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Neural representation of stimulus-response associations during task preparation

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ABSTRACT

A partially informative cue presented before a stimulus can facilitate the production of the response. Prior information about an upcoming target can increase brain activity in both stimulus (c.f., Desimone and Duncan, 1995) and response (c.f., Leuthold et al., 1996) processing regions; however, it is unclear how the representation of the task might influence the recruitment of this network of task-relevant regions. In the current experiment, we employed an event-related fMRI design with a response cuing procedure to investigate whether S-R pairings jointly influence activity in stimulus- and response-specific processing areas during the presentation of a cue. Participants learned S-R mappings in which pictures of faces and places were paired with either left or right hand finger responses. On some trials, a cue provided partial information about the upcoming trial (e.g., that the trial would involve a face or place stimuli or a left or right hand response). Importantly, because different stimulus types were associated with each hand, any informative cue implicitly indicated both a stimulus type and response hand, allowing participants to represent the task as two distinct subtasks. Region-of-interest analyses at the cue event demonstrated a biasing of response processing regions for both stimulus- and response-related cues, as well as increased connectivity with the associated stimulus-processing regions. The results suggest that the cue results in the recruitment of just the task-relevant subnetwork on each trial.

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1. Introduction

Environmental context guides our behavior and biases our cognitive processing (Hazeltine and Schumacher, 2016; Schumacher and Hazeltine). For example, we may plan to make either a sandwich or a hamburger for dinner. If looking in the breadbox reveals that we have hamburger buns, this information allows us to select the task file for making hamburgers. In this way, the additional environmental cue (the contents of the breadbox) allows us to adjust our behavior based on knowledge of our available resources. Laboratory research supports the idea that we can use partially informative cues to modify and facilitate behavioral responses dynamically during decision making (Miller, 1982; Rosenbaum, 1983). In other words, actions can be partially planned such that some parts of a future action or action sequence are specified, but other parts are based on future stimuli. We may plan to make a burger after looking in the breadbox, but we must leave many other actions (e.g. how to flavor the beef, how to cook the patties, etc.) unspecified until we gather additional information

from the environment (e.g., what are the available spices, is the grill working, etc.).

One area of research has been identifying the locus of the cue-preparation benefit. Miller (1982) conducted a series of experiments investigating this issue. In his procedure, stimuli consisted of four crosses on the screen that were spatially mapped to four buttons on a response box that were mapped to the index and middle fingers on each hand in order from left to right (i.e., left-most cross mapped to left middle finger, second cross to left index, and so on). For each trial, the participants saw a warning signal that showed all four crosses, followed by a cue signal which consisted of all four crosses (uninformative) or a subset of two (informative). The subset of two crosses could indicate any two of the four positions; that is, any two fingers could be indicated for the upcoming response. The uninformative cue indicated all four fingers for the potential response. Participants were finally presented with a single cross in one of the four possible positions, at which point they pressed the corresponding button. Unsurprisingly, participants were faster to respond when the cues were informative than when they were uninformative. However, not all informative cues produced equal benefits; cuing two responses on the same hand produced shorter RTs than cuing two responses on the same finger (i.e., an index or a middle finger response). Miller

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proposed that information was passed in discrete quanta to the motor system as it was made available; that is, information about a response that allows for the preparation of one salient subset of responses over another is processed as it arrives, reducing the remaining processing required upon the presentation of the stimulus. To explain the difference in the benefit of different types of cues, Miller proposed that the structure of the motor system affords a hand advantage because this information can be extracted and the response subset prepared more quickly than finer-grained information (see also, Rosenbaum (1980)).

Reeve and Proctor (1984); see also de Jong et al. (1988) proposed a different explanation. They argued that the hand advantage found in Miller's (1982) results was due, not to a response preparation advantage, but to the spatial correspondence between the visual cue positions and the associated response mapping. They showed that removing this stimulus-response correspondence in turn reduced the hand advantage. Specifically, they had participants complete Miller's task, but with their hands positioned to overlap one another so that the leftmost cross corresponded to the left middle finger, the second cross to the right index finger, the third cross to the left index finger, and the fourth cross to the right middle finger. In this position, cues indicating responses on the left hand (i.e., crosses shown in the first and third positions) were no longer presented in the left side of the screen. Proctor and Reeve posited that the cuing effect takes place in response selection. They proposed that the correspondence between the stimulus and response allows participants to translate a cue into a subset of potential pairs from which the response will be selected. Removing the visual-anatomical correspondence afforded by Miller's design limits the utility of the cue.

In parallel with this debate about the information processing locus of the cuing benefit, measures of brain activity have been used to investigate the neural correlates of cue-preparation benefits. At the response level, event-related potentials (ERPs) during cue preparation and have demonstrated preparatory activity in motor regions (Leuthold et al., 1996). Leuthold and colleagues used the lateralized readiness potential (LRP), a measure of the difference in activity between electrodes above both the left and right motor cortex. They found that the LRP increased to a cue indicating which hand would be required to produce the upcoming response, suggesting that motor regions may begin to prepare a response even when the actual digit necessary for the response remains unknown. There is also a wealth of data showing that sensory regions respond to cues, especially from investigations of selective attention. For example, many studies show that a cue indicating a relevant upcoming stimulus dimension increases activity in sensory regions that process the cued location or dimension. This increase in activity is associated with a corresponding facilitation in stimulus processing (for reviews see Desimone and Duncan, 1995 and Kastner and Ungerleider, 2000).

Thus, research shows both an early (stimulus) and late (response) effect on processing of a cue in the regions that process those types of information. However, the interaction between these effects has received less investigation. Here, the cognitive literature may lead to predictions about the relationship between stimulus- and response-level influences in the brain. Returning to the response cuing literature, Miller (1982) posited that locus of the cueing effect is in response preparation. If this is the case, motor preparatory activity during cue presentation should be independent of stimulus-related activity – that is, information contained in a cue should result in activity differences only in the region that processes the information directly indicated by the cue. For example, a cue for stimulus color should result in modulation only in V4. On the other hand, Reeve and Proctor (1984) posited that the cueing effect occurred in response selection – where responses are associated with stimuli. If this is the case, then one might expect not only that a cue will influence the regions that process that information, but also that there may be activity across both the stimulus- and response-related regions related to executing the indicated task.

A more recent cognitive theory that is consistent with the interaction between stimulus and response processing in cue preparation is the *grouping model* (Adam et al., 2003b; Adam et al., 2005). According to this account, the presentation of a cue initiates grouping processes that act on both stimulus and response representations. For example, in Miller's (1982) design, stimuli could occur in one of four spatial locations, which were mapped to the first two fingers of each hand in spatial order. The grouping model posits that participants group the stimuli into left and right hemifields, and group responses anatomically by hand. Cuing for either the left two or right two stimuli indicates salient groups at both the stimulus and response levels, resulting in a behavioral benefit. In this way, the model holds that cue information allows for the preparation of a salient set of stimulus-response pairs.

The grouping process described by Adam and colleagues (Adam et al., 2003a) results in the formation of a task file (Schumacher and Hazeltine), in which the scope of the possible stimulus and response features for a given task are bound together into associated pairs along with motivational and other contextual information that allow participants to perform the task. When preparing to perform a task, the relevant task file is activated, and actions are coordinated according to the associations within the active task file.

These task files may provide a cognitive mechanism for the complex pattern of behaviors observed in response cuing. Specifically, participants may use the grouping process to link salient subsets of the task into separate task files, with additional bound context (i.e., the relevant cue) for when to select each subset. Then, when participants are given one of the relevant cues on a given trial, they prepare the task file indicated by that cue, and execute the task according to the associations represented within that task file.

In the brain, cue-related activity may represent the preparation of these task files in anticipation of the task. Adam et al. (2003a) used fMRI to investigate this process. This study used Miller's (1982) design with consistent or inconsistent S-R mappings and compared blocks of cued activity to uncued activity, which allowed them to separate activity due to informative versus uninformative cues. They found activation in a number of regions relating to cued activity, including prefrontal cortex (PFC, including middle frontal gyrus, MFG; dorsal and lateral premotor cortex, DPMC/LPMC; supplementary motor area, SMA), parietal cortex (intra-parietal sulcus, IPS; superior parietal cortex, SPC; inferior parietal cortex, IPC) and basal ganglia. These regions, then, are specifically related to the processing and implementation of the information contained within a cue. Notably, a number of these regions are specifically related to stimulus and response processing (e.g., parietal cortex processes spatial information of stimuli).

The pattern of brain activity to the cue found by Adam et al. (2003a) closely corresponds to regions associated with response selection processes. Schumacher et al. (2003) used two choice-reaction tasks to investigate the neural correlates of spatial and non-spatial response selection. For each task, the authors varied the number of possible stimulus-response pairs on a given trial using a precue that indicated some subset of the available options. fMRI data recorded during the performance of each task showed distinct regions of activation in parietal, temporal, and frontal cortices for spatial versus non-spatial tasks. The frontal activity corresponded with premotor regions, which are involved in motor response preparation. The parietal and temporal activity, on the other hand, corresponded to regions involved in stimulus processing. Moreover, the activity in parietal cortex was more dorsal

for the spatial task and more ventral for the non-spatial, consistent with previous research that has described a similar division of stimulus processing along these lines (Ungerleider et al., 1998). These results lend support to the idea that cuing effects may in fact reflect preparation in the specific processing region(s) involved in executing the upcoming task corresponding to the relevant stimuli and responses (Adam et al., 2003b; Adam et al., 2005; Reeve and Proctor, 1984).

Many of the regions identified by Adam et al. (2003a) have been proposed to mediate a wide range of cognitive control processes (for review, see Fuster (2001) and Miller and Cohen (2001)), so the assumption that they play a role in biasing attention to S-R pairs is consistent with its putative role mediating cognitive control. However, the method employed in that study did not allow for the isolation of activity for the different task files that Schumacher and Hazeltine would predict to be driving behavior on each trial; thus, the exact nature of the biasing mechanisms and how control affects stimulus and response processing remains unknown. If, as Miller (1982) proposed, the cue benefit occurs during response preparation, then the cue benefit may operate independently on stimulus- and response-related processing regions. On the other hand, if the cue benefit is the result of the response selection processes posited by Proctor and Reeve, then one might expect both downstream (response) and upstream (stimulus) effects of either a stimulus and/or response cue, consistent with a response selection locus (Reeve and Proctor, 1984). In this latter case, there are two possible instantiations of this process: either the cue may result in nonspecific preparatory processes that cover the full scope of the task, regardless of the information contained in the cue; or preparation may operate within the scope of the indicated task file, resulting in a bias of activity only in regions involved in processing that subset of the task.

To investigate this, we employed event-related fMRI during a response-cuing task. Participants learned stimulus-response mappings in which images of faces and places were mapped separately to the left and right hands, and were instructed to respond with the corresponding button press each time a picture appeared on screen. On some trials, a cue presented before the stimulus told the participant either what type of picture (face or place) would be presented or what hand (left or right) would be used to make the response. Importantly, the separation of stimulus type by hand allowed participants to represent the task as two subtasks, each associated with a unique stimulus type and response hand. Additionally, this meant that any informative cue implicitly indicated both a stimulus type and response hand, regardless of what specific information was imparted by the cue. The trial structure and mapping are illustrated in Fig. 1.

Motor responses are mediated by contralateral motor cortical regions and ipsilateral cerebellar regions (Kandel et al., 2000). Previous literature has also demonstrated the existence of regions specialized for both face (viz., fusiform face area, FFA; Kanwisher et al., 1997; Kanwisher and Yovel, 2006) and place (parahippocampal place area, PPA; Epstein and Kanwisher, 1998) processing. We made use of this known functional architecture to investigate the interaction between stimulus and response cuing effects. To investigate the specific effects of specific stimulus- and response-informative cues on brain regions previously identified as showing cuing effects, we compared activity in the regions of interest (ROIs) for stimulus- and response-specific cue types (i.e., face versus place stimulus cues and left versus right response cues); these ROIs are visualized in Fig. 2. To understand how the cue affected activity in these stimulus and response ROIs, we investigated two comparisons. The *explicit cue* comparison was based on the stimulus or response that was directly referenced by the cue. For example, for a participant whose mapping involved
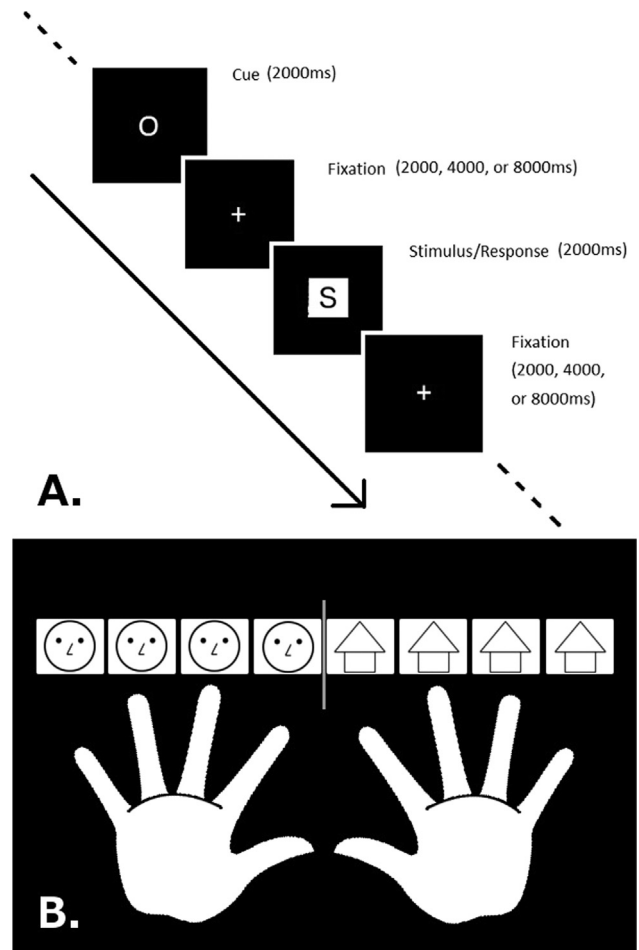

Fig. 1. Trial structure and mapping for the current experiment. (A) Trial structure. In each trial, participants saw either a neutral cue or one of the informative cues for the cue type associated with that block. This was followed by the CSI and subsequent stimulus presentation. Cues were 100% valid. (B) Mapping example. Faces and places were mapped to the four fingers of each hand, separated by anatomical side. Real pictures of faces and places were used. Mappings were counterbalanced across hands and between fingers within a hand.

making left hand responses to face stimuli and right hand responses to place stimuli, an F presented during the cue period explicitly cued an upcoming face stimulus (and therefore FFA). The *implicit cue* comparison was based on the stimulus or response that was indirectly indicated by a cue. In the previous example, the same F cue, while explicitly cuing a face stimulus, also indirectly indicated that the upcoming response required the left hand (and therefore right PMC and other response-related regions).

If stimulus and response cues result in independent modulation of their respective stimulus or response regions, this supports a peripheral locus (sensory or response preparation processes) of the cuing benefit. If instead, the cuing effect has a response selection locus, two outcomes are possible. If the task is simply represented as a single task file (across all S-R associations), then we may see a general activation of all of the task-related regions on every trial, regardless of the cue information. These regions should furthermore show mutual connectivity across cue types. If, on the other hand, stimulus type and response hand are bound together in a representation specific to the subtasks (face or place stimuli), then cuing one dimension (e.g. 'faces') may cause increased activity in brain areas recruited for both the indicated dimension as well as the associated dimension (e.g. 'left hand'), even though the link to the associated dimension is implicit. Additionally, we predict that these regions may show increased connectivity between
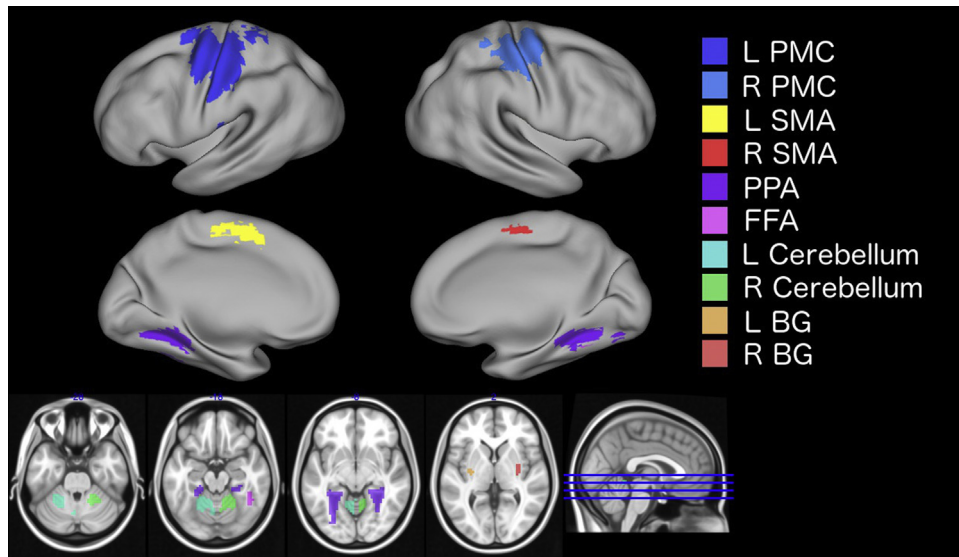
Fig. 2. Colored areas show regions-of-interest (ROIs) on inflated surface images or slices of a normalized brain. Ten ROIs were identified from the uncued stimulus trial event.

Table 1
Accuracy by cue type versus CSI duration.

		CSI		
		2 s	4 s	8 s
Cue	Neutral	.9333	.9367	.9683
	Stimulus	.9450	.9500	.9617
	Response	.9492	.9583	.9483

Note. CSI=cue-stimulus interval; s=seconds.

regions that process the relevant pairs of stimulus type and response hand as a function of the mapping.

2. Results

2.1. Behavioral results

All analyses were conducted on the data from Session 2, error bars in all graphs represent the standard error of the relevant effect. Accuracies approached ceiling (Overall average=94.8%) and were analyzed using a modified arcsine transformation ($X=\sin^{-1}(\sqrt{x})$, corrected for ceiling effects; Sheskin, 2003). A two-factor, repeated measures ANOVA for cue type and CSI duration showed no main effect of cue type, $F(2,48)=.52$, $p=.600$, but did show a main effect of CSI, $F(2,48)=5.80$, $p=.006$, as well as a significant interaction, $F(4,96)=2.78$, $p=.031$ (means presented in Table 1). Post hoc t-tests revealed that the main effect of cue type was due to a significant difference for CSIs of 8 s versus other CSI durations. This result indicates that participants were approximately 1.5% more accurate with an 8-s delay between the cue and stimulus than in other trials. This is not unexpected, as in these trials, participants have the longest time to prepare their response set. Still, this difference corresponds to an average of approximately 5 more errors per subject in the 2 and 4 s CSI conditions across the entire experiment (288 trials overall). Thus, this effect likely reflects behavioral benefits primarily on response speed, rather than a simple speed-accuracy tradeoff. The analyses described subsequently (both RT and fMRI) used correct trials only.

Cues were presented in separate blocks of stimulus (F or P) and response (L or R) cue types. A t-test of RTs for neutral cues
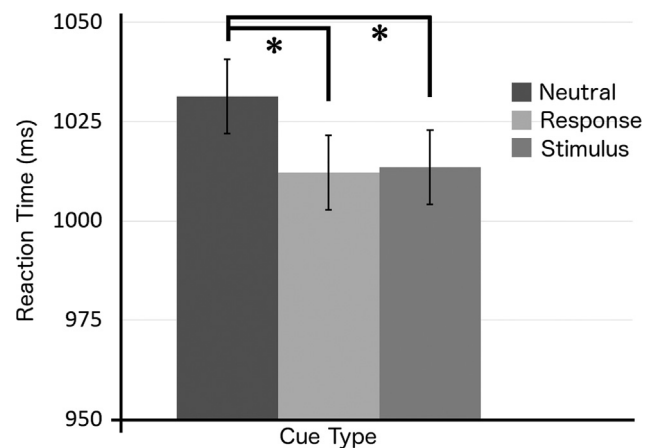

Fig. 3. RT by cue type collapsed across block type and CSI duration. Planned comparisons between cue types showed a significant difference in RTs for Neutral versus Response cues and Neutral versus Stimulus cues. The difference between RTs for Response and Stimulus cues was not significant.

between blocks of stimulus and response cue types was not significant, $t(24)=.95$, $p=.354$, therefore, we collapsed across block type for subsequent analyses. A two-factor, repeated measures ANOVA compared correct RTs for cue type and CSI. The ANOVA revealed a main effect for cue type, $F(2, 48)=6.15$, $p=.004$, $\eta^2=.204$. The main effect of CSI was not significant, $F(2, 48)=1.22$, $p=.303$. There was no significant interaction between cue type and CSI, $F(4, 96)=.73$, $p=.576$. Because there was no significant main effect of CSI nor interaction, we collapsed across CSI for subsequent analyses.

We next ran planned comparisons to characterize the effect of cue type using one-tailed, paired t-tests. The neutral versus response cue comparison (O–R=23.15 ± 8.95 ms) was statistically significant, $t(24)=2.587$, $p=.008$. Likewise, the neutral versus stimulus cue comparison (O–S=27.39 ± 7.55 ms) was also statistically significant, $t(24)=3.63$, $p<.001$. Thus, mean RT decreased for both informative cue types relative to uninformative cues. The stimulus- versus response-cue comparison (S–R=4.24 ± 8.65 ms) was not significant, $t(24)=.49$, $p=.315$. These means are plotted in Fig. 3.

2.2. Imaging results

2.2.1. Regions-of-interest analysis

Activity for cued versus uncued trials at the cue did not survive whole-brain correction. Similarly, neither the face versus place cues nor the left versus right cues showed significant whole-brain activity. Therefore, we focused on activity in a set of functionally defined ROIs. ROIs for stimulus- and response-processing regions were identified from contrasts for face versus place stimuli and left versus right-hand responses respectively at the stimulus event. Stimulus-related regions included right fusiform gyrus for face stimuli (FFA) and bilateral parahippocampal gyrus and lingual gyrus for place stimuli (PPA). Response related regions included premotor/motor cortex, supplementary motor area, and basal ganglia regions contralateral to the response hand, as well as cerebellar regions ipsilateral to the response hand.

2.2.2. Generic cue-related activity

We first investigated general cue-related activity across the ROIs by collapsing across trial types and assessing the percent signal change for all cued trials versus uncued trials within each region. A two-tailed, paired t-test revealed significant activity for cued versus uncued trials in FFA (C–N = .098 ± .040), $t(24) = 2.49$, $p = .010$, and in PPA (C–N = −.053 ± .024), $t(24) = -2.22$, $p = .018$ (Fig. 4). Surprisingly, FFA showed an increase in activity to informative cues over uninformative regardless of the specific type of cue presented, while PPA likewise showed less activity to informative versus informative cues. No other regions showed significant general cuing effects (i.e., when cue types were combined).

2.2.3. Cue-specific activity

To investigate cue-specific activity for the two informative cue types (stimulus- and response-informative), we compared the average percent signal change between pairs of regions for each cue (face versus place or left versus right, respectively). Because mappings were counterbalanced across participants, 12 participants had face stimuli mapped to the left hand, while 13 participants had face stimuli mapped to the right hand. Therefore, to allow for comparisons across both groups, we defined our ROI pairs according to the stimulus type-response side mapping for each participant, rather than according to absolute side.

2.2.3.1. Explicit cuing effects. To investigate explicit cue effects in the response-cued blocks, we investigated activity to "L" versus "R" cues in the left versus right response-related ROIs (e.g., left and
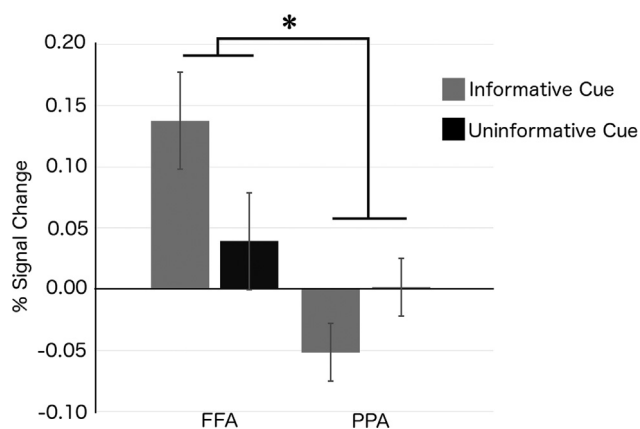

Fig. 4. Activity for informative versus uninformative cues in stimulus processing regions. FFA showed increased activity to informative cues, while PPA showed decreased activity.
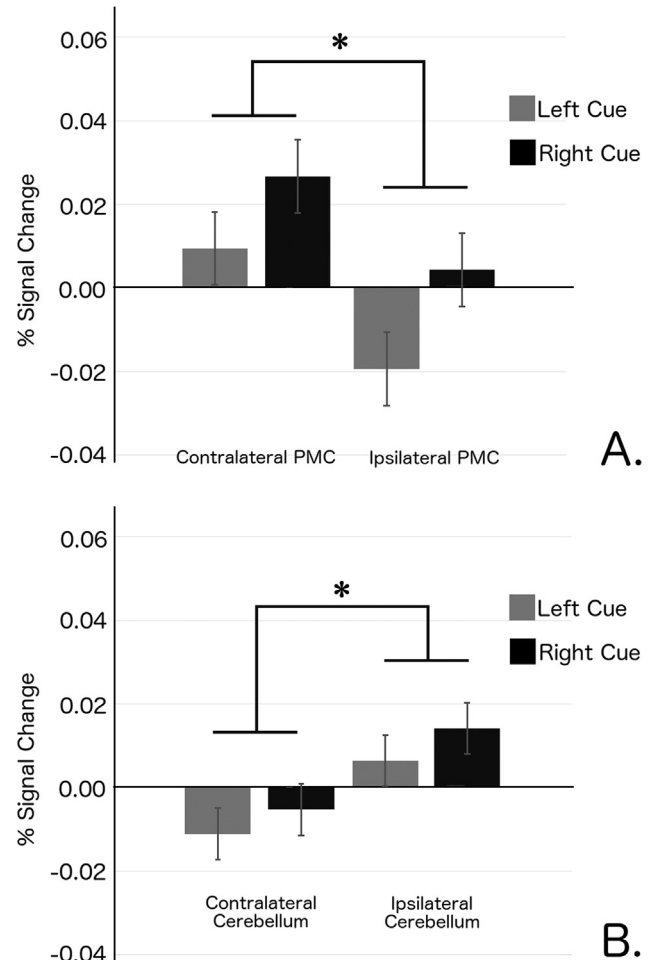

Fig. 5. Activity for response cues in response processing regions. Cues produced increased activity in the PMC region contralateral to the cued side and the cerebellar region ipsilateral to the cued side.

right PMC). For this comparison, the most theoretically relevant comparison is the interaction between cue type and region. That is, we expected "L" cues to result in higher activity in left versus right response pairs, and the reverse pattern for "R" cues. The results showed no main effects for cue type in any of the ROI pairs. A significant main effect of region (left versus right) was identified in SMA, $F(1, 24) = 4.30$, $p = .049$, $\eta^2 = .152$, indicating increased activity in right over left SMA. This interaction was significant in the following regions: premotor cortex, $F(1,24) = 8.71$, $p = .007$, $\eta^2 = .266$; SMA, $F(1,24) = 5.16$, $p = .032$, $\eta^2 = .177$; and cerebellum, $F(1,24) = 10.31$, $p = .004$, $\eta^2 = .300$. As shown in Fig. 5 (SMA not shown), activity was biased toward the region contralateral to the cue-indicated response hand in PMC and toward the ipsilateral region in the cerebellum.[1] The basal ganglia did not show this interaction for this comparison, $F(1,24) = 1.35$, $p = .257$, $\eta^2 = .177$.

Likewise, to investigate explicit cue effects in the stimulus-cued blocks, we looked at activity at F versus P cues in the face and place processing-related regions. The theoretically relevant comparison in this case is also the interaction term. As shown in Fig. 6, this comparison showed a significant main effect of region, $F(1,24) = 31.413$, $p < .001$, $\eta^2 = .567$; no other effects or interactions were significant. More specifically, the FFA ROI showed

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[1] The results for SMA are not shown in Fig. 5 because, although the effect for explicit cues was significant in this comparison, the activity patterns in SMA for the different cue types were not consistent.
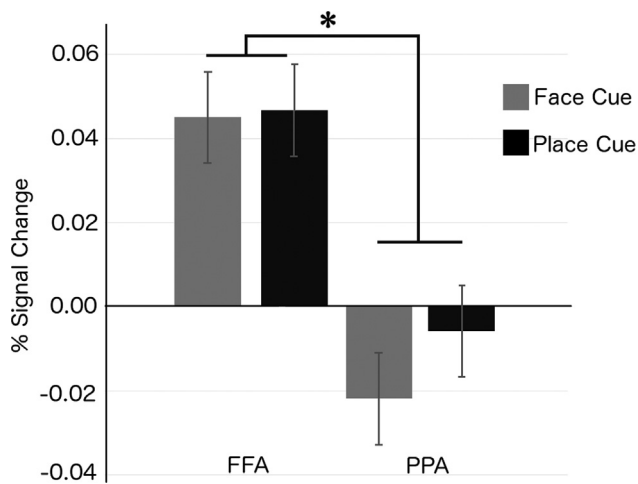
Fig. 6. Activity for stimulus cues in stimulus processing regions. Cues produced increased activity in the FFA compared to the PPA, regardless of cue type.

consistently elevated activity to both cue types compared to the PPA ROI.

2.2.3.2. Implicit cuing effects. To investigate implicit cue effects in response-related regions, we looked at activity at F versus P cues in the contralateral versus ipsilateral response-related region pairs according to the mapping assigned to each participant. In this case, because regions were defined based on their correspondence to the cues, the theoretically relevant effect was the main effect of region; that is, we expected that the response-related region that mapped contralateral to the hand indicated by the stimulus cue to show increased activity versus the region mapped ipsilateral to that hand for cortical response ROIs (i.e., PMC, SMA, and BG), whereas the reverse pattern was expected for cerebellar ROIs. The results showed a main effect of region (contra- versus ipsilateral) in premotor cortex, $F(1,24)=5.68$, $p=.025$, $\eta^2=.191$; and cerebellum, $F(1,24)=5.63$, $p=.026$, $\eta^2=.190$; no other effects were found in any comparisons. As shown in Fig. 7, similar to the explicit cue condition, activity was biased toward the region contralateral to the cue-indicated response hand in PMC and toward the ipsilateral region in the cerebellum. For example, in the group in which face stimuli were mapped to the left hand, a F cue resulted in increased activity in right PMC and left cerebellum. This pattern was not seen in basal ganglia, $F(1,24)=1.09$, $p=.245$, $\eta^2=.056$, nor SMA, $F(1,24)=1.09$, $p=.308$, $\eta^2=.043$.

For implicit cue effects in stimulus processing regions, we looked at "L" versus "R" cues in the FFA and PPA ROIs, again according to the assigned mapping structure; in this case, the interaction term was the theoretically relevant comparison. The results showed a main effect of ROI, $F(1,24)=11.82$, $p=.002$, $\eta^2=.330$. As shown in Fig. 8, similar to the explicit cue condition, FFA showed generally increased activity over PPA, regardless of the specific cue presented.

2.2.4. Pairwise correlations

The implicit cuing effect found in the PMC and cerebellum ROIs show that response regions are affected by stimulus cues. However, a corresponding effect was not found in stimulus regions; instead, FFA showed generally increased activity regardless of what stimulus or response was cued. To investigate the role of stimulus regions in response cuing further, we conducted a pairwise correlation between the timecourses of the cortical response ROIs (left and right PMC) and stimulus ROIs (FFA, PPA). We compared the correlations acquired for each participant between pairs of regions that corresponded due to the participant's mapping
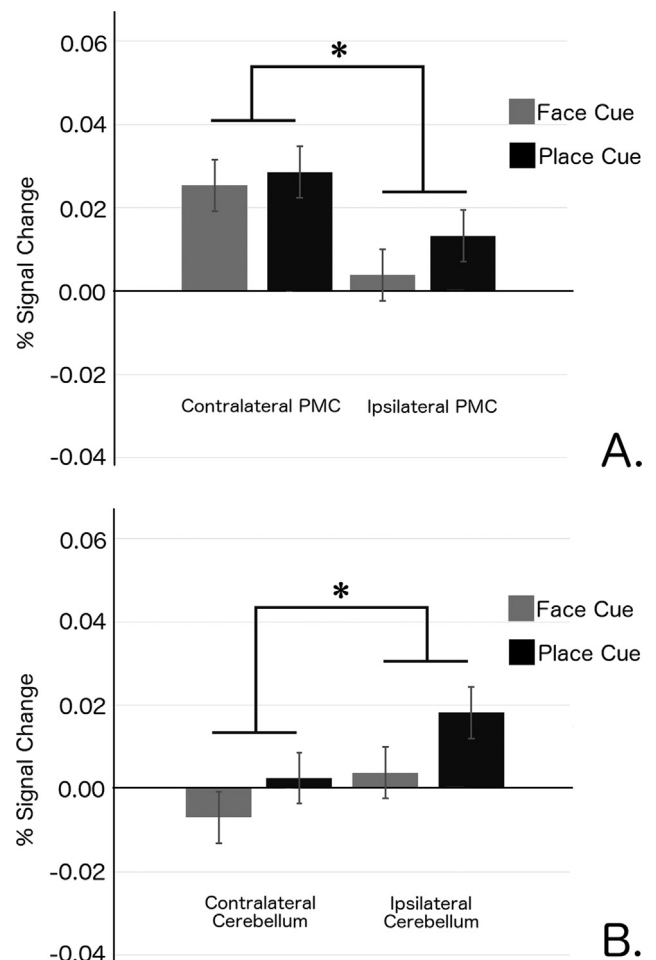

Fig. 7. Activity for stimulus cues in response processing regions. Cues produced increased activity in the PMC region contralateral to the response side associated with the cue and in the cerebellar region ipsilateral to the response side.
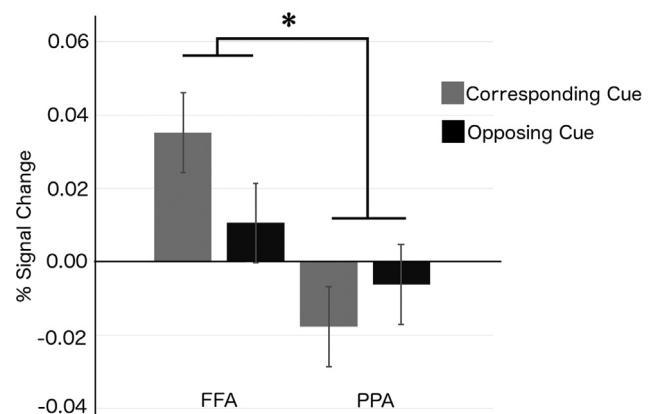
Fig. 8. Activity for response cues in stimulus processing regions. Cues produced increased activity in the FFA compared to the PPA, regardless of cue type. For example, when faces were mapped to the left hand, both L and R cues resulted in increased activity in FFA over PPA.

with those acquired in non-corresponding ROI pairs. For example, for a participant with face stimuli mapped to the left hand and place stimuli to the right, we compared the correlation between FFA and right PMC (matched pairs) to FFA and left PMC (mismatched pairs), and the opposite combinations between PPA and PMC.

We conducted a two-factor, repeated measures ANOVA on the z-transformed correlations for stimulus region and S-R region

Table 2
Stimulus region – PMC pairwise correlations.

	Match		Mismatch	
	r	SE	r	SE
FFA	.4957	.1575	.4808	.1505
PPA	.5756	.1028	.5218	.1204

Note. Match and mismatch indicate the motor area paired with and paired opposite the stimulus type, respectively, of the indicated stimulus processing region according to each participant's mapping. Statistical analyses were conducted on the Z-scored correlations. *r*=correlation coefficient; *SE*=standard error; FFA=fusiform face area; PPA=parahippocampal place area.

correspondence. The critical comparison was the main effect of correspondence, or whether there was a stronger correlation between regions that were associated by the S-R mapping than the opposite pair. The ANOVA showed a main effect of correspondence, $F(1,24)=20.289$, $p<.001$, $\eta^2=.458$, as well as a trending main effect of stimulus region, $F(1,24)=4.087$, $p=.055$, $\eta^2=.146$; means for each pairing are shown in Table 2. That is, participants showed increased connectivity between stimulus and response regions that were jointly task relevant over regions that were not associated by the task mapping, but this effect was larger for PPA than FFA.

3. Discussion

The present experiment used an event-related response-cuing procedure to investigate brain activity to stimulus and response cues to identify how S-R pairings affect processing. Our experiment used a response cuing design in which participants learned a mapping that could be represented as two task files associating each response hand with a unique stimulus type. Cues given at the start of each trial could give no information, stimulus information, or response information. Informative cues then could result in: independent modulation of the stimulus- and response-related processing regions, with minimal changes in connectivity (consistent with a peripheral cuing locus); general activation across the task-related regions, with generally increased connectivity between regions (consistent with a task representation that included all S-R pairs); or activity biasing in pairs of stimulus- and response-processing regions according to the information presented in the cue (consistent with separate task file representations for each subtask).

The results supported the separate task file hypothesis. First, the ROI activity results supported this prediction specifically in many of the response-related regions. There were increases in activity in lateralized PMC, cerebellum, and SMA for the corresponding explicit cues, replicating the results of previous investigations that showed response region biasing for upcoming responses (Leuthold et al., 1996). Furthermore, this activity pattern was also found in lateralized PMC and cerebellum for the corresponding implicit cues, which is a novel result. This result shows that presenting a cue for either part of the S-R pair is sufficient to initiate preparation processes for the corresponding motor response, and that this preparation is confined to the subset of task-related regions that are indicated by the cue as being involved in a given trial.

The same result was not found the activity patterns found in the stimulus-related regions. Instead, we found a general increase in activation for FFA – regardless of cue. That is, FFA was more active to all informative than uninformative cues. In other words, there was no biasing of activity in FFA for either explicit or implicit

cues. Conversely, the PPA showed decreased activity to informative versus uninformative cues. The lack a selective effect to specific cues in FFA is surprising given the demonstrated face selectivity of this region in the literature (Kanwisher et al., 1997; Kanwisher and Yovel, 2006). It is unclear why the expected increase was not observed. It may suggest that stimulus regions do not play a major role in cue-related processing. Informative cues may lead to activity biasing in corresponding response regions, even when the cue contains stimulus-related information, but the S-R pairing does not likewise lead to activation biasing in stimulus processing regions. This interpretation could be consistent with the hypothesis that cuing effects occur in response preparation (Miller, 1982). However, it is still in contrast with previous work on selective attention, which suggests that at least stimulus cues should result in the expected explicit cue biasing seen in the response regions.

It is worth noting that the current experiment used a small set of face and place stimuli (four each). Conversely, typical studies investigating FFA and PPA activity use a much larger stimulus set. For example, Epstein and Kanwisher (1998) showed 20 unique pictures per block per type, with 8 different stimulus types, over 16 runs. Our small stimulus set may have resulted in unexpected strategies in stimulus processing that may explain the unexpected results in our stimulus-processing regions. Perhaps the familiarity of the place stimuli caused participants to process both stimulus types holistically (e.g., Tanaka and Farah, 1993; Tarr and Gauthier, 2000). Such "expert" processing may be handled primarily by the FFA, regardless of the exact nature of the stimulus (Gauthier and Tarr, 1997). This would explain the general increase in FFA activity at the cue presentation.

Despite this anomaly, the subsequent analysis of functional connectivity does suggest a role for both stimulus regions in response cuing (i.e., that S-R pairs drive the cue benefit). As predicted by the task file hypothesis, the connectivity results indicate a biasing of connectivity between stimulus and response processing regions in favor of pairs of regions that matched with the learned S-R associations (especially in PPA) versus regions that constituted a mismatch. That is, there was increased connectivity between stimulus-processing regions and the motor regions associated with it by the mapping structure. Despite the lack of stimulus-related activity for the cues, the connectivity results demonstrate a neural relationship for the S-R pairs. Thus, it appears that the behavioral control processes initiated by informative cues are accomplished through a coordinated biasing of activity in response processing regions (PMC and cerebellum) and an increase in connectivity between relevant stimulus and response regions. These results (especially those relating to connectivity) are consistent with the hypothesis that response-cuing effects involve response selection (Adam et al., 2003b; Adam et al., 2005; Reeve and Proctor, 1984) according to a hierarchical task file structure.

The presented results leave a number of questions to be investigated in future studies. First, what neural mechanisms allow this coordination process? Research on oscillatory activity in neurons may provide a potential answer. Voytek et al. (2015) used electrocorticography recordings to demonstrate phase-amplitude coupling between subregions of PFC when high-level task information from rostral PFC was needed to coordinate low-level response selection in caudal PFC. More specifically, gamma-band amplitude, which reflected local population activity, was entrained to theta-band phase across the PFC, where the extent of the regions involved depended on the abstractness of the rules required to execute the task. Similar phase-amplitude coupling has been suggested as a mechanism for inter-areal communication in a variety of other contexts as well (see Canolty and Knight (2010), for review). Such a mechanism may likewise subserve the coordination of activity in stimulus and response processing regions during response selection.

Second, how is the PFC involved in implementing these cue-related preparatory biasing effects? PFC has been suggested to subserve a wide variety of executive functions beyond response selection, including, but not limited to, working memory maintenance and manipulation, goal setting, skill learning, and executive attention (Damasio, 1995; Dubois et al., 1995; Duncan and Owen, 2000; Kane and Engle, 2002; Miller, 2000; Shimamura, 1995). While the current experiment did not show significant whole-brain activity in prefrontal regions, previous research has found prefrontal activity to the presentation of cues (Adam et al., 2003a; Hopfinger et al., 2000). Thus, it is initially surprising that the current experiment did not replicate this previous research. However, the small stimulus set may also explain the lack of activity in our whole-brain analysis. Using 8 well-learned S-R pairs may have minimized the complexity or rule structure of the task, which according to some rostro-caudal theories of prefrontal organization (Badre, 2008; Christoff and Gabrieli, 2000) may have resulted in low-magnitude recruitment of PFC that did not survive statistical thresholding. Furthermore, the presented analysis used a particularly conservative approach for identifying our cue related activity; whereas previous studies of cue effects have analyzed complete trials (e.g., Adam et al., 2003a), the present analysis investigated only the cue-related trial period on each trial. While this reduced the total quantity of data available for analysis, it ensured that we did not include response-related activity in our results. Yet, it may have reduced the power to find PFC regions, which may nevertheless be involved in this type of processing (as predicted by previous research).

In conclusion, the present study has provided new evidence for both the cognitive and .neural mechanisms of cuing benefits. Specifically, these results have demonstrated that the cuing effect is driven by task files that hierarchically associate subsets of S-R pairs with task related context that allows participants to select between these task files flexibly on a given trial based on the information contained in the cue. Future research on the source of implementation and temporal dynamics of this effect and is necessary to lead to additional insights into how stimulus and response pairs and their corresponding processing regions connect and activate to lead to this response cuing benefit.

4. Methods and materials

4.1. Participants

Participants included 44 volunteers from the Georgia Institute of Technology community between the ages of 18 and 38 years old (15 female, 28 male). Six participants (3 female, 3 male) withdrew from the study before completion of both sessions; an additional 12 (5 female, 7 male) were not included in the analyses due to performance issues (1 sleeping, 1 not responding to stimuli) or excess motion (repeated translations of greater than 1 mm across a single block; position changes were measured in real-time) during the scan. A total of 25 participants were included in the analyses. Participants had no prior record of brain injuries, had normal or corrected to normal vision, and were not otherwise contraindicated for the fMRI scanner.

4.2. Apparatus

Session 1 was conducted in the PST MRI simulator available at the Center for Advanced Brain Imaging (CABI) at the Georgia Institute of Technology. In this session, only behavioral data were collected. In Session 2, MRI data were collected using the Siemens 3 T Trio Magnetic Resonance Imaging System with a 12 channel headcoil. Visual stimuli for the experiment were shown using the Avotec Silent Vision 6011 projector. Participants made responses using two hand-specific Current Designs fORP 4-button boxes; fingers of the left hand were mapped to the left box, and fingers of the right hand to the right box. Boxes were positioned on the abdomen in both sessions, with a Velcro foam pad used in session 2 to fix the boxes to the correct sides. The experiment was run on E*Prime 2.0.10 software.

Participants lay facing up in the scanner with a mirror adjusted to a comfortable distance from the eyes for viewing the experiment screen. During Session 1, the participants wore over-ear headphones and heard pre-recorded scanner sounds to simulate the experience of being in the scanner. During Session 2, participants wore earplugs and Avotec Silent Scan 3100 headphones. Foam padding and medical tape were used to minimize head motion during the MRI scan.

4.3. Stimuli

Face images were taken from the AR Face Database (Martinez and Benavente, 1998). Face images started at the shoulders and included hair; all images showed people in black t-shirts on a dark gray background with black and white coloration. Place images consisted of 4 black and white pictures of buildings. All participants saw the same 8 images.

Cues consisted of the letters F, P, L, R, and O, shown in white on a black background in the center of the screen. F and P corresponded to an upcoming face or place stimulus, respectively; similarly, L and R represented left and right responses. O was used as an uninformative cue. The fixation cross was likewise white and centered.

4.4. Procedure

Session 1 was conducted no less than 1 d and no more than 7 d prior to Session 2. In Session 1, participants were given a set of mappings that associated the stimuli to the 8 buttons of the two button boxes and instructed to learn these associations. For all participants, faces were mapped to the buttons on one hand and places to the buttons on the other. Mappings were counterbalanced between- and within-hand such that faces and places each appeared on the left hand in half of subjects, with the subset of face and place images appearing in 4 different possible orders within their respective hands.

Participants were given a single block with only neutral cues to practice these mappings; then the experimental blocks commenced. For each trial, participants were shown a cue consisting of a single letter at the center of the screen for 2 s. This cue was either informative for the upcoming stimulus (F=face, P=place), the upcoming response hand (R=right hand, L=left hand), or neither (O, neutral cue). Cues indicated the upcoming stimulus with 100% accuracy. They were blocked so that participants only saw one of the two informative cue types in a single block (i.e., the cue type presented was alternated by block). The cue was followed by a cue-stimulus interval (CSI), which consisted of a centrally located fixation cross. This CSI was presented with a jitter of 2, 4, or 8 s, with a 2-s CSI occurring on half of the trials and 4- and 8-s CSIs each occurring on ¼ of the trials (Ollinger et al., 2001a; Ollinger et al., 2001b). The CSI was followed by the presentation of one of the 8 possible stimulus images for 2 s. Participants were instructed to respond to the stimulus within the 2-s presentation window. After the stimulus interval, an inter-trial interval (ITI) was presented. This ITI had the same jitter structure as the CSI. In the case of a correct response on the preceding trial, the ITI showed a fixation cross; in the case of an incorrect response, the ITI showed the stimulus-response mappings. This trial structure and mapping are illustrated in Fig. 1. Each block consisted of 48 trials, with

6 experimental blocks for a total of 288 experimental trials per subject.

Session 2 started with a structural T1 scan, during which participants completed a practice block of experimental trials.[2] Participants then completed 6 experimental blocks using the same experimental procedure as session 1, but with feedback on their average performance presented only at the end of the trial, rather than trial-wise feedback.

4.4.1. Practice block

During the acquisition of structural scan, participants completed a short practice block of neutral cue-only trials (30 trials, 75% of a full block, random inclusion of trials).

4.4.2. Feedback structure

In Session 2, the feedback structure was changed such that the ITI always showed a fixation cross, and average accuracy and RT for the current block was shown at the end of the block. The ITI jitter structure remained the same.

4.5. fMRI procedure

A three-plane localizer and high-resolution 3D MPRAGE structural scan (1 mm isotropic voxels) were collected at the beginning of the MRI session. An echoplanar sequence (TR=2000 ms, TE=30 ms) was used to acquire data sensitive to the blood oxygen level dependent signal. Each functional volume contained 37 axial slices of 3 mm isotropic voxels. The functional localizer was run first (about 4:06 min, 123 volumes/run), followed by 6 experimental blocks (about 9:40 min each, 290 volumes/run).

4.6. Behavioral analysis

Mean reaction times (RTs) and accuracies were calculated for each subject as a function of cue type (stimulus-informative, response-informative, or uninformative) and CSI. Overall accuracy was calculated as well across subjects and conditions. A two-way repeated measures analysis of variance (ANOVA) was performed on the RT and accuracy data with cue type and CSI as within-subjects factors. Post-hoc comparisons were conducted on the RT data using a Bonferroni correction procedure for multiple comparisons (adjusted α=.01333).

4.7. fMRI processing and analysis

Data reconstruction, processing and analyses for each participant were performed using the Analysis of Functional NeuroImages software package (Cox, 1996). After reconstruction, the 3-D+time data were despiked; slice acquisition timing differences were corrected; the structural image was normalized to the Montreal Neurological Institute (MNI) reference brain; head-motion artifacts were corrected to the second sub-brick with a least squares approach using a six- parameter, rigid-body transformation algorithm (Friston et al., 1995); and the data were smoothed with a 6.0 mm full-width half-maximum Gaussian kernel.

4.7.1. Whole brain analysis

Data were analyzed using a modified general linear model (Worsley and Friston, 1995). We created design matrices for each participant with covariates for each event (viz., cue and stimulus

presentations) corresponding to a correct response; error trials were represented by an error covariate. Cue events were separately identified by cue type (viz, face/place/left/right/neutral). These covariates were convolved with an idealized hemodynamic response function. A high-pass filter removed frequencies below .00345 Hz. Contrast images were computed for each participant for group analyses.

4.7.2. Regions of interest and small-volume correction

The question addressed here (viz., how stimulus and response cues affect sensory and motor activity at the presentation of the cue) involves comparing activity during the cue event across the cue types (i.e., face cue versus place and left cue versus right) in brain regions previously implicated in sensorimotor processing at stimulus presentation. Therefore, we used a small volume correction (Worsley and Friston, 1995) to investigate activity in our contrasts of interest. Specifically, we used stimulus event-related activity to identify regions activated by face versus place stimuli and left- versus right-hand responses to identify stimulus and response-processing regions, respectively. To define our regions of interest for each contrast, we statistically thresholded (FDR corrected q=.05 except where otherwise noted) the group contrasts and extracted the surviving task-relevant clusters for the positive and negative contrasts. The left- versus right-response contrast[3] yielded lateralized motor processing regions in motor/premotor cortex, cerebellum, SMA, and basal ganglia. Likewise, the face-versus place-stimulus contrast yielded right fusiform activity for faces and parahippocampal and lingual activity for places. Percent signal change for each cue condition was extracted from these ROIs for subsequent analysis. The set of ROIs is visualized in Fig. 2.

4.7.3. Pairwise correlation analysis

To further investigate the patterns of activity driven by cue-related task information, we conducted a pairwise correlation of the BOLD timecourse between FFA and PPA and the left and right PMC by run. For each mapping group, we identified the stimulus-response ROI pairings that matched the established set and those that were opposite the set. For example, for the group in which the faces were mapped to left hand responses and places to right hand responses, FFA and right PMC constituted a matching pair, while FFA and left PMC constituted a mismatch. We then conducted a 2×2 repeated measures ANOVA with match type (match vs mismatch) and the stimulus-related region included in the pair (FFA or PPA) included as factors. Following this, we conducted separate t-tests between the match and mismatch pairs by stimulus region.

References

Adam, J.J., et al., 2003a. Rapid visuomotor preparation in the human brain: a functional MRI study. Brain Res. Cognit. Brain Res. 16, 1–10.

Adam, J.J., Hommel, B., Umiltà, C., 2003b. Preparing for perception and action (I): the role of grouping in the response-cuing paradigm. Cognit. Psychol., 46.

Adam, J.J., Hommel, B., Umiltà, C., 2005. Preparing for perception and action (II): automatic and effortful processes in response cueing. Vis. Cogn., 12.

Badre, D., 2008. Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. Trends Cogn. Sci. 12, 193–200.

Canolty, R., Knight, R., 2010. The functional role of cross-frequency coupling. Trends Cognit. Sci. 14, 506–515.

Christoff, K., Gabrieli, J.E., 2000. The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. Psychobiology 28, 168–186.

Cox, R., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. Int. J. 29, 162–173.

Damasio, A.R., 1995. On some functions of the human prefrontal cortexa. Ann. N. Y. Acad. Sci. 769, 241–252.

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[2] Following this, a functional localizer for face and place stimuli was collected; however, we ultimately used the stimulus period to identify the FFA and PPA/LG regions and not a functional localizer so that the source of these ROIs would be the same for the sensory and motor regions. The regions from the stimulus period were similar to those identified by the functional localizer.

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[3] Left response-related regions were thresholded at q=.0434 to allow the separation of anatomically distinct regions.

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu Rev. Neurosci. 18, 193–222.

Dubois, B., et al., 1995. Experimental approach to prefrontal functions in humans. Ann. N. Y. Acad. Sci. 769, 41–60.

Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 23, 475–483.

Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392, 598–601.

Friston, K.J., et al., 1995. Analysis of fMRI time-series revisited. NeuroImage 2, 45–53.

Fuster, J.M., 2001. The prefrontal cortex–an update: time is of the essence. Neuron 30, 319–333.

Gauthier, I., Tarr, M.J., 1997. Becoming a "Greeble" expert: exploring mechanisms for face recognition. Vis. Res. 37, 1673–1682.

Hazeltine, E., Schumacher, E.H., 2016. Understanding Central Processes: The Case against Simple Stimulus-Response Associations and for Complex Task Representation.

Hopfinger, J., Buonocore, M., Mangun, G., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

de Jong, R., et al., 1988. Use of partial stimulus information in response processing. J. Exp. Psychol. Hum. Percept. Perform. 14, 682–692.

Kandel, E.R., Schwartz, J.H., Jessell, T.M., 2000. Principles of Neural Science. 4. McGraw-Hill, New York.

Kane, M.J., Engle, R.W., 2002. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. Psychon. Bull. Rev. 9, 637–671.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. 17, 4302–4311.

Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Philos. Trans. R. Soc. B: Biol. Sci. 361, 2109–2128.

Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. 23, 315–341.

Leuthold, H., Sommer, W., Ulrich, R., 1996. Partial advance information and response preparation: inferences from the lateralized readiness potential. J. Exp. Psychol.: Gen. 125, 307–323.

Martinez, A.M., Benavente, R., 1998. The AR face database. CVC Technical Report. 24.

Miller, E.K., 2000. The prefrontal cortex and cognitive control. Nat. Rev. Neurosci. 1, 59–65.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu Rev. Neurosci. 24, 167–202.

Miller, J., 1982. Discrete versus continuous stage models of human information processing: in search of partial output. J. Exp. Psychol. Hum. Percept. Perform. 8, 273–296.

Ollinger, J.M., Corbetta, M., Shulman, G.L., 2001a. Separating processes within a trial in event-related functional MRI. Neuroimage 13, 218–229.

Ollinger, J.M., Shulman, G.L., Corbetta, M., 2001b. Separating processes within a trial in event-related functional MRI. Neuroimage 13, 210–217.

Reeve, T., Proctor, R., 1984. On the advance preparation of discrete finger responses. J. Exp. Psychol.: Gen. 10, 541–553.

Rosenbaum, D.A., 1980. Human movement initiation: specification of arm, direction, and extent. J. Exp. Psychol.: Gen. 109, 444.

Rosenbaum, D.A., 1983. The movement precuing technique: assumptions, applications, and extensions. Adv. Psychol. 12, 231–274.

Schumacher, E.H., Elston, P.A., D'Esposito, M., 2003. Neural evidence for representation-specific response selection. J. Cogn. Neurosci. 15, 1111–1121.

Schumacher, E.H., Hazeltine, E., Hierarchical task representation: task files and response selection, In preparation.

Sheskin, D.J., 2003. Handbook of Parametric and Nonparametric Statistical Procedures. CRC Press, United States.

Shimamura, A.P., 1995. Memory and the Prefrontal Cortexa. Ann. N. Y. Acad. Sci. 769, 151–160.

Tanaka, J.W., Farah, M.J., 1993. Parts and wholes in face recognition. Q. J. Exp. Psychol. Sect. A 46, 225–245.

Tarr, M.J., Gauthier, I., 2000. FFA: a flexible fusiform area for subordinate-level visual processing automatized by expertise. Nat. Neurosci. 3, 764–769.

Ungerleider, L.G., Courtney, S.M., Haxby, J.V., 1998. A neural system for human visual working memory. Proc. Natl. Acad. Sci. USA 95, 883–890.

Voytek, B., et al., 2015. Oscillatory dynamics coordinating human frontal networks in support of goal maintenance. Nat. Neurosci. 18, 1318–1324.

Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited—again. NeuroImage 2, 173–181.