Meaningful inhibition: Exploring the role of meaning and modality in response inhibition

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ABSTRACT

We frequently guide our decisions about when and how to act based on the meanings of perceptual inputs: we might avoid treading on a flower, but not on a leaf. However, most research on response inhibition has used simple perceptual stimuli devoid of meaning. In two Go/No-Go experiments, we examined whether the neural mechanisms supporting response inhibition are influenced by the relevance of meaning to the decision, and by presentation modality (whether concepts were presented as words or images). In an on-line fMRI experiment, we found common regions for response inhibition across perceptual and conceptual decisions. These included the bilateral intraparietal sulcus and the right inferior frontal sulcus, whose neural responses have been linked to diverse cognitive demands in previous studies. In addition, we identified a cluster in ventral lateral occipital cortex that was sensitive to the modality of input, with a stronger response to No-Go than Go trials for meaningful images, compared to words with the same semantic content. In a second experiment, using resting-state fMRI, we explored how individual variation in the intrinsic connectivity of these activated regions related to variation in behavioural performance. Participants who showed stronger connectivity between common inhibition regions and limbic areas in medial temporal and subgenual anterior cingulate cortex were better at inhibition when this was driven by the meaning of the items. In addition, regions with a specific role in picture inhibition were more connected to a cluster in the thalamus/caudate for participants who were better at performing the picture task outside of the scanner. Together these studies indicate that the capacity to appropriately withhold action depends on interactions between common control regions, which are important across multiple types of input and decision, and other brain regions linked to specific inputs (i.e., visual features) or representations (e.g., memory).

Introduction

The emergence of adaptive human behaviour requires the co-ordinated action of multiple brain regions to achieve complex goals. When our goals require stimulus-response contingencies that align well with our past experiences, representations in memory may be sufficient to guide action. For example, we know stinging nettles hurt if they are touched – and processing along the ventral visual to semantic pathway allows us to apparently effortlessly avoid these plants when picking berries. In other situations, successful execution of our goals requires us to diverge from the response that was typical in the past. For example, if we decide to deliberately pick stinging nettles in order to clear a path, we must over-ride our pre-potent response based on our past experience with these plants. These different types of behavioural control are likely to rely to differing degrees on the multiple-demand network – a set of

distributed brain regions which show a common pattern of activation across a broad range of tasks that require cognitive control (Duncan, 2001, Duncan, 2010). The multiple-demand network includes inferior frontal sulcus (IFS), intraparietal sulcus (IPS) and pre-supplementary motor area (pre-SMA) bilaterally. These regions respond across multiple domains and paradigms when there is a requirement to produce flexible patterns of behaviour not supported by long-term memory; for example, when we follow arbitrary stimulus-response mappings provided in the task instructions, or when we change or inhibit a response that is already established.

While multiple-demand regions show patterns of common activation across diverse tasks (Cole et al., 2013; Crittenden and Duncan, 2014; Crittenden et al., 2016; Fedorenko et al., 2013), less is known about the degree of functional specialization within this network (see Banich and Depue, 2015, for a review). Distinctions between multiple-demand

regions can reflect different processes, such as the distinction between goal-driven attention (dorsal attention network) and stimulus-driven attention (ventral attention network) (Corbetta and Shulman, 2002), or the distinction between a fronto-parietal network (inferior frontal sulcus and intraparietal sulcus) and a separate cingulo-opercular network engaging the dorsal anterior cingulate, anterior insula and the anterior prefrontal cortex (Crittenden et al., 2016; Dosenbach et al., 2008). Evidence for heterogeneity also comes from the degree of lateralization in neural processing linked to the application of control to different domains. The inhibitory control of behaviour, for example, is linked to right-lateralised multiple-demand areas and bilateral pre-SMA (Aron et al., 2004, Aron et al., 2014; Criaud and Boulinguez, 2013; Garavan et al., 1999). The importance of right-hemisphere structures in response inhibition is supported by clinical and lesion studies (Aron et al., 2003; Bellgrove et al., 2006; Chambers et al., 2006; Floden and Stuss, 2006; Mostofsky and Simmonds, 2008; Picton et al., 2007). In contrast, the application of control to semantic information engages a strongly-left lateralised network that involves left inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG) and dorsal angular gyrus/intraparietal sulcus (AG/IPS, Lambon Ralph et al., 2016; Noonan et al., 2013). Neuroimaging studies show recruitment of this left-lateralised network across multiple tasks when controlled semantic decisions are contrasted with more automatic semantic retrieval (Badre et al., 2005; Krieger-Redwood et al., 2015; Noonan et al., 2013; Thompson-Schill et al., 1997). The role of left hemisphere regions in controlled semantic retrieval is also supported by evidence that infarcts in these regions lead to problems in shaping semantic activation to suit the task or context (Jefferies and Lambon Ralph, 2006; Jefferies, 2013; Noonan et al., 2010). Finally, regions that support cognitive control may also be functionally segregated by their association with particular input modalities (Duncan, 2010). For example, lateral occipital complex in the multiple-demand network is activated by difficult tasks, yet this region is also important for object recognition and shape processing (Cant and Goodale, 2007; Grill-Spector et al., 2001; Kim et al., 2009). This region might support difficult tasks by maintaining task-relevant visual features. Nonetheless, intrinsic connectivity measures show coupling between lateral occipital cortex and other multiple-demand network regions, suggesting that these regions form a network even in the absence of a task (Crittenden and Duncan, 2014; Stiers et al., 2010).

The present study explored the functional heterogeneity of the multiple-demand network in two experiments using functional magnetic resonance imaging (fMRI). In both studies, we used a Go/No-Go paradigm in which participants were asked to withhold their responses to infrequent targets. In some blocks the No-Go targets were defined based on the meaning of the stimulus (whether it was an animal or a man-made object), while in other blocks No-Go targets were defined by perceptual features (the degree of slant of a box). We searched for regions that showed a different response to inhibition demands depending on the nature of the decision (semantic vs. perceptual) or the modality of the input (words vs. pictures). Since the categorisation of pictures is typically faster than the categorisation of words (Bajo, 1988; Kiefer, 2001; Potter and Faulconer, 1975), the control blocks varied in difficulty, to provide a more balanced design. Experiment 1 measured neural activity online using task-based fMRI, while Experiment 2 explored whether individual differences in behavioural performance across conditions were related to patterns of intrinsic connectivity using resting-state fMRI. Experiment 1 allows us to characterise the neural response that supports response inhibition as it varies with respect to the relevance of meaning and the modality of presentation. Experiment 2 allows us to identify the patterns of intrinsic connectivity at rest that support variation in how effectively these different processes can be engaged.

Methods

This study was approved by the University of York Neuroimaging Centre and by the Department of Psychology ethics committees. All

volunteers provided informed written consent.

Design

Experiment 1 used on-line fMRI to characterise the neural response to Go/No-Go tasks based on different types of decisions (semantic vs. perceptual) and inputs (words vs. pictures). Participants were scanned whilst performing a Go/No-Go task lasting for 26 min. We examined contrasts of No-Go over Go events for semantic and non-semantic trials, to identify a commonly-recruited network. We also computed interactions between the Go/No-Go contrast and the role of meaning (semantic vs. non-semantic decisions), plus the effect of stimulus type (words vs. pictures).

Experiment 2 focused on resting-state functional connectivity. In this experiment, a group of participants for whom we had already collected resting state data were invited to come into the laboratory to perform the same inhibitory control tasks. We investigated whether the functional connectivity of the regions activated in Experiment 1 would predict individual variation in performance on these tasks. Participants took part in a 9 min functional MRI resting state scan where they viewed a central fixation cross on a grey screen. On a separate session, they performed the Go/No-Go task outside the scanner for 26 min. Individual differences in intrinsic connectivity were then related to behavioural performance on the Go/No-Go task measured outside the scanner. For this experiment, we used activation maps from Experiment 1 as seed regions (details of this approach are provided in Sormaz et al., 2017).

Participants

For Experiment 1, we tested 34 right-handed, native English-speakers with normal or corrected to normal vision, with no history of neurological or psychiatric illness. One participant was excluded due to not understanding the instructions and performing the task incorrectly, another two were excluded due to excessive motion artefacts (>5 mm in at least one run),[1] and four due to problems during MRI acquisition (failure to record the onset time for stimuli), leaving a final sample size of 27 (mean age = 20.7, 19 females). For Experiment 2, an additional 60 participants (14 of whom had already performed the first experiment) were recruited (mean age = 20.2, 37 females). We used a separate sample of 145 participants (mean age = 20.5, 96 females) in whom we recorded structural MRI and intrinsic connectivity at rest (for details of acquisition see Sormaz et al., 2017), to examine the intrinsic connectivity of regions identified in Experiments 1 and 2. This sample did not overlap with the participants in Experiment 1 and 2.

Materials

Go/no-go paradigm

The participants took part in a Go/No-Go task designed to probe semantic inhibition. Each trial consisted of a fixation cross, followed by the stimulus. The duration of the fixations and stimuli were jittered between 0.5-1s and 0.75–1.25s for fixation and stimulus respectively. The stimuli consisted of pictures/words framed by a box that was slanted to different degrees (slight slant, medium slant or pronounced slant).

The task was divided into three blocks: in the 'Word' blocks, the participants saw a series of words referring to either animals or man-made objects, while in the 'Picture' blocks, they saw pictures depicting

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[1] At the request of a reviewer, we re-analysed the data excluding all runs where a participant showed an absolute mean displacement greater than 1 mm. The results of this re-analysis are similar: there was one additional cluster for the Picture > Word interaction term in left fusiform gyrus – i.e., this effect became bilateral. No other clusters deviated in important ways from the previous analysis. The results of this re-analysis are publically available in Neurovault (https://neurovault.org/collections/3158/).

these same categories; their task was to press a button every time they saw a word or picture referring to a man-made object (Go event), and refrain from pressing when they saw an animal (No-Go event). In the 'Perceptual' (non-semantic) blocks, stimuli were scrambled images generated from the word and picture stimuli ensuring that basic features like luminance were constant across the experiment (See the 'Stimuli Generation' section for details). In this condition, participants were asked to inhibit responses when they saw that the framing box was more slanted than usual (No-Go event) and to press the button for the usual, slight degree of slant (Go event). This last condition was further sub-divided in Easy and Hard trials based on the degree of slant: The Easy trials involved discriminating between slight and pronounced slants, while the Hard trials involved discriminating between the slight and medium slants (this was harder to do, as there was only a slight difference between them). This manipulation was included to provide perceptual decisions that matched in difficulty to both word and picture semantic trials. Examples of the Go and No-Go trials, as well as the behavioural results from the paradigm are presented in Fig. 1.

For Experiment 1, neural data was recorded in six blocks (two for each condition) containing 46–54 stimuli each, with the order of blocks counterbalanced across participants. Each block contained 80% Go events and 20% No-Go events. We divided these into two 3-block runs, each lasting 13 min. The distribution of Go and No-Go events within the blocks was pseudorandomised, with 1–6 Go events between No-Go events. Each block started with a cue to inform the participant which type of stimuli to expect, and ended with a screen informing the participant they had a 5 s break before the next block. In Experiment 2, participants performed these same 6 blocks, but in a single 26-min session. Our design made it necessary to trade off the number of No-Go events with the strength of the inhibition effect (which is maximised by having predominately Go events and relatively few No-Go events). We opted for approximately 20 No-Go events against 80 Go events per condition.

Stimuli Generation

In order to ensure the stimuli could be clearly distinguished as man-made or animal, we presented images from the *Bank of Standardized Stimuli* (Brodeur et al., 2010, 2014) to four native British English speakers, who provided as many names as possible for each picture, and decided if the item belonged to the category of animal or man-made object. Based on this, we chose a subset of pictures given a single non-ambiguous word as a name (i.e., with a single meaning). This provided 174 pictures of man-made objects and 51 of animals. Subsequently, we used independent samples t-tests to verify that the names assigned to

the man-made objects and animals did not differ significantly in lexical frequency and letter length using Celex implemented in N-Watch (Davis, 2005). There were no significant differences in lexical frequency (man-made objects: M = 13.1 counts per million, SD = 22.6; animals: M = 12.0, SD = 27.5; t (219) < 1), or letter length (man-made objects: M = 6.2, SD = 2.1; animals: M = 6.1, SD = 2.2; t (219) < 1). The scrambled images were derived from these selected picture and word trials. We submitted the original pictures to a scrambler that broke them down in 160 equilateral 'tiles', and then randomly assigned a place to each tile to create a scrambled image of 40 × 40 tiles where no meaning was discernible. We did the same for the visually-presented words used in the word condition. The resulting scrambled pictures constituted the stimuli of the Perceptual trials.

Image acquisition

Structural and functional data were acquired using a 3T GE HDx Excite MRI scanner utilising an eight-channel phased array head coil (GE) tuned to 127.4 MHz, at the York Neuroimaging Centre, University of York. Structural MRI acquisition in all participants was based on a T1-weighted 3D fast spoiled gradient echo sequence (TR = 7.8 ms, TE = minimum full, flip angle 20°, matrix size = 256 × 256, 176 slices, voxel size = 1.13 × 1.13 × 1 mm). Task-based and resting-state activity was recorded using single-shot 2D gradient-echo echo planar imaging (EPI) with a flip angle = 90°, TE = minimum full, voxel size = 3 × 3 × 3 mm^3. Other scan parameters slightly varied for task-based fMRI (field of view (FOV) = 192 mm^2, TR = 2000 ms, matrix size = 64 × 64 x 38 slices, 376 vol per run, for a total of 2 runs) and resting-state fMRI (whole brain, TR = 3000 ms, matrix size = 64 × 64 x 60 slices 180 vol). An intermediary FLAIR scan with the same orientation as the functional scans was collected to improve the co-registration between subject-specific structural and functional scans.

Data pre-processing and analysis

Task-based fMRI

Analyses were conducted at the first and higher level using FSL-FEAT version 6.0, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Pre-processing included slice timing correction using Fourier-space time-series phase-shifting (interleaved), motion scrubbing (using the fsl_motion_outliers tool) to identify volumes that exceeded a threshold of 0.9 using framewise displacement as the metric, which then were entered
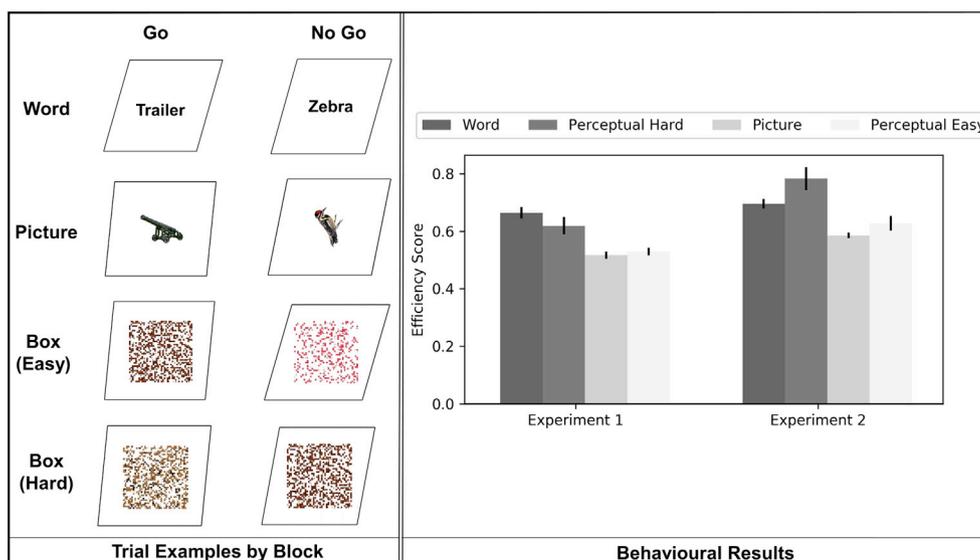
Fig. 1. The left-hand panel depicts example stimuli per block. In WORD blocks, participants pressed for words denoting man-made objects and withheld this response for words denoting animals. In PICTURE blocks, participants pressed for pictures of man-made objects and withheld this response for pictures of animals. In BOX blocks, participants pressed for slightly slanted boxes and withheld this response for more strongly slanting boxes. Difficulty in the BOX trials was manipulated by adjusting the size of the slant. The right-hand panel shows behavioural results for the Go/No-Go paradigm expressed as efficiency scores (a proportion of reaction time divided by accuracy). The error bars depict the standard error of the mean. In Experiment 1, the task was performed inside the scanner, while in Experiment 2 it was performed outside.

as confounds, motion correction using MCFLIRT (Jenkinson et al., 2002), high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50s), brain extraction (Smith, 2002), linear co-registration to the corresponding T1-weighted image followed by linear co-registration to MNI152 standard space using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002), spatial smoothing using a Gaussian kernel with full-width-half-maximum (FWHM) of 5 mm and grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor.

Pre-processed time series data were modelled using a general linear model, using FILM correcting for local autocorrelation (Woolrich et al., 2001). We used an event-related design – the linear model included ten Explanatory Variables (EV): Button presses and Instruction screens, which were modelled to control and exclude from the contrasts of interest, and Go and No-Go events for each of the three conditions: Word, Picture and Perceptual (i.e., non-semantic control), which was subdivided into Easy and Hard.

Our analysis focused on the comparison of inhibition events involving different types of judgements (semantic and perceptual) and different modalities of presentation (pictures and words). We examined the main effect of inhibition for the tasks separately: Semantic No-Go > Go (collapsing across word and picture trials), and Perceptual No-Go > Go (collapsing the easy and hard trials). We were then able to identify common inhibition regions via a formal conjunction analysis, using FSL's 'easythresh_conj' tool (Nichols et al., 2005). We also examined main effects of task type: Semantic > Perceptual; Words > Pictures and the reverse. Most importantly, we defined interaction terms to examine differential effects of the No-Go > Go contrast between words and pictures, and between matched sets of semantic and perceptual conditions (Picture and Perceptual Easy, Word and Perceptual Hard). At the group-level, analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME1) stage 1 with automatic outlier detection (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008), using a (corrected) cluster significance threshold of p = 0.05, with a z-statistic threshold of 3.1 (Eklund et al., 2016) to define contiguous clusters.

While the analyses below focus on whole-brain contrasts, in Supplementary Analyses, we also examined regions of interest defined by prior studies. First, we examined the same contrasts within the semantic control network, defined by the meta-analysis of Noonan et al. (2013; Supplementary Analysis 1). Secondly, we examined activation within spherical regions of interest (3 mm in radius) placed at key sites in the multiple-demand system defined by Duncan (2010; Supplementary Analysis 2).

Resting-state fMRI

Analyses were conducted at the first and higher level using FSL-FEAT version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Pre-processing steps were as for task-based fMRI, except for Gaussian low-pass temporal filtering, with sigma = 2.8s, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 100.0s), no motion scrubbing, and spatial smoothing using a Gaussian kernel with FWHM of 6 mm. Regions of Interest (ROI) were taken from the task-based fMRI results (see Results section), and binarised using FSL Maths. We extracted the time series from each ROI mask and used these as explanatory variables in connectivity analyses at the single subject level. In each analysis, we entered 11 nuisance regressors; the top five principal components extracted from white matter (WM) and cerebrospinal fluid (CSF) masks based on the CompCor method (Behzadi et al., 2007) and six head motion parameters. WM and CSF masks were generated from each individual's high resolution structural image (Zhang et al., 2001). No global signal regression was performed, following the method implemented in Murphy et al. (2009). At the group-level, analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME1)

Table 1

Response time and accuracy for the Behavioural Data. Note. Means with standard deviations in parentheses. RT on Go trials (i.e., when a response was required) is shown in seconds. Accuracy on No-Go trials (i.e., the successful suppression of a pre-potent response) is given as a percentage of trials.

Condition	Experiment 1 (n = 27)		Experiment 2 (n = 60)	
	RT	Accuracy	RT	Accuracy
Word	0.43 (0.04)	66.27 (12.51)	0.51 (0.05)	75.65 (11.97)
Picture	0.42 (0.07)	81.33 (12.35)	0.51 (0.06)	87.77 (8.87)
Perceptual Easy	0.41 (0.05)	79.05 (9.06)	0.49 (0.07)	81.06 (16.19)
Perceptual Hard	0.42 (0.06)	71.12 (17.98)	0.50 (0.07)	70.22 (17.87)

with automatic outlier detection (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008), using a cluster correction (p < .05), and a threshold of z = 3.1 to define contiguous clusters at the group level. This analysis included behavioural regressors (efficiency scores for each condition, i.e. No-Go accuracy/Go RT) to evaluate whether performance correlated with individual differences in intrinsic connectivity, and a motion regressor using the mean (across time/frames) of the absolute values for framewise displacement for each participant. The connectivity maps resulting from these analyses were uploaded to Neurovault (Gorgolewski et al., 2015, URL: https://neurovault.org/collections/3158/) and decoded using Neurosynth (Yarkoni et al., 2011), allowing us to extract key terms associated with each connectivity pattern.

*Decoding and automated meta-analysis using neurosynth (Yarkoni et al., 2011)*

Neurosynth is an automated meta-analysis tool that associates spatial activation maps with descriptive terms from the neuroimaging literature. It uses text-mining tools to extract high frequency terms taken from the abstract and main body of neuroimaging articles and associates them with peak coordinates of activation (following certain criteria, such as only including terms used in at least 20 studies). In this way, it can generate 'reverse inference' maps associated with a particular term, such as "semantic". These maps show regions that are more likely to be activated for that particular term than for others (this approach was used in Fig. 9, Step 3). It can also be used to generate a set of terms frequently associated with a spatial map. This approach is used in Fig. 9, Steps 1 and 2. In presenting these results as word clouds, we manually excluded terms referring to neuroanatomy (e.g., "inferior" or "sulcus"), as well as repeated terms (e.g., "semantic" and "semantics"). The size of each word in the word cloud relates to the frequency of that term across studies.

Results

Behavioural results

We combined reaction time (RT) on Go events and the accuracy of participants' responses on No Go events into an efficiency score (a ratio of a participant's RT divided by accuracy) for each condition. Table 1 provides descriptive statistics for RT and accuracy, while response efficiency is shown in Fig. 1 (see Methods section).

In Experiment 1, the Word trials were more demanding than the Picture trials t (26) = 8.83, p < 0.0001 (see Fig. 1). Behavioural performance was matched for Word and Perceptual Hard conditions (t (26) = 1.68, p = 0.11), and Picture and Perceptual Easy conditions (t (26) = −0.84, p = 0.41). This pattern was mostly replicated in Experiment 2. There was a significant difference in the efficiency score for Word and Picture conditions (t (59) = 9.37, p < 0.0001). Again, there were no significant differences between the Picture and Perceptual Easy conditions (t (59) = −1.77, p = 0.082), but the difference between the Word and Perceptual Hard conditions was significant (t (59) = −2.52, p < 0.05).
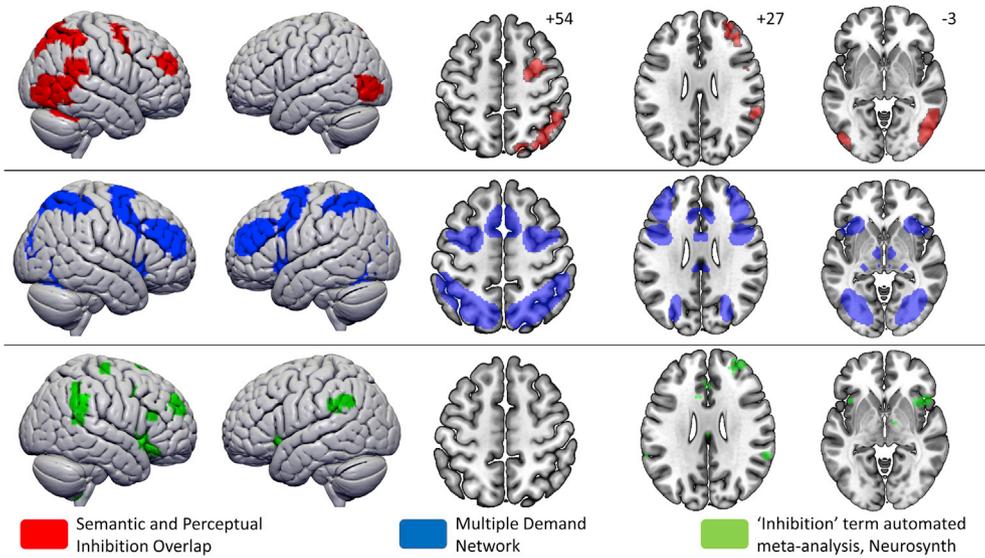
Fig. 2. Comparison of the neural activation from a formal conjunction of Semantic and Perceptual response inhibition (i.e., No-Go > Go trials; shown in red) with the multiple-demand network (shown in blue) and an automated meta-analysis of inhibition studies (shown in green). The semantic and perceptual inhibition maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05. Their conjunction was identified using FSL's 'easy-thresh_conj' tool.

fMRI results

Our fMRI analysis was performed in three separate steps. We first conducted task-based fMRI analysis, identifying areas that were involved in semantically and perceptually-guided inhibition, as well as any differences between semantic and perceptual processing, and any interactions between the Go/No-Go contrast and modality (Word and Picture) and/or difficulty (Perceptual Hard and Easy). Next we conducted resting-state functional connectivity analysis using the results from the task-based fMRI analysis as seeds, in order to identify regions whose functional connectivity with the seed predicted behavioural performance in the lab; in a separate dataset, we also described the intrinsic functional connectivity of the regions that were identified in these analyses. Finally, we decoded the resting state functional connectivity group maps using Neurosynth, an automated meta-analysis tool (Yarkoni et al., 2011), to obtain psychological terms associated with the patterns of activation in our results.

Experiment 1: task-based fMRI results

A comparison of the Semantic No-Go > Go and Perceptual No-Go > Go contrasts revealed overlapping networks that were lateralised to the right hemisphere. We compared the formal conjunction of semantic and perceptual inhibition contrasts with the multiple-demand network (map taken from Fedorenko et al., 2013) and a term-based, automated meta-analysis of inhibition from Neurosynth (Yarkoni et al., 2011). This is shown in Fig. 2. Both semantic and perceptual inhibition overlapped with the multiple-demand network in right intraparietal sulcus, right inferior frontal sulcus, and bilateral lateral occipital cortex. Both of these No-Go > Go contrasts also overlapped with the automated meta-analysis for inhibition in the right frontal pole and supramarginal gyrus. The interaction between semantic and perceptual inhibition (i.e. Semantic No-Go > Go > Perceptual No-Go > Go) yielded no significant clusters. Together these analyses show that semantic and perceptual inhibition recruit broadly the same right-lateralised regions of the multiple-demand network, and regions commonly engaged in general inhibition.

Having identified regions that show common neural activity for semantic and perceptual inhibition, we next examined whether the modality and/or meaningful content of the stimulus is important in determining the neural activity during response inhibition. Although the interaction between semantic and perceptual inputs and inhibitory demands (No-Go vs. Go) yielded no significant clusters, we did find significant differences in the areas that responded to semantic stimuli
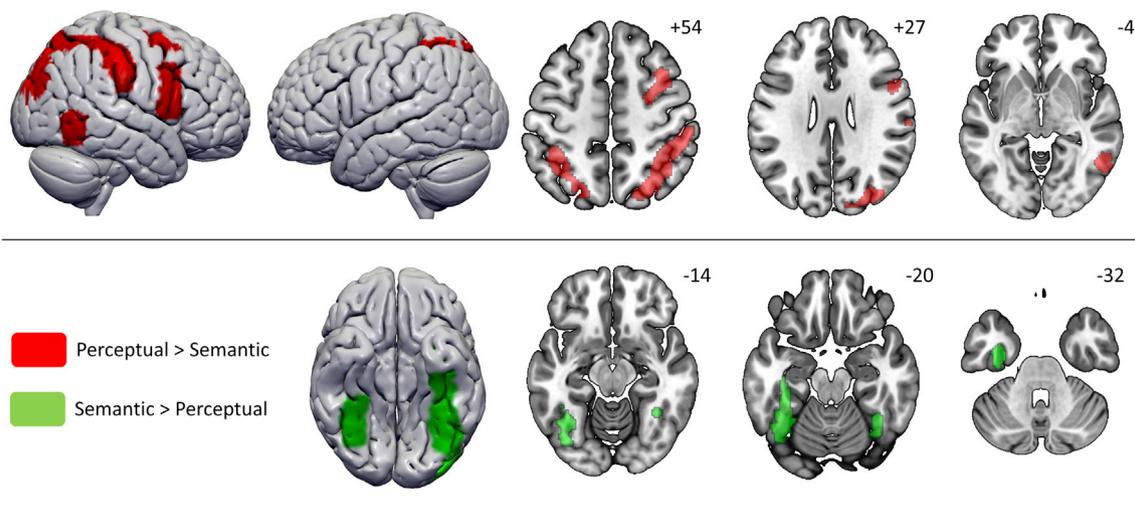
Fig. 3. Comparison between semantic and perceptual stimuli processing. Parietal, frontal and occipital regions involved in processing perceptual more than semantic stimuli, and temporal regions processing semantic more than perceptual stimuli. Both the semantic > perceptual and the perceptual > semantic result maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05.
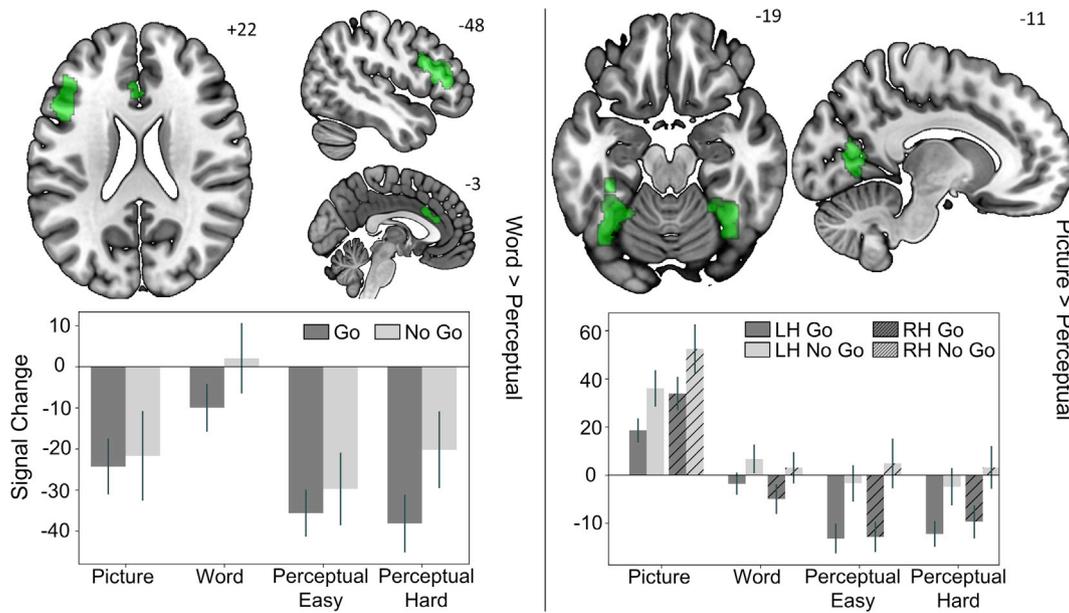
Fig. 4. Activation associated with word and picture trials. There was activation in left inferior frontal gyrus/anterior cingulate cortex for words (two clusters), and in bilateral fusiform for pictures, relative to non-semantic trials; z > 3.1, p < .05. The bar charts plot signal change for the specified contrast as a function of condition, with the error bars depicting the standard error of the mean.

(regardless of whether they were Go or No-Go trials) compared to the perceptual baseline and vice versa (Fig. 3). Right-sided inferior and middle frontal gyri, superior lateral occipital cortex and posterior middle temporal gyrus, as well as bilateral intraparietal sulcus, were more active for perceptual than semantic trials. Conversely, regions of bilateral fusiform cortex, extending into left anterior temporal lobe, were more active for semantic than perceptual trials.

We next focused on the semantic stimuli and considered whether there were differences in activation that reflected the modality of presentation. Contrasts of each modality against the perceptual baseline (Word > Perceptual, Picture > Perceptual) revealed two significant results: left IFG and bilateral anterior cingulate cortex showed increased activation when stimuli were presented as words compared to the perceptual baseline, while bilateral fusiform gyri and left intracalcarine cortex/lingual gyrus were more active in response to pictures than perceptual trials (Fig. 4). In addition, the contrast of Picture > Word revealed bilateral fusiform cortex (Fig. 6). These clusters overlapped with

the bilateral fusiform regions revealed by the contrast of Picture > Perceptual. The direct contrast of Word > Picture revealed no significant clusters.

To identify any regions that showed a differential response to inhibitory demands for either words or pictures, we considered the interaction of modality and inhibition. This analysis identified a region in right occipital cortex that was more active when inhibition was driven by pictures compared with words (Fig. 5). An examination of the parameter estimates suggested that the neural activity was highest in the picture condition and lowest in the word condition. Fig. 6 shows a comparison of this cluster with the main effects of input modality (Pictures > Words) and inhibition (No-Go > Go conjunction across conditions). Much of the interaction cluster fell within the region showing a main effect of modality (Pictures > Words). The interaction cluster also overlapped with regions implicated in inhibition across conditions.

Finally, since the analysis above failed to identify a role for left-lateralised semantic control regions (e.g., left inferior frontal cortex) in
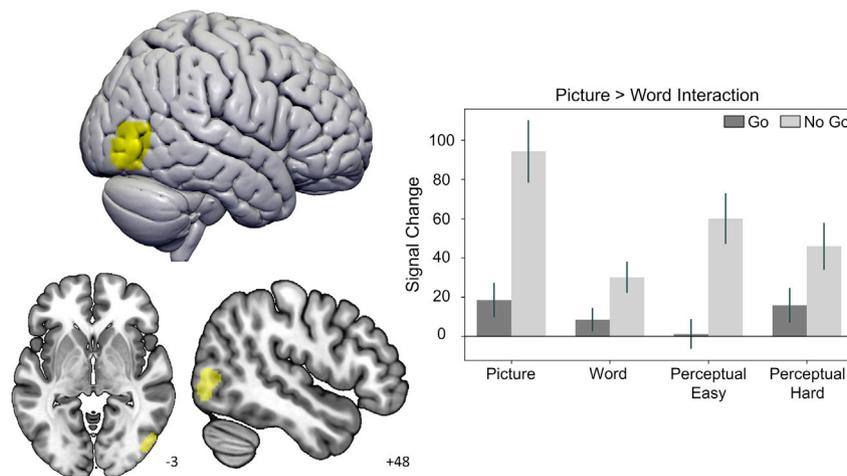
Fig. 5. Regions showing a stronger response to inhibition events that were picture-based rather than verbal. All maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05. The bar charts plot signal change for the specified contrast as a function of condition, with the error bars depicting the standard error of the mean.

semantically-guided inhibition, we performed the same contrasts within a mask encompassing areas important for semantic control from a meta-analysis (Noonan et al., 2013), to reduce the probability of a Type II error. This analysis yielded clusters in left inferior frontal gyrus, similar to the one shown in Fig. 4, for the main effects of words vs. perceptual decisions, pictures vs. perceptual decisions and semantic vs. perceptual decisions (see Supplementary Analysis 1 and Supplementary Figure S1). These effects overlapped in mid-IFG, consistent with a role for this region in semantic processing across modalities. However, there were no interactions between inhibitory demands and modality or task.

Experiment 2: Resting-state functional connectivity analysis

Experiment 1 demonstrated patterns of common and distinct neural activity supporting the different types of response inhibition measured by our paradigm. We found that across conditions, response inhibition is guided by right-lateralised areas that overlap with the multiple-demand network. In addition, we found a region of right lateral occipital cortex that was especially important when response inhibition was driven by the semantic properties of pictures as opposed to words. In Experiment 2 we sought to investigate whether the intrinsic connectivity of these regions at rest was predictive of performance on response inhibition at a later time-point. We would expect the connectivity between general inhibition regions and modality- or task-specific regions to relate to the efficiency of inhibitory control for specific kinds of input. To test this hypothesis, we first performed a whole brain functional connectivity analysis using these regions as seeds, and then used efficiency scores for the different inhibition conditions as regressors in a group level regression.

First, we took general inhibition regions that responded to No-Go more than Go events in Experiment 1 as a seed region. The seed was defined by the conjunction of semantic and perceptual inhibition and included clusters in prefrontal cortex, intraparietal cortex and bilateral lateral occipital cortex. These regions showed stronger intrinsic connectivity to clusters in medial temporal and sub-callosal cortex related to better inhibition on semantic relative to perceptual trials (Fig. 7).
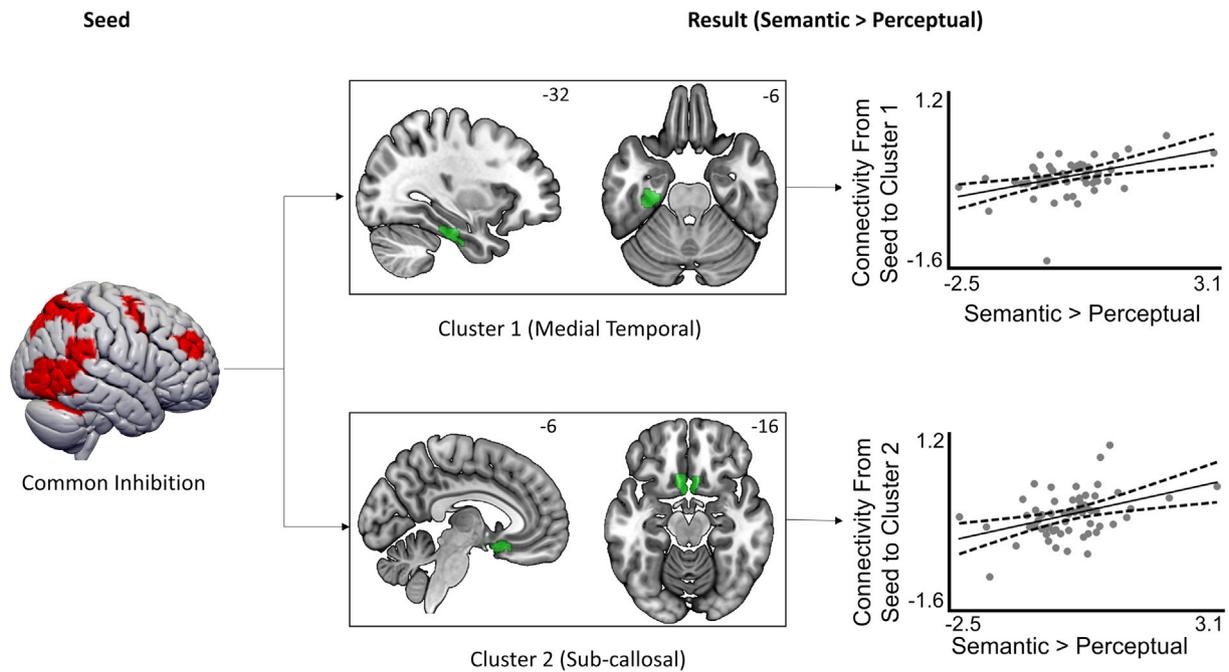
A second seed region in right lateral occipital cortex was defined by the interaction between modality and inhibition demands in Experiment 1. A whole-brain behavioural regression analysis for this seed revealed no clusters. However, the same analysis within a small volume defined by the multiple-demand network revealed stronger intrinsic connectivity to a cluster in thalamus/caudate for participants who were more efficient at inhibiting responses to pictures compared with both words and the matched perceptual condition. The clusters for these two effects showed a high degree of overlap (Fig. 8).

In a final step, we performed resting-state functional connectivity analysis in a separate sample of 145 healthy undergraduate participants available at the University of York and decoded the resulting maps using Neurosynth (Yarkoni et al., 2011). We first examined the intrinsic connectivity of the inhibition overlap from Experiment 1. Decoding this connectivity map yielded terms associated with cognitive control (Fig. 9, Step 1). Next we characterised the intrinsic connectivity of the behavioural regression result obtained from this seed in Experiment 2; i.e., regions that showed greater connectivity in participants with better semantic than perceptual inhibition (Fig. 9, Step 2). Decoding this connectivity map yielded terms associated with memory. This connectivity pattern also substantially overlapped with the meta-analytic map for the term "semantic" from Neurosynth (Fig. 9, Step 3). These results suggest that good semantically-guided inhibition is associated with greater coupling between domain-general inhibition regions and sites implicated in memory and meaning.

The lateral occipital cortex interaction cluster from Experiment 1 showed a pattern of connectivity associated with visual processing (Fig. 10, Step 1). The pattern of intrinsic connectivity from the behavioural regression cluster in Experiment 2, which was associated with relatively good picture-based inhibition, showed substantial overlap with the multiple-demand network (Fig. 10, Steps 2 and 3). Neurosynth's decoding tool revealed terms associated with motivation (Fig. 10, Step 2). Therefore, good picture-based inhibition was associated with greater coupling between visual cortex and regions implicated in the control of behaviour.
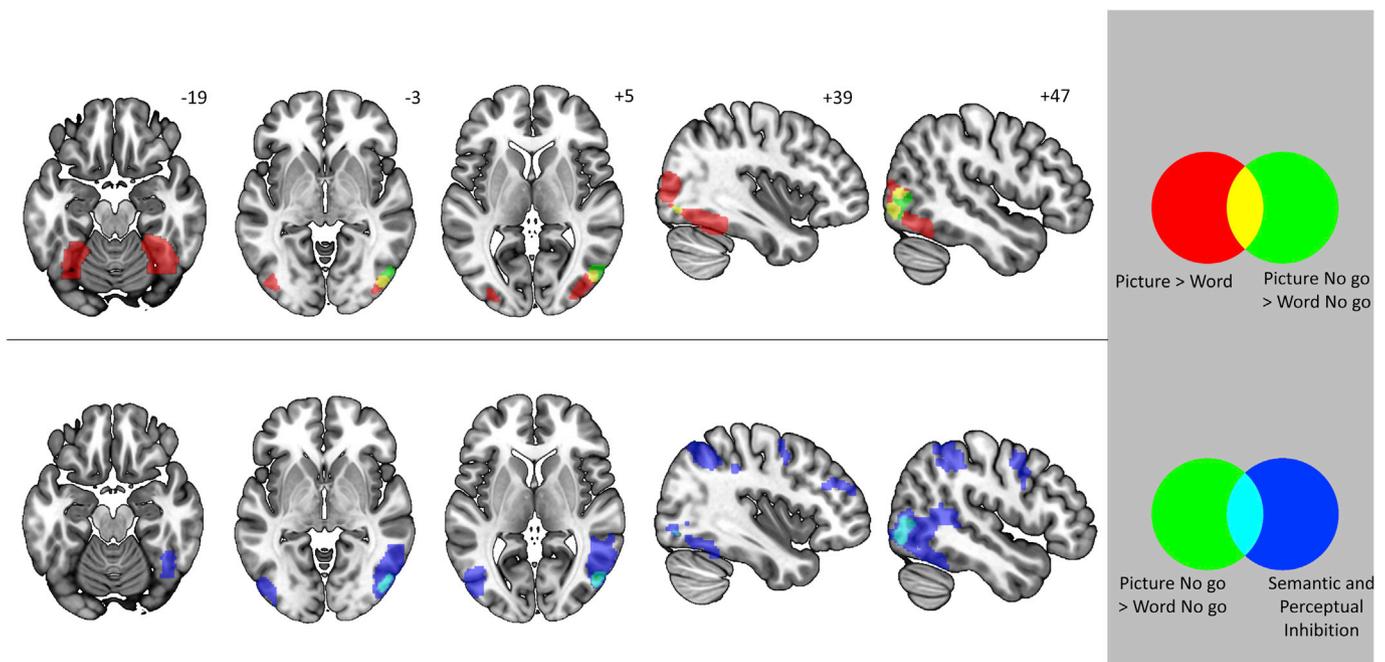
Fig. 6. A comparison of the interaction cluster for picture-based inhibition with (i) the main effect for Pictures > Words (top row) and (ii) the inhibition conjunction (No-Go > Go across semantic and perceptual conditions; bottom row). All maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05.

Seed   **Result (Semantic > Perceptual)**

Common Inhibition

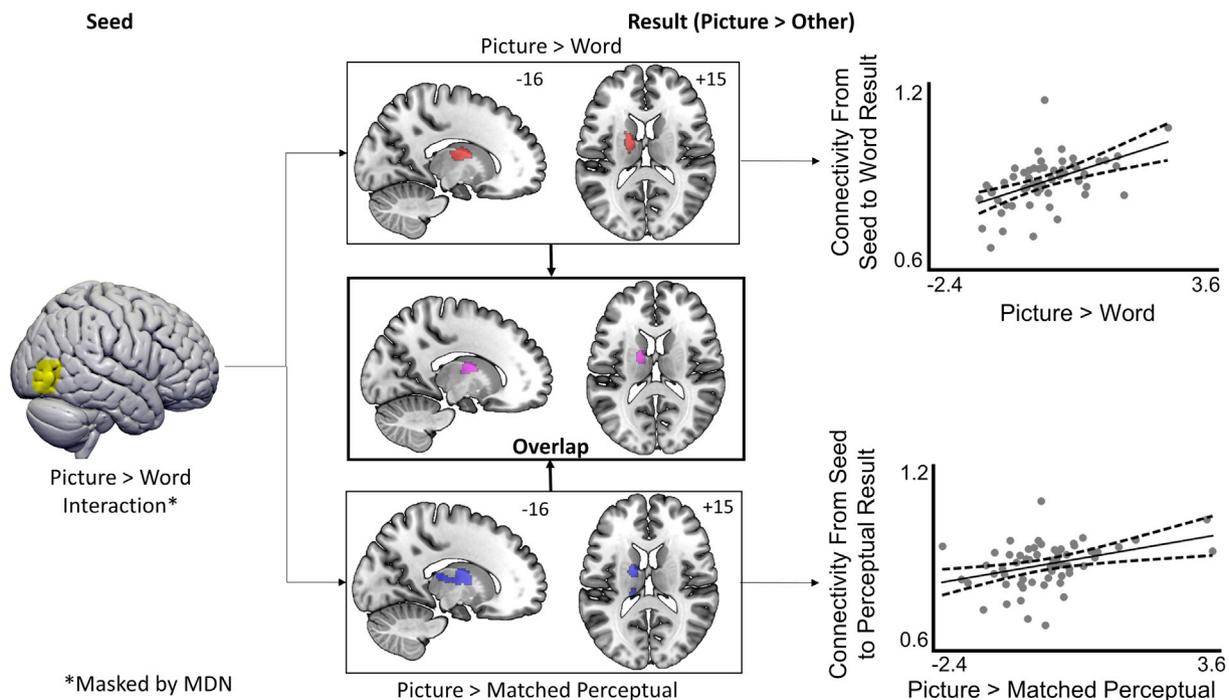Cluster 1 (Medial Temporal)

Cluster 2 (Sub-callosal)

Fig. 7. Results of a whole brain functional connectivity analysis indicating regions of heightened connectivity associated with differential performance on semantic and perceptual inhibition tasks. This identified two clusters, in medial temporal and sub-callosal cortex, which showed stronger functional connectivity for people who were better at semantic than perceptual inhibition. All maps were thresholded at $z > 3.1$ ($p < 0.05$).

Discussion

Inhibition activates regions implicated in cognitive control across domains (Criaud and Boulinguez, 2013; Duncan, 2010; O'Connell et al., 2007; Simmonds et al., 2008). However, inhibitory control can be guided by different types of inputs and representations. In two experiments, we used task and resting-state fMRI to examine whether the inhibitory control of behaviour recruits different neural networks depending on (i) the nature of the task (e.g., whether semantic or perceptual features determine the

response) and (ii) the modality of the stimulus (e.g., whether items are presented as written words or pictures). We considered three alternative hypotheses. (i) There may be little or no difference in the No-Go > Go response across conditions: all tasks might activate right-lateralised regions in the multiple-demand network, irrespective of stimulus meaning and modality, reflecting shared cognitive control processes. (ii) There could be a shift towards left-lateralised regions implicated in semantic control when item meaning determines when a response must be withheld. By this view, although response inhibition paradigms commonly

Seed   **Result (Picture > Other)**

Picture > Word

Picture > Word
Interaction*

Overlap

Picture > Matched Perceptual

*Masked by MDN

Fig. 8. Functional connectivity analysis indicating regions of heightened connectivity associated with more efficient inhibition for pictures vs. words and for pictures vs. matched perceptual stimuli. These two clusters were highly overlapping. All maps were thresholded at $z > 3.1$ ($p < 0.05$). MDN = Multiple-demand network.

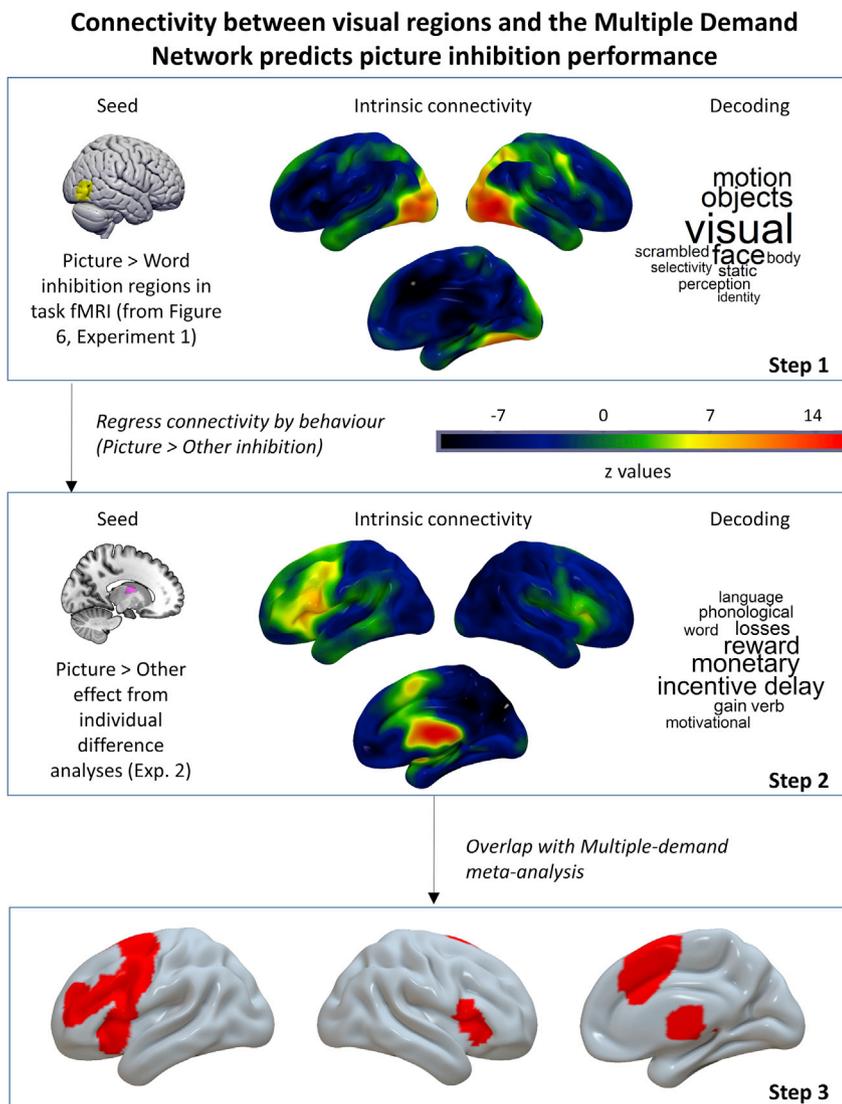## Connectivity between common inhibition and semantic regions predicts semantically guided inhibition
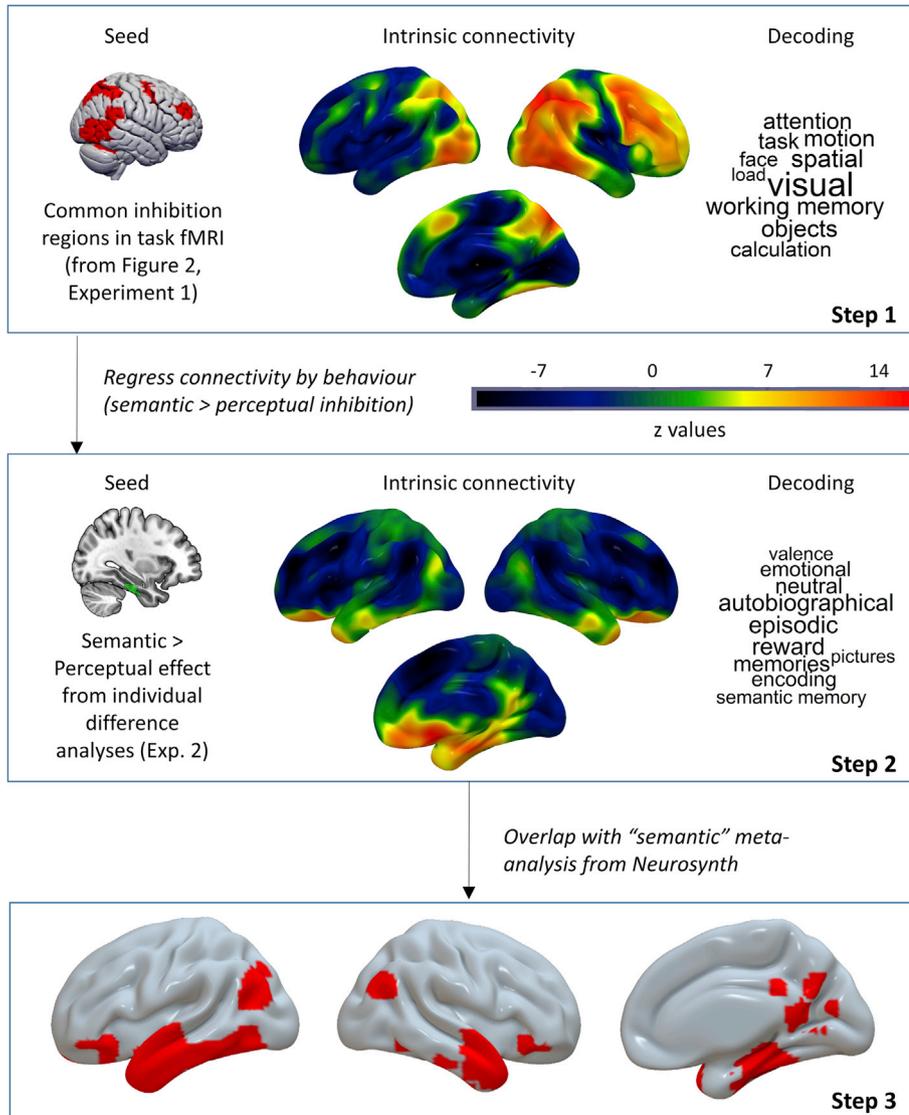
Fig. 9. Summary of the pattern of connectivity linked to good semantic inhibition. The top row (Step 1) shows the unthresholded z-statistic intrinsic connectivity map for the common inhibition regions identified using task-based fMRI in Experiment 1, which were used as a seed in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to visual attention. The middle row (Step 2) shows the unthresholded z-statistic intrinsic connectivity map for significant clusters obtained from resting-state behavioural regressions in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to memory. The bottom row (Step 3) shows an overlap of the resting-state group maps from Step 2 with a meta-analytic map for the term 'Semantic' from Neurosynth. Better semantic inhibition was linked to increased connectivity between domain-general inhibition regions and memory regions in medial temporal/ventral prefrontal regions. For further details about Neurosynth decoding and meta-analysis, see Methods and Yarkoni et al. (2011).

activate a right-lateralised executive network, this lateralization might be reduced or reversed in the semantic conditions. (iii) Given Go/No-Go tasks are thought to involve attentional processes and working memory, we might expect modulation of activation in regions associated with input processing or the representation of features relevant for determining the appropriate response: for example, visual regions implicated in object recognition might show a stronger response when the features of visually-presented objects determine when to respond.

In our task-based study, we found support for the first and last of these hypotheses. First, we found that inhibition based on either semantic or perceptual features engaged a common right-lateralised network that overlapped with aspects of the multiple-demand system (Duncan, 2010). Our successful manipulation of neural activity in regions of cortex with a well-established role in accessing meaning (ventral visual stream) through the contrast of semantic and perceptual trials indicates that this common pattern cannot be attributed to a failure of the task manipulation. Instead, our data are consistent with the view that the nature of the stimulus that guides response inhibition does not markedly change activation within the multiple-demand network (Camilleri et al., 2018; Crittenden et al., 2016; Duncan, 2001, Duncan, 2010; Fedorenko et al., 2013). As well as response inhibition per se, processes such as goal maintenance and attentional

regulation (to promote unusual or unexpected inputs) are thought to increase on No-Go trials; the multiple-demand network is likely to underpin these various aspects of cognitive control whatever the task or stimulus (Hampshire et al., 2010; Sharp et al., 2010). A similar network is activated when a specific response, as opposed to response inhibition, is required on oddball trials – the critical factor therefore appears to be detecting a change in the relevant domain and rapidly switching from a prepotent response to an alternative behaviour (Hampshire et al., 2010; Bledowski et al., 2004). In our study, participants had to dissociate no-go targets based on either perceptual templates (How slanted was the box?) or semantic templates (Does the input represent an animal?), indicating that this process of regulation can utilise different forms of information. In general, inhibition based on meaning was guided by the same right-lateralised network that has been consistently identified in previous literature in situations with minimal semantic content (Criaud and Boulinguez, 2013; Simmonds et al., 2008). We found little evidence for engagement of the left-lateralised semantic control network (Noonan et al., 2013), even when semantic information determined when a prepotent response should be withheld.

Our results are broadly consistent with the model of Aron et al. (2004, 2014), who proposed an inhibition circuit reliant on right lateral prefrontal

Connectivity between visual regions and the Multiple Demand Network predicts picture inhibition performance

Fig. 10. Summary of the pattern of connectivity linked to good picture-based inhibition. The top row (Step 1) shows the unthresholded z-statistic intrinsic connectivity map for the task-based fMRI cluster in lateral occipital cortex revealed by the interaction of modality and inhibition from Experiment 1, used as seed in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to visual processing. The middle row (Step 2) shows the unthresholded z-statistic intrinsic connectivity map for significant clusters obtained from resting-state behavioural regressions in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to motivation. The bottom row (Step 3) shows an overlap of the resting-state group maps from Step 2 with a meta-analytic map for the multiple-demand network from Fedorenko et al. (2013). Better picture-based inhibition was linked to increased connectivity between lateral occipital cortex and regions in thalamus/caudate. For further details about Neurosynth decoding and meta-analysis, see Methods and Yarkoni et al. (2011).

cortex (particularly pars opercularis within inferior frontal gyrus) and anterior insula, alongside subcortical projections to the basal ganglia. The effect of inhibition across all tasks was strongly *right-lateralised*, particularly in inferior frontal cortex, in line with this standpoint. Right inferior frontal cortex showed a strong effect of inhibition irrespective of task. In contrast, left inferior frontal cortex showed a preference for verbal and semantic tasks over perceptual tasks. Moreover, the peak response for common inhibition in our study fell within right dorsolateral prefrontal cortex (associated in this framework with representing task rules and conditional stopping), as opposed to right inferior frontal gyrus (associated with stopping per se). This pattern fits well with our data, given our paradigm required participants to use different rules to determine when to withhold a response on each block. However, right lateral prefrontal cortex was not unique in showing this response profile: left IPS also showed no differences between tasks and a strong response to inhibition, while right IPS showed a stronger response in non-meaningful tasks.

We also found important effects of modality on brain activation. Consistent with previous studies, there was a main effect of modality in Experiment 1: left IFG showed a stronger response to words than to perceptual targets (cf. Poldrack et al., 1999; Price, 2012), and regions of fusiform cortex responded more when stimuli were pictures than perceptual stimuli (cf. Carlson et al., 2013; Visser et al., 2012). Most importantly, a ventral cluster in lateral occipital/fusiform cortex showed an interaction between inhibitory demands and modality: this site

responded more strongly when response inhibition was guided by images rather than words that described the same information. The interaction cluster in lateral occipital/fusiform cortex overlapped with the main effect of modality, and did not fall within common inhibition regions activated across tasks in our study (Fig. 6). This observation is also consistent with the strong intrinsic connectivity of this cluster to visual cortex (Fig. 9). Consequently, the interaction effect reflected visually responsive cortex showing an elevated response during picture inhibition, as opposed to domain-general control cortex showing a stronger inhibition effect for one modality than another. Lateral occipital cortex might participate in cognitive control because visual codes are often critical in controlling behaviour. This is not without precedent in the literature: (i) Lateral occipital cortex shows functional connectivity to regions in the multiple-demand network (Crittenden and Duncan, 2014; Stiers et al., 2010), (ii) it is implicated in visual working memory (Ferber et al., 2003) and (iii) it does not respond to stimuli beyond conscious awareness, consistent with a role in attention (Carlson et al., 2007).

Individuals who were better at regulating behaviour from picture inputs showed greater intrinsic connectivity between this lateral occipital region and sub-cortical regions within thalamus/caudate nucleus, which showed a pattern of intrinsic connectivity associated with the multiple-demand network. The caudate nucleus within the dorsal striatum is implicated in the 'indirect' inhibitory pathway: when a sensory cue indicates the need to suppress a prepotent response, projections from

cortex to dorsal striatum are thought to control behaviour via the thalamus (e.g., Hikosaka and Isoda, 2010). Individual differences in the strength of connections between cortex and caudate have been previously linked to behavioural differences in inhibition tasks (Jahfari et al., 2011). Our findings are consistent with these theories and findings although our cluster did not fall solely in the caudate.

Our study also provides important constraints on our more general understanding of how we exploit meaning from the environment to regulate behaviour. Although meaningful words and pictures recruited left inferior frontal gyrus more than a perceptual task, we found little evidence that when the No-Go target was defined by semantic features, the regulation of behaviour depended on the left lateralised semantic control network (see Supplementary Analysis 1). This suggests an important difference between semantic control and the regulation of simple behaviour by meaning. Activation of the semantic control network occurs when conceptual retrieval must be shaped to suit task demands – i.e., when unusual aspects of knowledge must be brought to the fore (Davey et al., 2016; Jefferies, 2013). Our Go/No-Go task, however, did not involve control over semantic retrieval itself – rather, semantic categorisation was used to control a simple motor response (i.e., press a button or withhold press). Based on our data, the semantic control network is not required for *all* situations in which semantic representations guide behaviour in a controlled manner. However, interaction between multiple-demand cortex activated by inhibitory demands across tasks and regions linked to memory might be critical when semantic information is used to determine when to act. In Experiment 2, we found that individuals who were better at regulating behaviour from meaning showed stronger connectivity between common inhibition regions, activated across all No-Go conditions, and clusters in medial temporal lobe and sub-genual anterior cingulate cortex. These limbic regions are linked to conceptual, episodic and emotional memory (Dolcos et al., 2004; Euston et al., 2012; Simons and Spiers, 2003; Wang et al., 2010). We speculate that connectivity between domain-general response inhibition regions and areas implicated in memory representation is critical to the regulation of behaviour that is afforded by meaning.

Conclusion

Behavioural inhibition, regardless of whether it is guided by semantic or perceptual content, depends on right-lateralised regions of the multiple-demand network. However, our data show that these domain-general control regions work in concert with specialised regions of cortex, depending on the nature of the task or the input modality. When behavioural inhibition is guided by the semantic category of pictures as opposed to words, there is increased activation within a region of visual cortex associated with processing complex features (lateral occipital cortex); moreover, people who are good at this task show stronger connectivity between this region thought to represent task-relevant features and aspects of the thalamus/caudate implicated in behavioural control. Interestingly, the classic left-lateralised semantic control network (Davey et al., 2016; Noonan et al., 2013) did not appear to be critical to behavioural inhibition, even when responses were guided by meaning. Instead, we found that strong semantically-guided inhibition was associated with greater intrinsic connectivity between limbic regions implicated in memory and multiple-demand regions.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.06.074.

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