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Issue: *The Year in Cognitive Neuroscience***Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating**Benjamin J. Levy<sup>1</sup> and Anthony D. Wagner<sup>1,2</sup><sup>1</sup>Department of Psychology and <sup>2</sup>Neurosciences Program, Stanford University, Stanford, California

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Delineating the functional organization of the prefrontal cortex is central to advancing models of goal-directed cognition. Considerable evidence indicates that specific forms of cognitive control are associated with distinct subregions of the left ventrolateral prefrontal cortex (VLPFC), but less is known about functional specialization within the right VLPFC. We report a functional MRI meta-analysis of two prominent theories of right VLPFC function: stopping of motor responses and reflexive orienting to abrupt perceptual onsets. Along with a broader review of right VLPFC function, extant data indicate that stopping and reflexive orienting similarly recruit the inferior frontal junction (IFJ), suggesting that IFJ supports the detection of behaviorally relevant stimuli. By contrast, other right VLPFC subregions are consistently active during motor inhibition, but not reflexive reorienting tasks, with posterior-VLPFC being active during the updating of action plans and mid-VLPFC responding to decision uncertainty. These results highlight the rich functional heterogeneity that exists within right VLPFC.

**Keywords:** response inhibition; reorienting; inferior frontal gyrus; fMRI

In many situations, input from the environment is sufficient to drive cognition in a bottom-up fashion resulting in the production of appropriate behavior. At other times, such prepotent responses are not contextually appropriate, and we must exert top-down control to shape cognition and achieve a desired behavior. The prefrontal cortex (PFC) is thought to enable top-down control by biasing processing in other brain regions toward contextually appropriate representations.<sup>1–3</sup> Extensive evidence indicates that PFC-mediated cognitive control encompasses a wide range of specific operations.<sup>4–10</sup> For example, upon hearing a phone ring you must decide whether to (a) execute the motor actions involved in answering your phone, (b) resist the inappropriate urge to answer your friend's phone, (c) attempt to ignore the sound as an auditory distraction, or (d) quickly attempt to silence your cell phone in order to minimize your embarrassment at the talk you are attending.

The lateral PFC consists of multiple subregions that differ in their cytoarchitectonics and

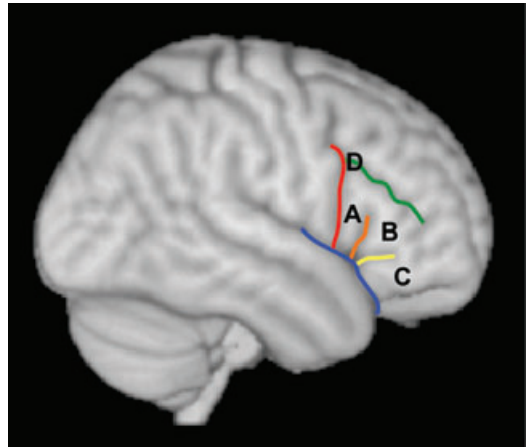
their patterns of connectivity with posterior cortical sites.<sup>5,10–13</sup> Remarkable progress has been made in the last two decades toward understanding the function-to-structure mapping that constitutes lateral PFC's macroscopic functional organization.<sup>14–24</sup> This body of research suggests that PFC is a heterogeneous structure with distinct subregions relating to specific cognitive control operations. Progress has also been made in understanding the broader principles of PFC organization, such as the possibility that PFC is hierarchically organized along its rostro-caudal axis, with higher-order goals encoded by more anterior regions and increasingly specific subgoals encoded as one moves posteriorly through PFC.<sup>18,25–34</sup>

Importantly, for present purposes, key advances have arisen from an extensive literature focused on the organization of left ventrolateral PFC (VLPFC), with extant data documenting functional distinctions between the anterior (Brodmann's area [BA] 47), mid- (BA 45), and posterior (BA 44) subregions of left VLPFC.<sup>21,22,34–40</sup> By contrast, considerably

less is known about the functional organization of right PFC, and, in particular, it remains largely unclear whether the specific subdivisions of right VLPFC are functionally distinct and, if so, how to characterize their underlying computations.

While right VLPFC function is not well understood, neuroimaging studies employing various cognitive tasks have implicated this region as a critical substrate of control. At present, two prominent theories feature right VLPFC as a key functional region. From one perspective, right VLPFC is thought to play a critical role in motor inhibition, where control is engaged to stop or override motor responses.<sup>41</sup> Consistent with this view, neuroimaging studies of tasks thought to require motor inhibition typically reveal activation in right VLPFC, among other regions.<sup>42–44</sup> In addition, patients with damage to the inferior extent of right PFC take longer to override a prepotent response compared to healthy adults or even patients with damage to other PFC subregions.<sup>45</sup> Based on this evidence, Aron *et al.*<sup>41</sup> argued that right VLPFC plays a critical role in motor inhibition.

Alternatively, Corbetta and Shulman<sup>46,47</sup> have advanced the hypothesis that there are two distinct frontoparietal networks involved in spatial attention, with right VLPFC being a component of a right-lateralized ventral attention network that governs reflexive reorienting. From this perspective, right lateral PFC, along with a region spanning right temporoparietal junction and the inferior parietal lobule, are engaged when abrupt onsets occur in the environment, suggesting that these regions are involved in reorienting attention to perceptual events that occur outside the current focus of attention. While much of the research brought to bear in support of this theoretical framework has focused on activity within lateral parietal cortex, the performance of tasks thought to tap reflexive reorienting also typically gives rise to robust right lateral PFC activation.<sup>a</sup> Nevertheless, the precise operations me-



**Figure 1.** Anatomical divisions within the ventrolateral prefrontal cortex (VLPFC). VLPFC, or inferior frontal gyrus, is bounded superiorly by the inferior frontal sulcus (green) and inferiorly by the lateral sulcus (blue). Cytoarchitectonic and connectivity patterns,<sup>11–13</sup> as well as neuroimaging dissociations within the left hemisphere,<sup>21,22,34–40</sup> suggest functional distinctions between three distinct subregions within VLPFC. The most caudal extent (A), which we refer to as posterior-VLPFC, is bounded by the precentral sulcus (red) and the ascending ramus of the lateral sulcus (orange). This region corresponds roughly to the region referred to as pars opercularis or Brodmann area (BA 44). Rostral to the ascending ramus (orange) is mid-VLPFC (B), which corresponds roughly to pars triangularis or BA 45. The horizontal ramus of the lateral sulcus (yellow) separates mid-VLPFC from anterior-VLPFC (C), which roughly corresponds to pars orbitalis or BA 47. In addition to these three VLPFC subregions, recent evidence also suggests that there may be another distinct functional subregion<sup>72–74</sup> that falls at the most posterior and superior region of VLPFC, where VLPFC intersects with the middle frontal gyrus dorsally and the premotor cortex caudally. This region (D) is referred to as the inferior frontal junction (IFJ) and is situated at the intersection of the posterior end of the inferior frontal sulcus (green) and the precentral sulcus (red).

diated by right VLPFC in response to abrupt onsets remain unclear.

The motor inhibition and reflexive reorienting frameworks have gained traction in the last decade and have guided an explosion of functional imaging research.<sup>44,51–71</sup> The prominence of these theories has also motivated reverse inferences, wherein right VLPFC activation in a given task is attributed to either engagement of motor inhibition or attentional orienting processes. At present, however, it is unclear whether these two frameworks implicate the

<sup>a</sup> Both TPJ and lateral PFC are engaged during attentional reorienting and analyses of resting state activity indicate that these regions demonstrate functionally correlated responses,<sup>48,49</sup> which suggests that these regions act as part of a functional network. Importantly, though, recent data have shown that TPJ and lateral PFC show distinct patterns of activity across different orienting de-

mands,<sup>50</sup> suggesting that these regions may play distinct functional roles during reorienting.

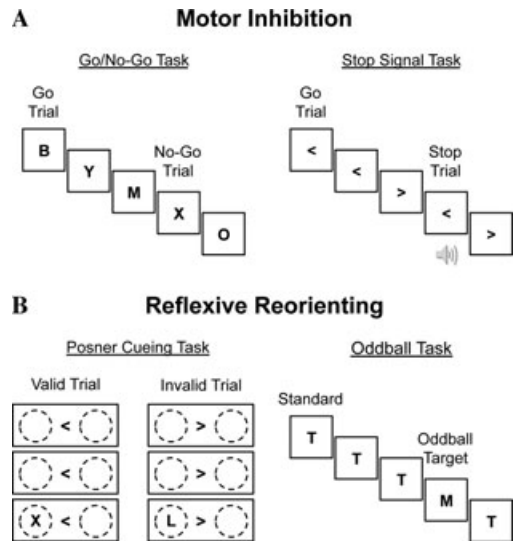
same or distinct subregions within right lateral PFC (Fig. 1), and, at a process level, it is unclear how these two frameworks relate to each other. One possibility is that the VLPFC activity observed during one set of tasks can be explained in terms of the other putative control mechanism. For example, recent data suggest that stopping tasks often confound motor inhibition with the need to orient to behaviorally relevant cues and that this orienting response may be what drives right VLPFC engagement when stopping is required.<sup>70,71</sup> Alternatively, tasks designed to target reflexive reorienting might also involve some demands on motor inhibition.<sup>75</sup>

Here we examine the relationship between these two theories of right PFC function by performing a meta-analysis of the functional magnetic resonance imaging (fMRI) literatures on motor inhibition and reflexive reorienting. The goal is to determine whether distinct PFC subregions respond similarly or differently to these two different types of cognitive control tasks. The results are then considered within the context of the broader empirical literature, as many behavioral tasks beyond those in the meta-analysis lead to the recruitment of right VLPFC. From the current findings and our review of the literature, we then provide initial conclusions about the nature of functional heterogeneity within right VLPFC, with the ultimate goal of sparking future empirical work that will test these emerging hypotheses about the role of right VLPFC in cognitive control.

## Meta-analysis of motor inhibition and reflexive reorienting

### Study selection

For each domain we selected two tasks that are typically used to study the putative mechanism. Theories of motor inhibition rely on the Go/No-Go and Stop Signal tasks as evidence for the involvement of right VLPFC in stopping (see Fig. 2A for explanation of these tasks). There have already been several meta-analyses of these tasks,<sup>76–80</sup> providing a starting pool of studies that was then augmented through an additional literature search. Moreover, because we employed somewhat different screening criteria relative to prior meta-analyses, some studies present in earlier reviews were excluded here. In particular, the inclusion/exclusion criteria for Go/No-Go and Stop Signal studies were as follows.



**Figure 2.** Behavioral tasks used to study motor inhibition and reflexive reorienting. (A) Motor inhibition is typically studied using either the Go/No-Go or Stop Signal task. In the Go/No-Go task, subjects see a stream of centrally presented stimuli and must make a button-press for every stimulus except one, the no-go stimulus (here shown as an “X”). Behavioral performance is measured by the subject’s ability to withhold their response on the no-go trials. In the Stop Signal task, subjects also see a stream of centrally presented stimuli and typically must make a decision about each stimulus (e.g., is the arrow pointing right or left?). On a minority of trials a stop signal (e.g., a tone) is presented, indicating that the subject should withhold their response on that trial. Behavioral performance is assessed by computing a stop signal reaction time (SSRT), which provides an estimate of how long it takes to cancel an initiated movement. In both motor inhibition tasks, brain activity putatively associated with motor inhibition is measured by contrasting activity during the inhibition trials (no-go and Stop Signal) with activity during go trials. (B) Reflexive reorienting is typically studied using either the Posner Cueing or Oddball task. In the Posner Cueing task, a cue orients subjects to attend to one of two spatial positions. Then the subject is asked to make a judgment about a stimulus when it appears (e.g., is the letter an “L” or an “X”?). On valid trials subjects are correctly cued to the spatial position where the target will appear, but on infrequent invalid trials they are instructed to attend to the wrong position. The behavioral index of attentional engagement in this paradigm is that subjects are typically slower to respond on invalidly cued trials than during validly cued trials. Brain activity putatively associated with attentional capture is assessed by contrasting activity during invalid trials with activity during valid trials. In the Oddball task, subjects are asked to attend to a stream of stimuli. Most trials present the same “standard” stimulus, but infrequently an oddball appears and this requires subjects to press a button to note its occurrence. Behavioral performance is measured by the subject’s ability to detect these oddballs and brain activity putatively associated with attentional capture is measured by contrasting activity in response to the oddballs compared to when the standards are presented.

- (1) Similar to earlier meta-analyses, we only included studies of healthy, young adults that reported whole-brain group-level coordinates in a standardized coordinate space (Talairach or MNI).
  - (2) We required that studies contrast activity during stopping trials (no-go or Stop Signal trials) with go trials, excluding studies that simply contrasted stopping trials with baseline activity.
  - (3) We excluded Go/No-Go studies where the identity of the no-go stimulus was defined by the prior trial history.<sup>81</sup> In these studies, subjects had to avoid responding whenever a particular stimulus repeats within the context of a regularly alternating sequence. While this variant shares many similarities with other Go/No-Go studies, it requires additional cognitive operations not present in the typical versions (e.g., maintaining a working memory load), which complicates the interpretation of these contrasts and lessens their similarity to other Go/No-Go studies.
  - (4) The current meta-analysis included studies that used oculomotor or vocal responses, in addition to the more prevalent manual button responses, although these were few in number. Excluding these studies did not change any of our conclusions.
  - (5) Also included are blocked designs where blocks of intermixed go and no-go trials were contrasted with activity during blocks of only go trials.
- (1) As above, we only included studies of healthy, young adults that reported whole-brain group-level coordinates in a standardized coordinate space.
  - (2) For the Posner Cueing tasks, we only included studies that reported the direct contrast of invalidly cued trials with validly cued trials.
  - (3) The Oddball task was the only task where we allowed a comparison of the critical condition, oddball targets that required a motor response, with an unmodeled baseline, since the typical analysis approach in these studies was to not model responses to the standards.
  - (4) In the Oddball task, we excluded contrasts that examined activity for oddballs that did not require a behavioral response.
  - (5) Along with the typical oddball versus target contrasts, we also included two Go/No-Go paradigms that contrasted infrequent-go trials with frequent-go trials,<sup>68,116</sup> as these trials were behaviorally infrequent oddballs within the context of a task that nevertheless required a response.

These selection criteria produced a set of 38 reflexive reorienting contrasts, including 25 Oddball contrasts and 13 Posner Cueing contrasts (Table 2).

#### *Meta-analytic approach*

Selected contrasts were submitted to activation likelihood estimation (ALE) analyses to determine whether there was spatial convergence in the peaks of activation across a given set of studies. First, all foci were converted into the same coordinate system (MNI), with studies reported in Talairach space being converted using Ginger ALE's "Talairach to MNI (SPM)" transform.<sup>139</sup> Second, since the foci/peaks from each study provide an imperfect localization of the activated region, these foci were smoothed by a three-dimensional Gaussian function to create localization probability distributions.<sup>140</sup> The degree of uncertainty associated with each peak was determined by the sample size of the study,<sup>141</sup> as larger samples should yield more stable estimates of active regions. Third, the union of these probability distributions was obtained to create a "modeled activation" map for each individual contrast. These modeled activation maps represent the likelihood that each voxel reflects a true peak of activation from that study. Fourth, topographic

These selection criteria yielded a set of 49 motor inhibition contrasts, including 32 Go/No-Go contrasts and 17 Stop Signal contrasts (Table 1).

We performed a similar literature search for the reflexive reorienting domain. In support of the involvement of right PFC in attentional orienting, Corbetta and Shulman<sup>46,47</sup> cite evidence from the Oddball and Posner Cueing paradigms (see Fig. 2B for explanation of these tasks). There have been prior meta-analyses of the reflexive reorienting literature,<sup>113–115</sup> although those papers restricted their analyses to parietal cortex. The set of studies cited in those papers were used as an initial base for the current set, which was then augmented with a literature search. The inclusion/exclusion criteria for Oddball and Posner Cueing studies were as follows.

**Table 1.** Studies included in the motor inhibition meta-analysis

First Author	Year	Task	Task demands
Altshuler <sup>82</sup>	2005	Go/No-Go	Response uncertainty
Asahi <sup>83</sup>	2004	Go/No-Go	Response uncertainty
Blasi <sup>53</sup>	2006	Go/No-Go	Response uncertainty
Booth <sup>84</sup>	2003	Go/No-Go	Response uncertainty
Bunge <sup>85</sup>	2002	Go/No-Go	Response uncertainty
Falconer <sup>86</sup>	2008	Go/No-Go	Response uncertainty
Horn <sup>87</sup>	2003	Go/No-Go	Response uncertainty
Kaladjian <sup>a,88</sup>	2009	Go/No-Go	Response uncertainty
Kaladjian <sup>89</sup>	2009	Go/No-Go	Response uncertainty
Konishi <sup>90</sup>	1998	Go/No-Go	Response uncertainty
Konishi <sup>91</sup>	1999	Go/No-Go	Response uncertainty
Laurens <sup>92</sup>	2005	Go/No-Go	Response uncertainty
Lawrence <sup>93</sup>	2009	Go/No-Go	Response uncertainty
Liddle <sup>94</sup>	2001	Go/No-Go	Response uncertainty
Maguire <sup>95</sup>	2003	Go/No-Go	Response uncertainty
Mazzola-Pomietto <sup>96</sup>	2009	Go/No-Go	Response uncertainty
Menon <sup>43</sup>	2001	Go/No-Go	Response uncertainty
Mobbs <sup>97</sup>	2007	Go/No-Go	Response uncertainty
Rubia <sup>98</sup>	2005	Go/No-Go	Response uncertainty
Rubia <sup>99</sup>	2006	Go/No-Go	Response uncertainty
Watanabe <sup>100</sup>	2002	Go/No-Go	Response uncertainty
Brown <sup>101</sup>	2006	Go/No-Go	N/A
Brown <sup>102</sup>	2008	Go/No-Go	N/A
Roth <sup>103</sup>	2007	Go/No-Go	N/A
Wager <sup>104</sup>	2005	Go/No-Go	N/A
Chikazoe <sup>68</sup>	2009	Go/No-Go	Response override
de Zubicaray <sup>105</sup>	2000	Go/No-Go	Response override
Durston <sup>106</sup>	2002	Go/No-Go	Response override
Maltby <sup>107</sup>	2005	Go/No-Go	Response override
McNab <sup>62</sup>	2008	Go/No-Go	Response override
Zheng <sup>65</sup>	2008	Go/No-Go	Response override
Aron <sup>44</sup>	2006	Stop Signal	Response override
Aron <sup>57</sup>	2007	Stop Signal	Response override
Cai <sup>a,66</sup>	2009	Stop Signal	Response override
Chamberlain <sup>108</sup>	2009	Stop Signal	Response override
Chevrier <sup>58</sup>	2007	Stop Signal	Response override
Chikazoe <sup>67</sup>	2009	Stop Signal	Response override
Cohen <sup>109</sup>	2010	Stop Signal	Response override
Leung <sup>110</sup>	2007	Stop Signal	Response override
McNab <sup>62</sup>	2008	Stop Signal	Response override
Ramautar <sup>111</sup>	2006	Stop Signal	Response override
Sharp <sup>71</sup>	2010	Stop Signal	Response override
Vink <sup>112</sup>	2005	Stop Signal	Response override
Xue <sup>b,64</sup>	2008	Stop Signal	Response override
Zheng <sup>65</sup>	2008	Stop Signal	Response override

<sup>a</sup>Contributed two contrasts.

<sup>b</sup>Contributed three contrasts.

N/A: not applicable.

**Table 2.** Studies included in the reflexive reorienting meta-analysis

First Author	Year	Task
Arrington <sup>75</sup>	2000	Posner cueing
Corbetta <sup>117</sup>	2002	Posner cueing
Doricchi <sup>118</sup>	2010	Posner cueing
Giessing <sup>119</sup>	2006	Posner cueing
Indovina <sup>59</sup>	2007	Posner cueing
Kincade <sup>120</sup>	2005	Posner cueing
Macaluso <sup>a,121</sup>	2002	Posner cueing
Macaluso <sup>60</sup>	2007	Posner cueing
Mayer <sup>54</sup>	2006	Posner cueing
Thiel <sup>51</sup>	2004	Posner cueing
Thiel <sup>122</sup>	2005	Posner cueing
Vossel <sup>55</sup>	2006	Posner cueing
Bledowski <sup>123</sup>	2004	Oddball
Brazdil <sup>124</sup>	2007	Oddball
Bryant <sup>125</sup>	2005	Oddball
Chikazoe <sup>68</sup>	2009	Oddball
Clark <sup>126</sup>	2000	Oddball
Gur <sup>127</sup>	2007	Oddball
Gur <sup>128</sup>	2007	Oddball
Kiehl <sup>129</sup>	2001	Oddball
Kiehl <sup>130</sup>	2005	Oddball
Lawrence <sup>93</sup>	2009	Oddball
Liddle <sup>131</sup>	2006	Oddball
Linden <sup>b,132</sup>	1999	Oddball
Menon <sup>133</sup>	1997	Oddball
Mulert <sup>134</sup>	2004	Oddball
Muller <sup>135</sup>	2003	Oddball
Ngan <sup>a,136</sup>	2003	Oddball
Stevens <sup>a,61</sup>	2000	Oddball
Wolf <sup>137</sup>	2008	Oddball
Yoshiura <sup>a,138</sup>	1999	Oddball

<sup>a</sup>Contributed two contrasts.

<sup>b</sup>Contributed four contrasts.

convergence across a set of similar contrasts was assessed by calculating an ALE score, which reflects the union of probabilities across all of the studies in a given set, for each individual voxel. In order to determine whether this set of contrasts shows more spatial clustering than would be expected by a random distribution of a similar number of peaks, this ALE map was tested against the null hypothesis that there is no convergence across the individual contrasts.<sup>141</sup> This was done by creating a similar union

of probabilities across the full set of studies, but where each modeled activation map was sampled from a random spatial location. Fifth, the resulting ALE maps were thresholded at  $P < 0.05$  (cluster corrected for multiple comparisons). All analyses were performed using the Ginger ALE software (version 2.0.4), using the standard default parameters (<http://brainmap.org/ale/>).

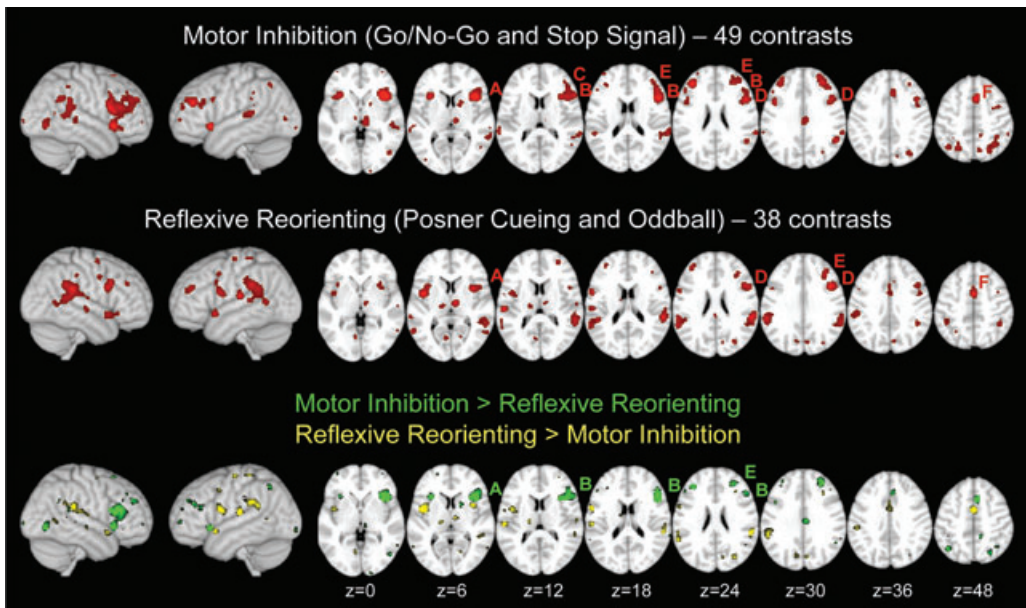
### *Right VLPFC convergence and divergence*

We began by first performing an ALE analysis for each of the two primary domains: motor inhibition and reflexive orienting. Subsequently, we considered differences between the regions associated with the two domains and within-domain task differences.

**Motor inhibition meta-analysis.** Collapsing across both types of stopping tasks revealed a large cluster of activity within right lateral PFC that included portions of the inferior and middle frontal gyri, extending into the frontal operculum (FO) and anterior insula (AI; Fig. 3 and Table 3). In addition to this right PFC cluster, smaller clusters of activity were observed in left PFC, including the posterior extent of the inferior frontal sulcus, the middle frontal gyrus, the FO, and AI. While this suggests that PFC activity during stopping is not strictly lateralized,<sup>80</sup> the effects were more robust on the right; the spatially extensive right VLPFC response, which included portions of both pars opercularis (BA 44) and pars triangularis (BA 45), was absent on the left.

In addition to effects in lateral PFC, there were additional regions that showed consistent across-study activation, including the medial surface of PFC, encompassing the presupplementary motor area (preSMA) and anterior cingulate cortex (ACC), right inferior parietal lobule, and bilateral intraparietal sulcus. While these regions are not the primary focus of the current paper, understanding the mechanistic role of right VLPFC will necessarily involve future analyses of the full networks recruited by these tasks (a point to which we later return). Interestingly, we also observed a subcortical region of activation that is consistent with the involvement of the right subthalamic nucleus during stopping.<sup>44</sup>

**Reflexive reorienting meta-analysis.** The reflexive reorienting tasks also activated regions within right lateral PFC. In particular, consistent across-study activation was present in the right inferior frontal junction (IFJ), middle frontal gyrus, and within the



**Figure 3.** Meta-analysis of motor inhibition and reflexive reorienting tasks. The top two rows display the activation likelihood estimate (ALE) maps for motor inhibition tasks, collapsing across Go/No-Go and Stop Signal tasks, and reflexive reorienting tasks, collapsing across Posner Cueing and Oddball tasks (thresholded at  $P < 0.05$ , cluster corrected for multiple comparisons). At the bottom is a voxel-wise map of the difference score between the two unthresholded ALE maps. This image is arbitrarily thresholded (at 0.0125) to show voxels where there are large differences in the two ALE maps; accordingly, this map provides qualitative leverage on possible differences between conditions but does not constitute a formal statistical comparison. On the axial slices, specific right VLPFC subregions are labeled: anterior insula (A), posterior-VLPFC (B), mid-VLPFC (C), inferior frontal junction (D), middle frontal gyrus (E), and presupplementary motor area (F).

AI (Fig. 3 and Table 4). In addition to these right lateral frontal regions, significant clusters were observed in left IFJ, ACC, and bilateral inferior parietal lobule.

**Differences between motor inhibition and reflexive reorienting.** The overall pattern of activity for the two domains was rather similar. Both elicited primarily right-lateralized frontoparietal responses. Within PFC, both task domains led to robust activity within right IFJ. At the same time, there appear to be differences in other regions of PFC. Most notably, the lateral surface of right VLPFC, including pars opercularis and pars triangularis, was robustly modulated by the stopping tasks, but not by reflexive reorienting tasks. This remained the case even when matching the number of contrasts in the two types of comparisons at 38 by randomly subsampling the motor inhibition contrasts. While our analysis approach did not support direct statistical comparisons between tasks,<sup>141</sup> for visualization purposes we also computed the raw difference scores between

the two respective ALE maps (Fig. 3). Consideration of these arbitrarily thresholded difference maps suggested that the right VLPFC activation likelihood measures markedly differed between stopping and orienting. This direct comparison also revealed that while FO/AI and middle frontal gyrus were consistently recruited by both tasks, these regions may be more reliably recruited by stopping tasks.

**Within-domain task differences.** While the preceding analyses pooled data across two tasks for each domain, there are important distinctions between the two classes of tasks within each domain. In particular, different motor inhibition tasks may not involve the same type of stopping.<sup>78,142–144</sup> Some stopping tasks require the subject to override a specific motor response, such as in the Stop Signal paradigm, where a subject typically has around 200–300 ms to initiate their button press prior to onset of the stop signal. By contrast, other stopping tasks do not appear to require subjects to override an already initiated response. Specifically, in many imaging

**Table 3.** Frontal regions that respond during motor inhibition tasks (Go/No-Go and Stop Signal)

Anatomical label	~BA	x	y	z	Volume (mm <sup>3</sup> )
R anterior insula	13	40	18	0	22056
R posterior-VLPFC	44	48	16	18	
R middle frontal gyrus	9/46	30	40	28	
R mid-VLPFC	45	48	28	18	
R inferior frontal junction	6/9/44	44	14	34	
R middle frontal gyrus	9/46	26	50	28	
R middle frontal gyrus	9/46	40	32	30	
R middle frontal gyrus	9/46	40	42	18	
R dorsal premotor cortex	6	40	2	46	
R dorsal premotor cortex	6	30	2	44	
R presupplementary motor area	6	6	16	50	5496
R presupplementary motor area	6	14	16	58	
R anterior cingulate	32	6	24	36	
L anterior insula	13	-42	16	-6	3624
L anterior insula	13	-32	20	4	
L middle frontal gyrus	9/46	-36	38	24	2416
L inferior frontal junction	6/9/44	-46	10	28	1088
L presupplementary motor area	6	-6	2	60	520
L middle frontal gyrus	9/46	-48	30	22	496
L middle frontal gyrus/frontal pole	9/10/46	-38	54	20	176
L dorsal premotor cortex	6	-26	-2	52	120

studies of the Go/No-Go task, there is an equal likelihood that a trial will contain a Go or No-Go stimulus. In equiprobable Go/No-Go tasks, it is unclear to what degree subjects engage in response preparation before the stimulus appears. To the extent that subjects either fail to initiate a motor response or prepare both potential motor responses, the nature of “stopping” in equiprobable Go/No-Go tasks is likely to be quite different from that in tasks where subjects must override a specific initiated action. Therefore, we divided the motor inhibition tasks into (a) tasks where subjects had a clear expected motor response that they could prepare and even begin to initiate before the stimulus appeared (all Stop Signal tasks; and any Go/No-Go task where Go trials were more frequent and the appropriate response was known ahead of time), which we refer to as response override tasks; and (b) tasks where they were unlikely to engage in differential preparation of a specific motor response before the stimulus appeared (Go/No-Go tasks where the trial types were equiprobable), which we refer to as response

uncertainty tasks (for related distinctions, see Refs. 142–144). Four stopping tasks were excluded from this analysis because they were difficult to classify.

A meta-analysis of the response override studies revealed consistent activity in right IFJ, bilateral middle frontal gyrus, and right posterior-VLPFC (pars opercularis; Fig. 4 and Table 5). Similarly, the meta-analysis of the response uncertainty contrasts revealed that these tasks consistently recruited bilateral IFJ and middle frontal gyrus, along with right VLPFC spanning both pars opercularis and pars triangularis (Fig. 4 and Table 6). Strikingly, the right mid-VLPFC (pars triangularis) effect seen in the response uncertainty studies was absent in the response override studies. Qualitatively, the voxel-wise difference scores between the two ALE maps highlighted this differential effect in mid-VLPFC during response uncertainty tasks, and also suggested that although right middle frontal gyrus and AI were recruited by both types of stopping tasks, they may be more consistently active during response override tasks (Fig. 4).



**Table 4.** Frontal regions that respond during reflexive reorienting tasks (Posner cueing and Oddball)

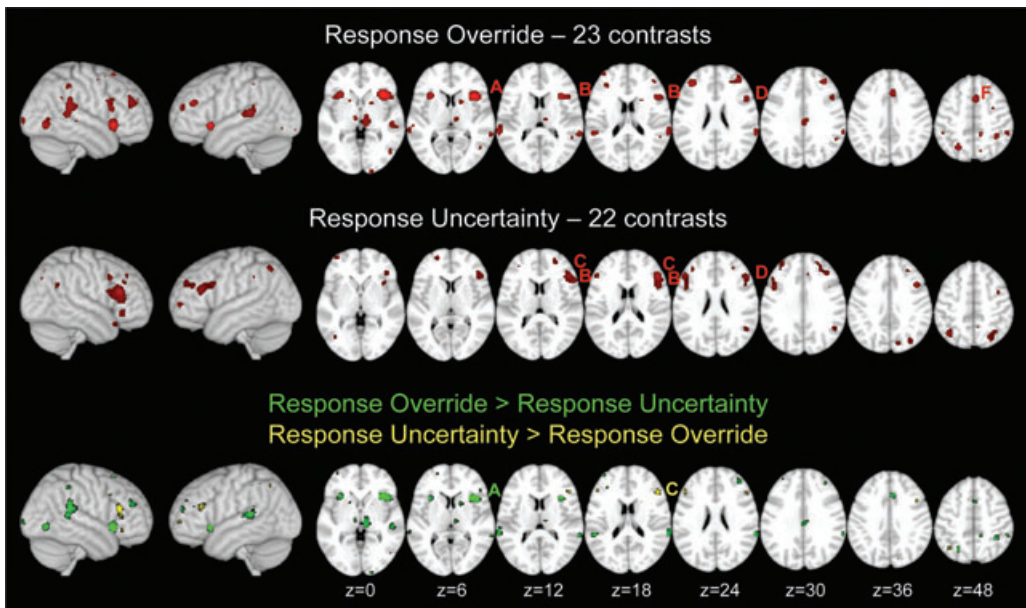
Anatomical label	~BA	x	y	z	Volume (mm <sup>3</sup> )
R inferior frontal junction	6/9/44	44	14	30	9472
R anterior insula	13	36	8	6	
R presupplementary motor area	6	28	-4	60	
R inferior frontal junction/premotor cortex	6/8	50	0	38	
R anterior insula	13	34	24	-6	
R inferior frontal junction/premotor cortex	6/8	44	-2	40	
R dorsal premotor cortex	6	40	4	44	
R anterior-VLPFC	47	46	24	-10	
Anterior cingulate/presupplementary motor area	6/32	0	0	46	4712
Presupplementary motor area	6	0	12	42	
Supplementary motor area	6	2	-12	56	
R anterior cingulate/presupplementary motor area	6/32	8	20	38	
L insula	13	-44	0	6	3216
L anterior insula	13	-36	12	4	
L anterior insula	13	-34	20	-8	
R middle frontal gyrus	9/46	34	30	30	1680
R middle frontal gyrus	9/46	36	36	30	
L ventral premotor cortex	6	-56	2	18	1216
L inferior frontal junction	6/9/44	-48	8	32	
L temporal pole/insula	38/13	-48	10	-10	920
L middle frontal gyrus/frontal pole	9/10/46	-36	42	24	824
R frontal pole	10	30	52	12	296
L inferior frontal junction	6/9	-48	6	44	224
Primary motor cortex	4	-36	-16	64	168

A similar comparison within the reflexive reorienting tasks was performed, as the Posner Cueing task and the Oddball task differ in a number of important ways. For example, the Cueing task involves a perceptual onset at an unexpected location in space, whereas Oddball targets appear in the central stream. Also, the onset that captures attention in the Posner Cueing task is the alternate location, but the actual location of the stimulus is irrelevant to the subject's decision (judging the identity of the stimulus), whereas the attention-capturing onset in the Oddball task is the occurrence of the oddball target and this defines what response the subject should make. Despite these differences, the ALE maps for the two sets of studies were remarkably similar and direct comparisons between the two tasks did not suggest any clear differentiation. This could be due to the low number of studies using the Posner Cueing task or perhaps because these task differences have little impact on the exact regions recruited. There is evidence from one within-subjects compar-

ison that both the Oddball and Posner Cueing task recruit IFJ, but that the Oddball task more reliably recruits a region in the inferior frontal sulcus, anterior to the IFJ;<sup>145</sup> this latter result was not observed in the current meta-analysis, however. Future research can profitably explore whether within-subjects differences are consistently observed in the functional neuroanatomy of these tasks.

### Implications for theories of right VLPFC function

Overall, the present meta-analysis revealed broad similarity in the regions recruited by motor inhibition and reflexive reorienting. Tasks thought to reflect both constructs led to consistent activity within a right-lateralized frontoparietal network. However, despite this general correspondence, there also appear to be important differences in the right lateral PFC subregions that are consistently activated by the two classes of tasks, a finding that provides initial traction on specifying the function-to-structure



**Figure 4.** Meta-analysis of two different types of motor inhibition tasks. The top row displays the ALE map for tasks that involve response override. These Stop Signal and Go/No-Go tasks encourage subjects to prepare a specific motor response before the stop cue appears, such that the cue triggers the need to cancel a prepared motor action. The second row displays the ALE map for tasks that involve response uncertainty. These are Go/No-Go tasks where the two trial types are equiprobable, such that subjects are unlikely to prepare a specific motor response before the trial begins. Accordingly, to the extent that they do not prepare a response, then there is no need to override a specific response. Instead, these tasks create a situation of high decision uncertainty. The bottom row displays a voxel-wise map of the difference score between the two unthresholded ALE maps. This image is arbitrarily thresholded (at 0.0125) to show voxels where there are large differences in the two ALE maps; accordingly, this map provides qualitative leverage on possible differences between conditions, but does not constitute a formal statistical comparison. On the axial slices, specific right VLPFC subregions are labeled: anterior insula (A), posterior-VLPFC (B), mid-VLPFC (C), inferior frontal junction (D), and presupplementary motor area (E).

mapping within right VLPFC. To further this goal, we next discuss the pattern of activation observed in specific right VLPFC subregions in our meta-analysis within the context of other findings from the broader neuroimaging, TMS, and lesion literatures. Finally, we conclude by offering an initial characterization of the mechanistic role each right VLPFC subregion may play in cognitive control.

### *Inferior frontal junction (IFJ)*

The IFJ was active across the motor inhibition and reflexive reorienting tasks included in our meta-analysis, which suggests that this region contributes to the detection of relevant stimuli in the environment. Interestingly, the response of this region was largely bilateral, which may distinguish IFJ from VLPFC (see sections below on VLPFC). As noted by others,<sup>70,71</sup> motor inhibition tasks require subjects to detect behaviorally relevant stop signals, and direct within-study comparisons indicate that IFJ

is similarly recruited across orienting and stopping contrasts.<sup>68,70,71</sup> The pattern of generalized recruitment seen in the present meta-analysis is also consistent with other work implicating IFJ across a broad range of cognitive tasks.<sup>72–74</sup> For example, Derrfuss *et al.*<sup>72</sup> reported that bilateral IFJ was active during task switching, n-back, and Stroop tasks. These findings suggest that the IFJ is recruited across many paradigms that require cognitive control.

Precisely what role the IFJ plays, though, remains unclear. Based on the results of the current meta-analysis, one possibility is that this region responds to the detection of infrequent stimuli, since the contrasts analyzed here mostly involve comparisons of infrequent trials against frequent ones (e.g., stop signals typically occur on only 20–30% of the trials and they are contrasted with Go trials that occur the other 70–80% of the time). The one exception in the current set of analyzed studies is the response uncertainty tasks, where the No-Go and Go trials were

**Table 5.** Frontal regions that respond during response override tasks

Anatomical label	~BA	x	y	z	Volume (mm <sup>3</sup> )
R anterior insula	13	38	20	-2	9464
R posterior-VLPFC	44	48	16	18	
R presupplementary motor area	6	14	16	58	4688
Supplementary motor area	6	6	8	60	
Supplementary motor area	6	-6	2	60	
Supplementary motor area	7	4	12	50	
L anterior insula	13	-42	16	-6	3320
L anterior insula	13	-32	20	4	
R middle frontal gyrus	9/46	34	42	28	1592
L middle frontal gyrus	9/46	-36	38	24	1224
Anterior cingulate	32	6	22	36	728
L middle frontal gyrus/frontal pole	9/46/10	-38	54	18	328
R dorsal premotor cortex	6	30	0	44	240
L dorsal premotor cortex	6	-26	-4	52	208

equiprobable. Even under such equiprobable conditions, greater activity on No-Go relative to Go trials was observed in IFJ. Moreover, in some of the tasks studied by Derrfuss *et al.*,<sup>72,74</sup> the critical contrasts do not compare infrequent trial types with frequent ones (e.g., Stroop), suggesting that this region does not respond simply to infrequent events.

An alternative interpretation of IFJ functional activations is that they may track the detection of behaviorally relevant stimuli, rather than rare events. This idea is consistent with the notion of a ventral attention system that responds to abrupt onsets in the environment. Importantly, all of the tasks reviewed here require subjects to explicitly search for some target, so these tasks likely do not elicit pure bottom-up, stimulus-driven activity. Rather, IFJ responses likely depend on an interaction between stimulus-driven processes and top-down behavioral goals.<sup>47,52</sup> For example, IFJ may actively maintain a specific target (e.g., a particular feature or an object identity) and then signal a match whenever it appears in the environment.<sup>146</sup> This kind of general monitoring role could explain the recruitment of IFJ across a diverse array of goal-directed tasks.

While we have interpreted the overlapping activation in IFJ as evidence that reflexive reorienting is recruited during stopping tasks, it is possible that the converse is true: reflexive reorienting tasks may involve response inhibition. In fact, Arrington *et al.*<sup>75</sup> suggested that right lateral PFC activity during in-

validly cued trials could reflect the suppression of inappropriate responding before attention has been reoriented to the correct spatial location. Arguing against this interpretation, though, is the fact that most oddball tasks do not involve any form of motor inhibition. To further address this possibility, we performed a meta-analysis restricted to 21 of the oddball contrasts where we can be reasonably sure that no component of the task required subjects to withhold a response—as happens, for example, in oddball tasks where subjects press a different button for the standard stimuli and must withhold this response when the oddball appears.<sup>132</sup> Importantly, even in this subset of studies, we observed robust activity within right IFJ suggesting that this region is recruited even when there is no need to suppress a motor response.

Greater mechanistic specificity regarding IFJ function is clearly still needed. Given the observation of IFJ activation across many cognitive control tasks, one useful next step in advancing models of IFJ function might include a more precise characterization of which tasks do not activate this region. For example, the monitoring role proposed above suggests that IFJ responds when the current stimulus matches the target feature that is currently being monitored for and, therefore, should not respond to task-irrelevant stimuli even when they are surprising. In contrast to this, one recent study has shown bilateral IFJ activity in response to the initial

**Table 6.** Frontal regions that respond during response uncertainty tasks

Anatomical label	~BA	x	y	z	Volume (mm <sup>3</sup> )
R mid-VLPFC	45	48	28	18	6752
R anterior-VLPFC	47	42	30	-8	
R posterior-VLPFC	44	48	14	18	
R posterior-VLPFC	44	56	22	12	
L inferior frontal junction	6/9/44	-46	12	28	2272
L middle frontal gyrus/mid-VLPFC	9/46/45	-48	30	22	
R middle frontal gyrus	9/46	38	32	30	1224
R middle frontal gyrus	9/46	30	40	28	
R middle frontal gyrus	9/46	30	36	40	
R frontal pole	10	24	48	30	
R inferior frontal junction/middle frontal gyrus	6/9	44	14	36	800
R inferior frontal junction	6/9/44	42	10	28	
L middle frontal gyrus	9/46	-36	40	26	776
L middle frontal gyrus	9/46	-32	48	30	
R dorsal premotor cortex	6	40	2	46	352
L frontal pole	10	-38	58	2	312
R frontal pole	10	24	52	12	288
L frontal pole	10	-22	58	6	272
R anterior insula	13	38	16	0	208
L anterior-VLPFC	47	-40	32	-10	176

presentations of unexpected task-irrelevant stimuli,<sup>147</sup> suggesting that this region may compute more than the occurrence of a particular target. More broadly, an analysis of divergent validity would likely provide useful constraints on the possible mechanistic contributions IFJ provides to goal-directed behavior.

### *Right posterior-VLPFC*

In contrast to task-general recruitment of IFJ, there was evidence for functional specialization in other PFC regions. In particular, right posterior-VLPFC (pars opercularis) was reliably recruited during stopping tasks, but not during reflexive reorienting tasks. This finding is consistent with the observation that lesions to this right VLPFC subregion are accompanied by stopping impairments,<sup>45</sup> and that TMS to this region, and not other PFC regions, disrupts stopping.<sup>148</sup> Strikingly, there was no evidence that any of the tasks studied here reliably recruited left posterior-VLPFC.

These findings suggest that right posterior-VLPFC is specifically involved in stopping and not in the capture of attention by behaviorally relevant

stimuli. Importantly, this dissociation between right posterior-VLPFC and right IFJ has also been observed using within-subject designs.<sup>68,149</sup> For example, Chikazoe *et al.*<sup>68</sup> modified the Go/No-Go task to include infrequent-go trials that (a) occurred at the same frequency as no-go trials (12.3%), but that (b) still required the same response as other go trials. As such, the infrequent-go trials did not require engagement of a putative stopping process, but nevertheless were oddballs that should capture attention in a stimulus-driven fashion. Importantly, right IFJ responded to both types of infrequent trials (infrequent-go and no-go), whereas right posterior-VLPFC responded to the no-go trials but not the infrequent-go trials (*cf.* Sharp *et al.*<sup>68</sup> for a failure to observe this dissociation in a similar paradigm). Similarly, Verbruggen *et al.*<sup>149</sup> used TMS to target right IFJ and right posterior-VLPFC during a Stop Signal task and found evidence that stimulating IFJ impaired the ability to detect behaviorally relevant stimuli, whereas stimulating posterior-VLPFC disrupted the ability to update action plans after the detection of a stop signal.

Collectively, the present meta-analysis as well as related within-subject directed contrasts suggest that right posterior-VLPFC plays a key role in stopping tasks that is distinct from the simple detection of stop signals in the environment. While this finding is consistent with the hypothesis that this region plays a critical role in motor inhibition,<sup>41</sup> it should be noted that our meta-analysis suggests that activation in this region does not differ between response override and response uncertainty versions of the stopping task, despite the fact that the former place greater demands on stopping (i.e., the motor plan has already been initiated and should therefore be more difficult to stop). Moreover, Verbruggen *et al.*<sup>149</sup> found that TMS-mediated disruption of right posterior-VLPFC not only slowed stopping, but also impaired the ability to use environmental cues to update behavior even when updating did not require stopping (subjects simply had to press the same button a second time). Verbruggen *et al.*<sup>149</sup> suggest that the role of right posterior-VLPFC is to update action plans after a behaviorally relevant stimulus has been detected; stopping is one instance of the class of situations in which such updating is required. Critically, difficulties in updating action plans would still explain why lesions to right posterior-VLPFC impair the ability to stop.<sup>45</sup> Interestingly, Oddball tasks do not reliably activate posterior-VLPFC. Responding to the detection of an oddball target clearly involves engaging an action plan, but importantly it does not involve revising a specific prepared plan in favor of an alternate action plan. This newly emerging view offers a critical reframing of the role of right posterior-VLPFC: rather than mediating motor inhibition, per se, this PFC subregion may contribute to the updating of action plans.

### *Right mid-VLPFC*

The present meta-analysis suggests that right mid-VLPFC activity was unique to response uncertainty tasks, which are stopping tasks where the go and no-go trials are equally likely to occur. In such tasks, the moment when the stimulus appears involves a high degree of uncertainty, as the subject must decide which response is currently relevant. This differs from the other tasks analyzed here, in which subjects can formulate a specific action plan prior to stimulus onset and then wait to execute that action (or counteraction) until the critical stimulus

occurs. For example, in Stop Signal tasks subjects can begin to initiate action, knowing that only if they hear the infrequent stopping tone do they need to stop the response. Thus, there is relatively little ambiguity in the Stop Signal task, even when the task is made difficult by delaying the stop signal. Similarly in the Oddball task, the subject spends most of the time not responding and only needs to be prepared to respond once an oddball appears, a situation that again involves little response ambiguity when the stimulus appears. In response uncertainty tasks, however, both responses are equiprobable, so subjects are not able engage in the kind of differential response preparation that occurs in other tasks. This means that (a) there is no specific prepotent action plan that needs to be cancelled, and (b) there is a high degree of ambiguity when the stimulus occurs and the subject must decide which of the two responses (go or no-go) is associated with it. It is possible that in these situations, subjects engage in minimal or even no preparation before the stimulus appears. However, because speeded responding is generally emphasized for go trials, we suggest that subjects are likely to prepare both responses in parallel, leading to a situation where appropriate behavior is underdetermined and these multiple incompatible responses produce conflict, triggering the need for cognitive control.<sup>150</sup>

While we have suggested that this mid-VLPFC response is driven by uncertainty, it is unclear what precise cognitive control process is triggered by uncertainty in this situation. One interpretative challenge stems from the fact that, while both equiprobable go and equiprobable no-go trials should be associated with a high degree of uncertainty, the contrasts that yield differential mid-VLPFC activity compare no-go with go trials. This suggests that this region is not simply driven by uncertainty, but rather is driven by no-go trials in contexts where uncertainty is high (i.e., there is an interaction between uncertainty and some factor related to no-go trials). One possibility relates to the framing of the task: no-go trials are typically emphasized in the task instructions and may, therefore, take on greater saliency or motivational significance (see also Refs. 151 and 152 for a similar discussion). Alternatively, withholding a response may place greater demands on cognitive control than executing any particular motor movement. It is interesting to note, in this

context, that the Oddball task is just an inverse version of the Go/No-Go task, where the typical trials require no response (rather than responding). In the studies analyzed here, oddballs were never presented on more than 20% of the trials, but one could try to gain leverage on this mid-VLPFC response by using an equiprobable Oddball design. If mid-VLPFC responds to target stimuli with higher salience under situations with high uncertainty, then mid-VLPFC should be engaged by equiprobable oddballs more than the standards. In contrast, if mid-VLPFC activity reflects increased demands related to withholding a response, one might predict that the oddballs would be associated with weaker mid-VLPFC activity. These predictions await further examination.

The recruitment of right mid-VLPFC when uncertainty is high is consistent with research implicating left mid-VLPFC in resolving decision-level conflict. Badre and Wagner<sup>22</sup> reviewed the literature on the cognitive control of memory and found that left mid-VLPFC is recruited postretrieval under conditions in which subjects had to select amongst multiple competing active representations (see also, Thompson-Schill *et al.*<sup>153</sup>). More recently, Race *et al.*<sup>34</sup> used a repetition priming paradigm to manipulate uncertainty at three different levels of representation—stimulus meaning, the mapping of the stimulus to task-relevant decision categories, and response selection—and observed that left mid-VLPFC activation tracked decision-level uncertainty (for related findings, see Race *et al.*<sup>154</sup>). At present, it remains unclear at what stage of processing the critical uncertainty arises in the response uncertainty tasks described here. In particular, equiprobable trials are likely associated with uncertainty both at the decision level, where subjects must categorize the stimulus, and at the response-level, where subjects must determine which behavior is currently relevant. The extant literature on the cognitive control of memory suggests that perhaps the critical form of uncertainty here relates to decision-level stimulus mapping, but this too awaits further investigation.

As was the case with posterior-VLPFC, the presently observed mid-VLPFC response during response uncertainty tasks was clearly lateralized and was not seen in the left hemisphere. Interestingly, the homologous left VLPFC regions are robustly modulated by other cognitive control tasks, partic-

ularly when linguistic stimuli are used.<sup>22,34</sup> By contrast, in the stopping and attention tasks reviewed here, verbal aspects of the stimuli are not critical to performance. Collectively, these similarities and differences between left and right mid-VLPFC suggest (a) that the difference in the types of materials being processed (verbal vs. nonverbal) affects the laterality of the mid-VLPFC response, but (b) that the mid-VLPFC response nevertheless may subservise the same basic function of resolving decision uncertainty regardless of stimulus type. This interpretation predicts that other tasks that measure decision uncertainty should also lead to mid-VLPFC recruitment.

An alternative, although not mutually exclusive, interpretation of the present meta-analytic findings is that the pattern of VLPFC activity during stopping tasks reflects a rostro-caudal hierarchical gradient of control.<sup>18,25–34</sup> According to this view, more anterior regions of PFC encode more abstract higher-order goals, which typically bridge longer spans of time, whereas more posterior regions of PFC encode progressively more specific subgoals, with the most posterior regions in premotor cortex instantiating specific action plans. In the current context, response override tasks involve a type of stopping that occurs late in information processing and is targeted at already prepared action plans, which may explain why these tasks reliably recruit the most posterior extent of VLPFC. Response uncertainty tasks, on the other hand, involve a more abstract form of control that involves selecting from among multiple viable action plans and therefore drives activity in the more rostral right mid-VLPFC region. Seen in this light, the current data resemble similar functional gradients that have been observed along the rostro-caudal axis of left PFC.<sup>18,25–34</sup>

### *Right AI/FO*

Across all of the reviewed tasks, there was some evidence for recruitment of the most ventral portion of lateral frontal cortex. When activations are observed in group-level maps near this area, it is often difficult to discern whether the clusters correspond to activity within the FO of VLPFC or the immediately adjacent AI. Nevertheless, in the reflexive reorienting tasks, the present meta-analyses suggest that the most ventral lateral frontal activations were relatively restricted and appear to fall within AI.

By contrast, the region recruited by stopping tasks clearly extended from AI into FO.

It appears clear that the AI is consistently engaged during both reflexive reorienting and motor inhibition tasks,<sup>70</sup> though right AI was more consistently activated by stopping and particularly by the response override tasks. The broader literature on the insula implicates this region in the processing of emotions and pain, as well as during situations requiring cognitive control.<sup>155</sup> It has been suggested that the broad role of the AI, in conjunction with the dorsal anterior cingulate, is in the processing of saliency, regardless of whether that saliency is emotional or cognitive.<sup>156–158</sup> This putative salience network is thought to respond to relevant stimuli in the environment and activate sympathetic responses, such as increasing heart rate and dilating the pupils, in order to better prepare the subject to respond to the salient event. It is not thought, however, to directly exert control itself (although, see Dosenbach *et al.*<sup>159</sup>).

Recent lesion evidence suggests that AI may play some critical functional role during motor inhibition tasks. In particular, based on a meta-analysis of the imaging literature as well as new lesion data, Swick *et al.*<sup>80</sup> argued that left frontal regions are also involved in stopping. They observed that patients with left frontal lesions, which included damage to both VLPFC and AI, made more errors in a Go/No-Go task, especially when no-go trials were infrequent. One possibility is that this impairment on the Go/No-Go task was due to damage to left AI as this region, and not left VLPFC, was implicated in stopping in the present meta-analysis and in that by Swick *et al.*<sup>80</sup> This interpretation would also be consistent with the observation that left PFC lesions do not disrupt stopping.<sup>45</sup> At the same time, it is unclear why damage to this left-lateralized region disrupts performance on the Go/No-Go task, and it could be for reasons that do not relate directly to motor inhibition (e.g., these regions might support rule maintenance or modulated arousal in response to the salience of the stop cues). Further imaging and lesion data are needed to understand whether left and right AI play a fundamental role in motor inhibition.

### *Interactions with medial PFC*

A full understanding of lateral PFC functioning requires a broader understanding of the networks sup-

porting specific forms of cognitive control. While the lateral frontal regions discussed above are the primary focus of this paper, they are not the only regions consistently activated by motor inhibition and reflexive reorienting tasks (Fig. 3). In particular, both task domains led to consistent across-study recruitment of medial prefrontal regions, although there was relatively little overlap in the precise regions recruited. Stopping tasks tended to activate the preSMA and ACC, whereas reflexive reorienting activations were more posterior and did not extend as far dorsally into preSMA. In addition, the stopping activations tended to be right lateralized, while the reflexive reorienting activations tended to be centered around the midline.

Medial PFC activity in Oddball and Go/No-Go tasks has been argued to track the infrequency of the stimuli, putatively reflecting the heightened conflict present whenever an infrequent response, of any type, is required.<sup>160</sup> Consistent with this view, we did not find evidence for the recruitment of ACC during equiprobable Go/No-Go tasks, whereas tasks that contrasted infrequent with frequent stimuli led to robust ACC activation (although these contrasts yielded different ACC regions depending on the task context, whereas Braver *et al.*<sup>160</sup> found a common ACC region that responded to infrequency in both Oddball and Go/No-Go tasks). While the specific ACC region recruited may differ, the general recruitment of ACC across these tasks is consistent with several competing accounts of ACC functioning,<sup>150,161–163</sup> all of which predict that response competition should occur due to the infrequency of the desired response. It is worth noting, though, that the equiprobable Go/No-Go tasks, which we have interpreted as reflecting decision uncertainty, do not reliably activate ACC, even though such tasks should involve response competition.

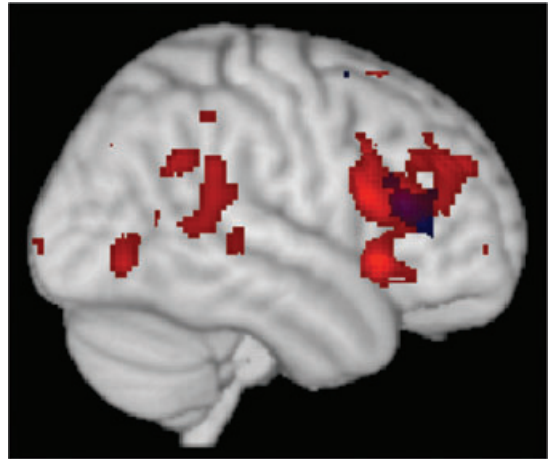
In the present meta-analysis, activation within preSMA appeared to be specific to the response override variants of stopping tasks. This finding is consistent with observations that preSMA is more active during correct stop signal trials than during go trials where an infrequent behaviorally irrelevant cue is presented,<sup>68,71</sup> suggesting that preSMA is involved in stopping rather than attentional capture (*cf.*, Hampshire *et al.*<sup>70</sup> failed to find a differentiation within preSMA for orienting and stopping in

a similar design<sup>b</sup>). There is also lesion evidence to suggest that damage to preSMA can lead to impaired stopping performance,<sup>164–166</sup> suggesting that, along with right posterior-VLPFC, this region may play a critical role in stopping tasks. Anatomically, Aron *et al.*<sup>57</sup> showed that preSMA is connected to right posterior-VLPFC and to the subthalamic nucleus (STN), both of which also showed consistent across-study activity here that was specific to the stopping tasks. These findings support the hypothesis that these regions interact as a network to support stopping performance,<sup>57</sup> with the present and other data suggesting a broader role of right posterior-VLPFC in action updating.

### Right VLPFC: beyond stopping and attention

While our focus in this review was to specifically address two dominant accounts of right VLPFC function, it is important to emphasize that activation of right VLPFC subregions has been observed during the performance of many tasks beyond those described here. For instance, neuroimaging studies of episodic memory encoding and retrieval often report that activation in VLPFC is strongly lateralized based on the type of stimuli being processed.<sup>167–175</sup> Verbal stimuli often lead to robust activation in left VLPFC, whereas visuospatial stimuli often result in activation in right VLPFC. Interestingly, in situations where visual stimuli are easy to verbally re-code (e.g., nameable famous faces or pictures of common objects), bilateral VLPFC activations are observed, suggesting that subjects engage both verbal and nonverbal processing mechanisms for these

<sup>b</sup> While Hampshire *et al.*<sup>70</sup> failed to find differentiation within preSMA for stopping and reorienting, interpretation of this outcome is complicated by a number of methodological factors. In particular, the orienting and stopping tasks were compared to different baselines, the orienting task involved a working memory component that was absent from the stopping task, and the orienting task always preceded the stopping task during scanning.<sup>68,71</sup> It is difficult to know which, if any, of these factors explain the divergence from other studies. It is also worth noting that while Hampshire *et al.*<sup>70</sup> reported a right VLPFC region that did not differentiate between orienting and stopping, this effect appears to fall ventral to the posterior-VLPFC region observed implicated in stopping by the present meta-analysis.



**Figure 5.** Encoding visuospatial information activates similar VLPFC regions as motor inhibition. Here the activations from the motor inhibition meta-analysis are replotted in red, and overlaid in blue is an ALE meta-analysis of three episodic memory encoding studies.<sup>168,171,174</sup> Each of these latter studies contrasted encoding phases with difficult-to-verbalize visuospatial stimuli (e.g., textures) to ones with verbal stimuli. While several other studies reported similar patterns both at encoding<sup>169,172,175</sup> and during retrieval,<sup>168,169</sup> many of these studies did not report peak coordinates. This sample was too small to justify a formal meta-analytic treatment; nevertheless, the apparent overlap suggests that similar right VLPFC regions are engaged during motor inhibition and during nonverbal episodic encoding tasks. This overlap would appear difficult to explain in terms of either motor inhibition or reflexive reorienting.

types of stimuli.<sup>167,175</sup> There is also some evidence for a similar material-specificity effect during working memory tasks, particularly when the tasks involve simple maintenance.<sup>176</sup> Importantly, these regions clearly overlap with the VLPFC responses observed here, particularly for the stopping tasks (Fig. 5).

Right VLPFC has also been implicated as a key region in the mirror neuron system.<sup>177,178</sup> Mirror neurons are cells that respond both to the execution of an action and to observing someone else performing the same action.<sup>179</sup> These neurons were first observed in the primate premotor and parietal cortices,<sup>180</sup> but this work has inspired functional neuroimaging studies of humans investigating which brain regions show these type of responses; the human neuroimaging literature has also extended these earlier studies to examine the role of mirror neurons in imitation, empathy, and social cognition generally. Importantly, these imaging studies have implicated bilateral VLPFC, along with other



regions, in action observation, execution, and imitation. A meta-analysis of this literature revealed that this lateral PFC response includes right IFJ along with posterior and mid-VLPFC regions that overlap with those observed here.<sup>178</sup>

These two examples provide an important, broader context for theorizing about what functions are subserved by right VLPFC. If a common VLPFC region is observed within-subjects to be engaged across these domains, it is unclear how the putative mechanisms discussed in the present review could explain those activations in the episodic encoding and mirror neuron literatures. Encoding of non-verbal stimuli and action imitation, for example, both likely involve orienting to behaviorally relevant stimuli as they appear in the environment, but in neither case is it obvious that the contrasts employed in those studies reflect the capture of attention. Furthermore, drawing on such an interpretation to explain these other effects leads to the prediction that the VLPFC regions implicated in orienting should be active whenever subjects encounter any type of behaviorally relevant stimuli. It is perhaps even less clear how the encoding and mirror neuron VLPFC data could be explained by a stopping mechanism, as neither encoding nor imitation involves the inhibition of a motor response. On the other hand, an action updating account of posterior-VLPFC may offer insight into why this region may also be involved in action representation in the mirror neuron system.

While the foregoing analysis suggests that the overlap in fMRI activations implies shared populations of neurons across tasks, it is also possible that there is intra-voxel functional heterogeneity. This issue could be explored by direct within-study comparisons that use repetition suppression strategies<sup>181</sup> to test whether the same populations of neurons are engaged by both tasks. Even if the same neurons are engaged by two classes of tasks (e.g., inhibition and encoding), though, the specific computations performed may fundamentally differ based on the other regions they interact with as part of larger networks.<sup>182</sup> If either of these possibilities were supported it would of course challenge theoretical views that proffer single function-to-structure mappings. To advance theories of right VLPFC function, we need to directly test whether the same populations of neurons are engaged across domains, and, if so, we must consider the broad array of tasks that par-

ticular VLPFC subregions support, being careful to consider mechanisms that could account for this kind of diversity.

Moving forward, the current results provide some initial traction on the pattern of functional specialization within right VLPFC. In particular, we observed that the IFJ responds generally to the onset of behaviorally relevant stimuli, suggesting that this region reflects an interaction between top-down behavioral goals and bottom-up capture by the relevant stimulus.<sup>47,52</sup> In contrast, posterior-VLPFC appears to respond when we must update a prepared action plan in order to engage an alternative response, with stopping being one such instance where this happens. Right mid-VLPFC shows yet another pattern of activity, as it was engaged by stopping specifically under situations with high uncertainty, suggesting an analogous role to the function of left mid-VLPFC.<sup>22-34</sup> Interestingly, though, we did not see clear evidence across any of the tasks for the involvement of right anterior-VLPFC, suggesting that the critical functions performed by this region were simply not captured by the cognitive mechanisms studied here.

As the above summary describes, rich functional heterogeneity exists within right VLPFC, which means that care should be taken when describing patterns of PFC activity in terms of the underlying anatomy. Importantly, future work will need to carefully test our proffered hypotheses about functional specialization, using within-subjects manipulations; we are encouraged that this work has already begun.<sup>68,149</sup> New research projects will also need to expand on these mechanistic accounts to see if they can accommodate findings of right VLPFC activation within other behavioral paradigms. Such work promises to advance understanding of the function-to-structure mapping of right VLPFC, which will ultimately lead to a more complete theory of how the PFC implements control over cognition and behavior.

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## Conflicts of interest

The authors declare no conflicts of interest.

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