 Memory of the pacing interval, plus associations between the numerical onscreen display and the
366 corresponding fingers, were required for accurate performance during motor tasks in this study.
367 These modest memory requirements might arguably require hippocampal input; neither spatial
368 nor temporal selectivity, however, is required to access this mnemonic information. Spatial
369 selectivity is unnecessary because the mapping between numerals and fingers never changed,
370 whereas temporal selectivity is unnecessary because widespread cortical rhythms (such as theta)
371 could serve to time events. The observed pattern of spatial and temporal selectivity is *required*
372 for cognitive control, however, to specify the finger to be moved and when.

373 An alternative explanation is that hippocampal connectivity in this study represents a form of
374 sensorimotor processing, facilitating the transformation of sensory signals into motor output

375 (108-111). This interpretation could explain why its topography and spatial selectivity were
376 most prominent in the postcentral gyrus. Even without hippocampal intervention, however,
377 extensive connections between pre- and postcentral gyrus provides sensory feedback (112), so
378 aside from cognitive control, the role of hippocampal sensorimotor processing in SMC is
379 unclear. Furthermore, facilitation of sensorimotor processing does not require temporal
380 specificity. Given the directional influence of the hippocampus on SMC (implicit in PPI
381 analysis), a hippocampal role in sensorimotor processing begs the question: what directs the
382 hippocampus to provide relevant spatio-temporal information to SMC as needed for task
383 performance? Considering the tight relationship between neural activity in the hippocampal
384 seeds and SMC (shown in Fig 2 of Part I), an additional control signal in SMC seems unlikely.

385 These considerations do not exclude the possibility of other sources of cognitive control under
386 different conditions. By analogy with the oculomotor system, damage to a single structure (e.g.,
387 FEF or SMC) can produce deficits without eliminating all function (eye movements or hand
388 movements) due to the preservation of other structures with overlapping functions (SEF / PEF,
389 premotor cortex / basal ganglia). Similarly, executive functions show deficits following damage
390 to prefrontal areas, yet are not eliminated (113-115). Hippocampal dysfunction in Alzheimer's
391 impairs volitional motor control (116), but with overlapping systems for cognitive control, it
392 would not eliminate volitional movements.
393

394 Implications and directions for future research

395 This study provides evidence that the hippocampus is involved in the cognitive control of
396 volitional finger movements. Whether this represents a new function, or represents another

397 component of a single cognitive function, is unclear. These alternative possibilities suggest two
398 broad experimental questions for further investigation.

399 First, how extensive is the hippocampal role in cognitive control during volitional movements?
400 Based on the criteria for cognitive control, hippocampal connectivity should be lost when
401 "mindless" finger movements are generated while simultaneously performing a mentally-
402 challenging task; connectivity also needs to be demonstrated during volitional movements of
403 other body parts. In addition, a fixed spatial relationship between fingers and button presses in
404 the current study allowed cortical specificity for finger movements to provide a measure of
405 spatial selectivity; it's unclear how the hippocampal pattern of cortical / spatial selectivity would
406 be affected by changes in the spatial target of finger movements.

407 Second, is the hippocampal role in cognitive control limited to volitional movements, or does it
408 extend to other cognitive activities? The hippocampus is critically involved in the formation and
409 recall of episodic and declarative memories, thus fulfilling the first criterion for cognitive control
410 (preferentially active during volitional states). Whether hippocampal interactions with cortical
411 areas meet the remaining criteria for cognitive control is unclear, although theoretical accounts of
412 memory function suggest they might. The hippocampus has been suggested to index memories,
413 selectively accessing the prefrontal site of memory storage during the time period when
414 memories are recalled (117-122). Such interactions provide cortical and temporal specificity,
415 and may explain how engrams located elsewhere are selected by the hippocampus during recall.
416 Similarly, spatial and temporal selectivity from hippocampal interactions with prefrontal cortex
417 may provide the context for interpreting sensory input (95, 96, 123-126); miscommunication
418 between the hippocampus and prefrontal cortex in schizophrenia would then produce abnormal
419 perceptions (104, 127, 128).

When spatial and temporal selectivity of hippocampal connectivity with cortical areas is necessary to perform cognitive tasks, a role of the hippocampus in cognitive control is implied. The role of the hippocampus in cognitive control may be evaluated through experimental manipulations that affect cognitive awareness and performance, evaluating effects of these variables on the connectivity of the hippocampus with brain areas directly involved in task performance. Comparing effects of these variables on hippocampal and prefrontal connectivity may help identify conditions where these regions are either complementary or synergistic in the cognitive control of behavior.

Conclusions

The hippocampus showed task-specific connectivity with SMC during paced movement tasks, meeting the criteria for cortical control adapted from studies of cognition in the oculomotor system: associated with volitional movements, restricted to the representations of the moving fingers, and selective for the timing of the movements. This pattern of connectivity is consistent with known hippocampal properties, yet cannot be explained by its established functions. A role for the hippocampus in cognitive control is indicated; a collaborative role with prefrontal cortex is suggested from their close functional relationship across tasks and neurological conditions.

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Fig S1. SMC topography from fMRI activation and PPI connectivity during paced tapping. The fMRI topography was demonstrated in the left SMC by contrasting activation by each finger in the right hand with all other fingers, applied to images acquired with 1mm in-plane resolution and 3mm slice thickness (Burman et al., 2009); the PPI topography in the right SMC of the current study was demonstrated through global connectivity from left and right hippocampal seeds reflecting interactions between adjacent fingers, applied to 4mm isotropic images. Despite differences in voxel size and hemisphere, the two methods provide good correspondence in topographical organization.

756

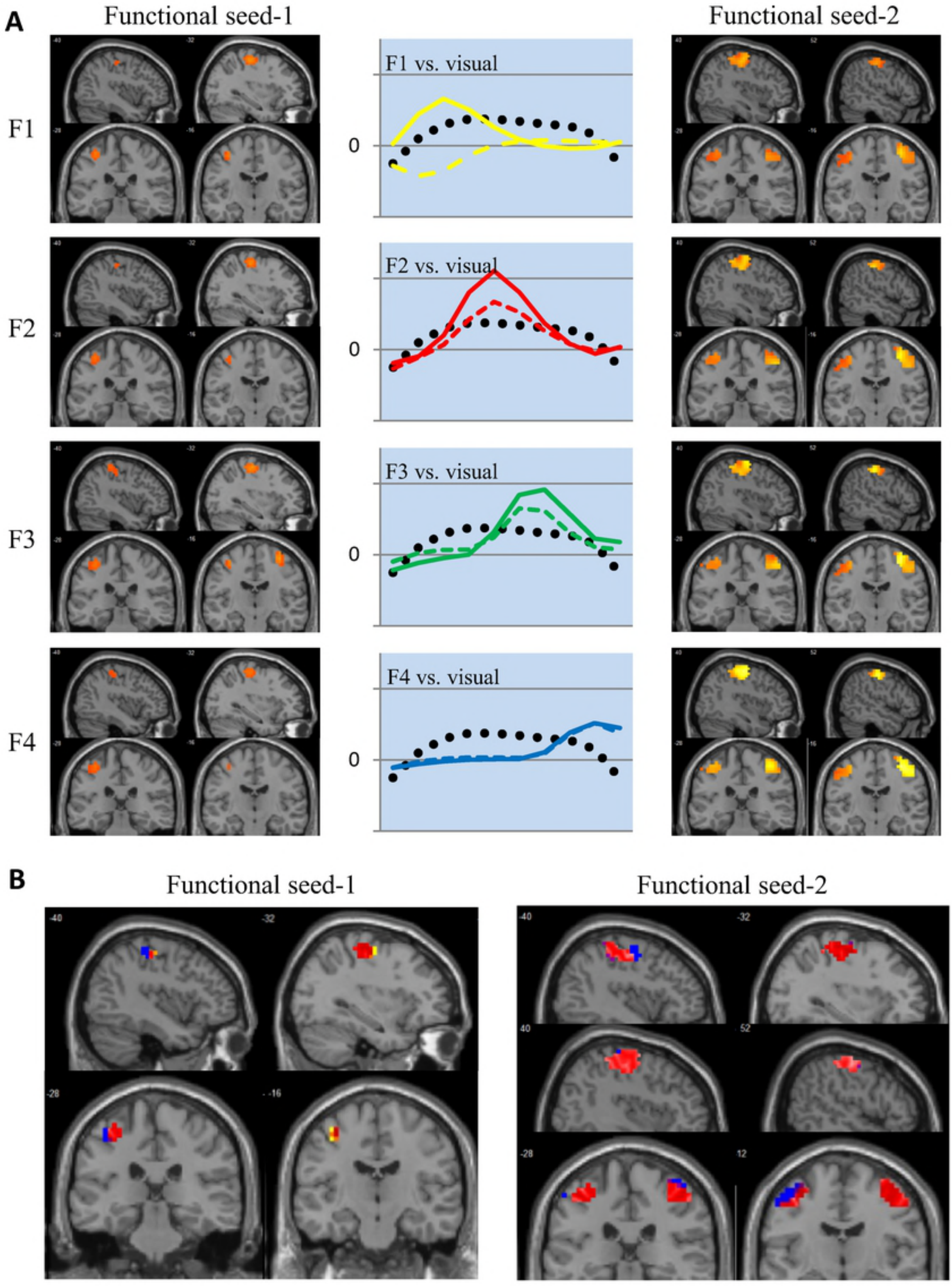
A
Functional seed-1
Functional seed-2
F1
F2
F3
F4
F1 vs. visual
F2 vs. visual
F3 vs. visual
F4 vs. visual
0
B
Functional seed-1
Functional seed-2

Fig 1

A

Functional seed-2

F1

Activation (all fingers)

F1 (vs. F2)

F2

F2 (vs. F1)

F2 (vs. F3)

F3

F3 (vs. F2)

F3 (vs. F4)

F4

F4 (vs. F3)

Activation (all fingers)

B

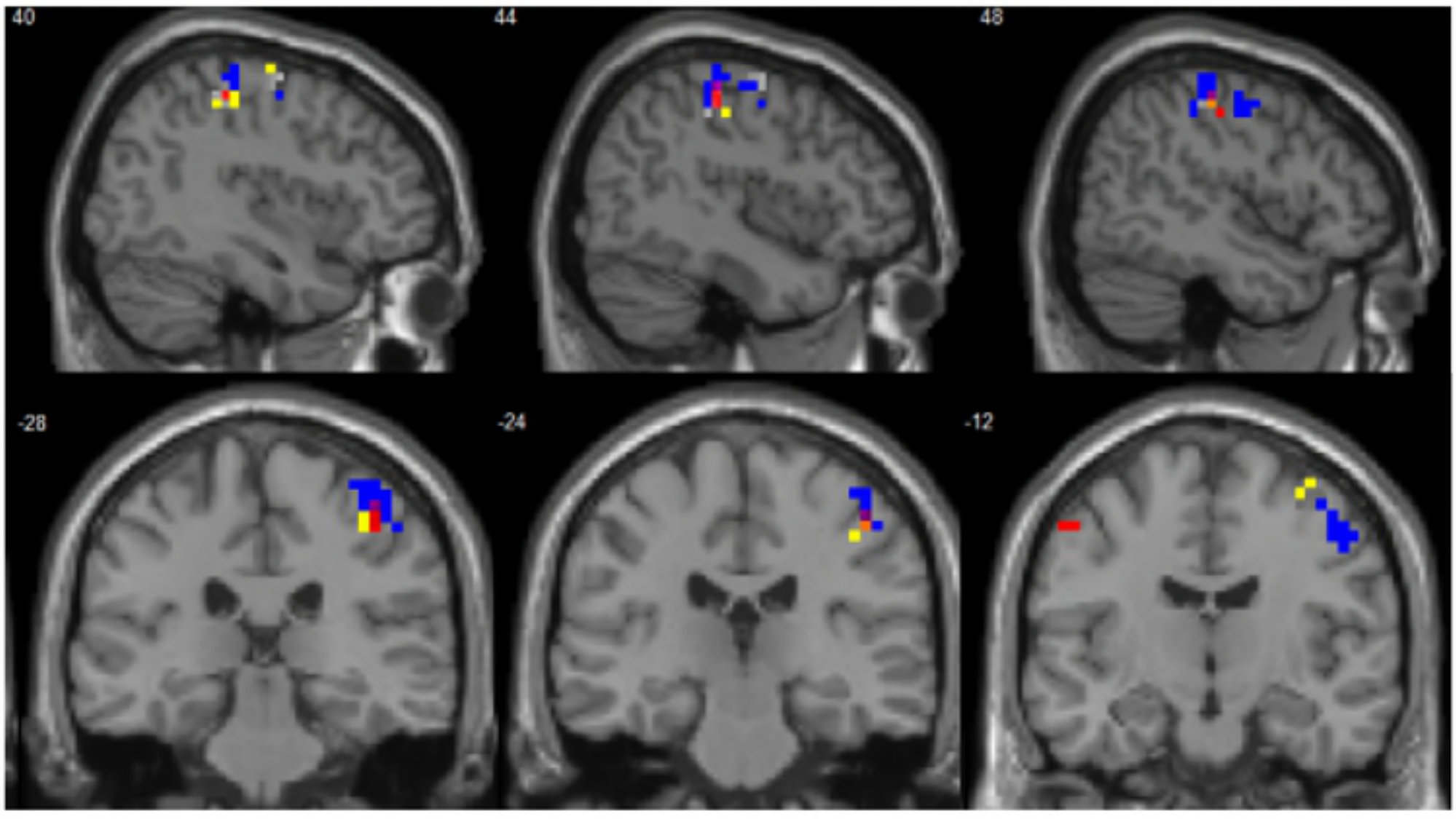

Fig 2

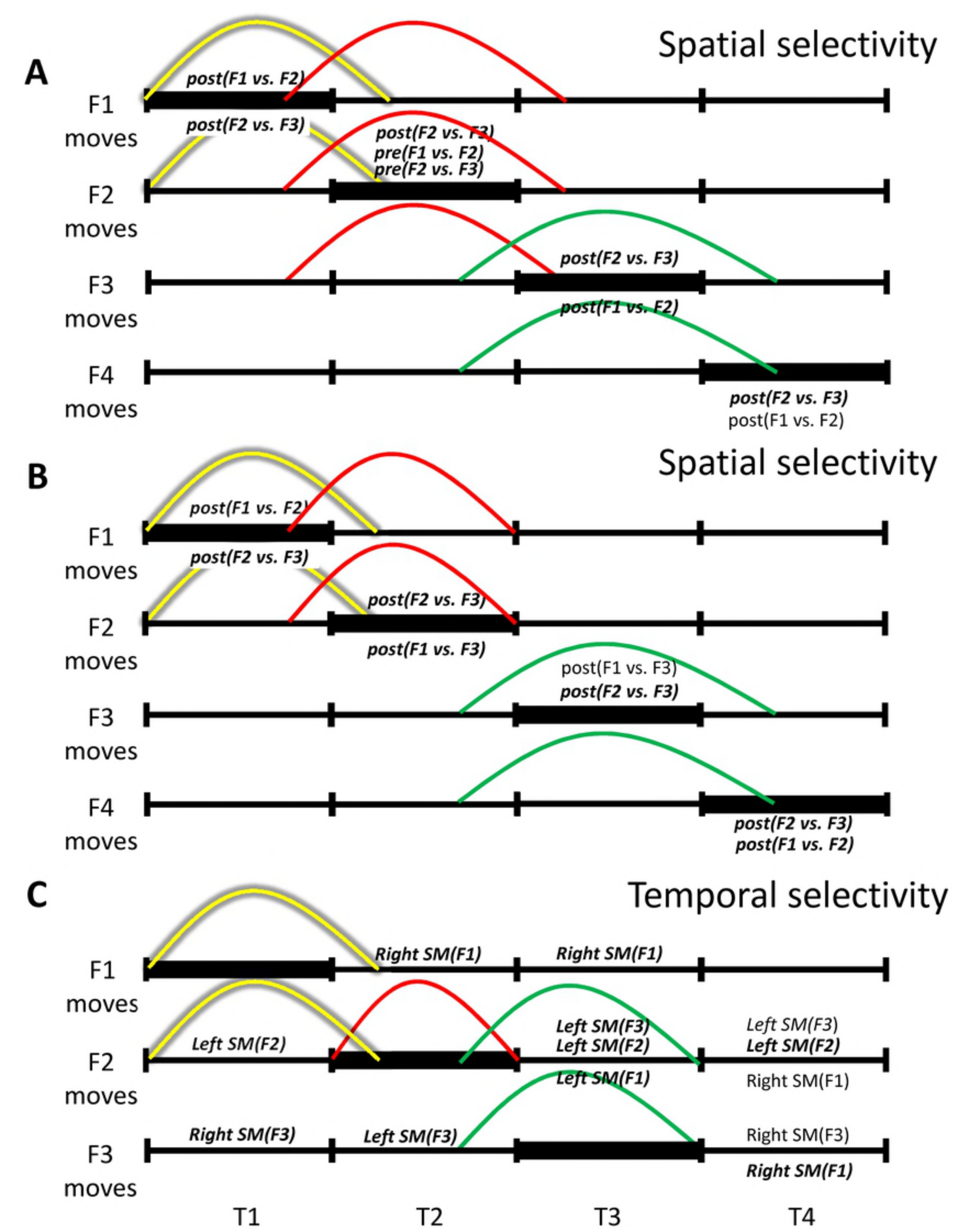
A
Spatial selectivity
F1 moves
post(F1 vs. F2)
F2 moves
post(F2 vs. F3)
post(F2 vs. F3)
pre(F1 vs. F2)
pre(F2 vs. F3)
F3 moves
post(F2 vs. F3)
F4 moves
post(F1 vs. F2)
post(F2 vs. F3)
post(F1 vs. F2)
B
Spatial selectivity
F1 moves
post(F1 vs. F2)
F2 moves
post(F2 vs. F3)
post(F2 vs. F3)
post(F1 vs. F3)
F3 moves
post(F1 vs. F3)
post(F2 vs. F3)
F4 moves
post(F2 vs. F3)
post(F1 vs. F2)
C
Temporal selectivity
F1 moves
Right SM(F1)
Right SM(F1)
F2 moves
Left SM(F2)
Left SM(F3)
Left SM(F2)
Left SM(F3)
Left SM(F2)
Left SM(F1)
Right SM(F1)
F3 moves
Right SM(F3)
Left SM(F3)
Right SM(F3)
Right SM(F1)
T1
T2
T3
T4

Fig 3