Multiple modes of clearing one's mind of current thoughts: Overlapping and distinct neural systems

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ABSTRACT

This study used the power of neuroimaging to identify the neural systems that remove information from working memory, a thorny issue to examine because it is difficult to confirm that individuals have actually modified their thoughts. To overcome this problem, brain activation as measured via fMRI was assessed when individuals had to clear their mind of all thought (global clear), clear their mind of a particular thought (targeted clear), or replace the current thought (replace), relative to maintaining an item in working memory. The pattern of activity in posterior sensory regions across these conditions confirmed compliance with task demands. A hierarchy of brain regions involved in cognitive control, including parietal, dorsolateral prefrontal and frontopolar regions, were engaged to varying degrees depending on the manner in which information was removed from working memory. In addition, individuals with greater difficulty in controlling internal thoughts exhibited greater activity in prefrontal brain regions associated with cognitive control, as well as in left lateral prefrontal areas including Broca's area, which is associated with inner speech.

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1. Introduction

How we select and control the information actively held in our current thoughts is central to understanding our mental inner life. We often make conscious decisions about what to keep in mind, such as rehearsing the telephone number for the local pizza parlor. Working memory (WM), which is of limited duration and capacity, maintains such information on line and serves to keep focus on the information critical to the current train of thought or task goals. But at some point the information held in working memory is no longer useful and must be removed. This study focuses on the cognitive control mechanisms that allow us to do so. This issue has received relatively scant attention because it is very difficult to address, as discussed below.

There are a variety of ways by which a now irrelevant item might be removed from working memory. One is to replace it with something else. For example, one might stop thinking about the telephone number of the local pizza parlor and replace it with thinking about the pizza toppings to be ordered (e.g., Tomlinson et al., 2009). Another way to remove information is to specifically target the current thought as one to be cleared, avoided, or removed from the focus of attention (e.g., Souza et al., 2014). For example, when dieting and in the grocery store, one might try to specifically *not think* about chocolate cake. A final means is to clear one's mind of all thought, much as is emphasized in mindfulness meditation (Teasdale et al., 1995). We will refer to these modes of removing information from working memory as replacement, targeted clearing and global clearing, respectively.

Understanding the neural mechanisms supporting these potentially different modes of removing current thought has important implications. Difficulty in clearing or inhibiting the contents of working memory is observed in many different types of psychopathology. For instance, in depression (Nolen–Hoeksema, 1991), obsessive-compulsive disorder (Tolin et al., 2002), and posttraumatic stress disorder (Ehlers and Steil, 1995), individuals can have an inability to clear depressive thoughts, obsessions, or traumatic memories, respectively.

One major obstacle to investigating this issue is that it is difficult, if not close to impossible, to know what an individual is thinking, and hence whether a current thought has indeed been removed or cleared. However, neuroimaging provides a way around this problem, offering a unique opportunity to shed light

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on this vexing question. More specifically, if a thought is cleared or inhibited, neural activity in regions supporting that thought should be decreased relative to when the thought is maintained or replaced by some other thought.

Previous research in our laboratory has demonstrated the utility of using neuroimaging to confirm that individuals are indeed inhibiting or suppressing thoughts and to identify the neural substrates that support such control operations (Depue et al., 2007). In our prior study, we examined the ability to inhibit the retrieval of information from long-term memory using the Think/No-Think paradigm (Anderson and Green, 2001; Anderson et al., 2004), which is considered a memory analog of the motoric Go/No-Go task (e.g., de Zubicaray et al., 2000; Garavan et al., 1999). In our version of the Think/No-Think paradigm, individuals learned cue-target pairs to a high degree of accuracy, with the cue being a face and the target being a negatively-valenced emotional picture (e.g., car crash). During the experimental phase, individuals were shown a cue. For some cues they were asked to "think" about the associated target, while for others they were instructed "don't think" about the associated target. The neuroimaging data confirmed that individuals complied with task demands. When asked to not think about a given item, activity decreased (relative to a fixation baseline) in brain regions that would support memory retrieval of those negative visual images – the ventral visual processing stream, the hippocampus, and amygdala. In contrast, when thinking about a given item, activity in all of these regions was substantially above baseline. Moreover, prefrontal brain regions involved in cognitive control (BA 10, BA 9/46, BA 44/45) exhibited greater activation when inhibiting retrieval of a memory than when actually retrieving a memory.

Using a new paradigm we take a similar approach in the current study but focus on removing the current information from working memory rather than on inhibiting retrieval of information from long-term memory. In this paradigm, individuals see or hear an item for four seconds. For the subsequent four seconds, participants are instructed to engage in one of three methods for removing the current information from working memory- via replacement (i.e., think of an alternative item), a targeted clearing (i.e., suppress the specific item in WM) or a global clearing (i.e., clear your mind of all thought). As a control condition, trials in which the current item is maintained are also included (see Fig. 1).

One of the issues in such a paradigm is verifying that individuals have complied with task demands (e.g., clearing an item from WM) in the absence of some overt response. To tackle this issue, we relied on activity in posterior brain regions as an index of whether an item was indeed being held in working memory or not. When information remains in working memory, either because the prior item was maintained or because of replacement with an alternative, one might expect activity in posterior brain regions supporting such a memory representation (e.g., ventral visual processing stream for visual stimuli and temporal cortex for auditory stimuli) (e.g., Johnson et al., 2007; Lewis-Peacock and Postle, 2008). A caveat, which is discussed in more detail in the

discussion, is that while univariate methods reveal elevated levels of brain activity for regions purportedly involved in maintaining information in working memory, recent work using multi-voxel pattern analysis (MVPA) suggests that when an item is no longer in the focus of attention in working memory, it is not in fact being maintained across a delay (e.g., Lewis-Peacock and Postle, 2012). Given these findings, one must be cautious in interpreting brain activation, as assessed by univariate methods, as being isomorphic with maintenance in working memory. Hence, based solely on univariate data, as used in the present study, we can more safely predict that activity in posterior brain areas should *not* be significantly above baseline for either the Targeted or the Global Clear conditions if indeed individuals are *not* maintaining an item in working memory. In contrast, we would expect that activity would be significantly above baseline in these posterior regions for both the Maintain and the Replace conditions. This increased activity, however, cannot differentiate whether or not a specific item remains within the focus of attention. To further assess whether participants on the whole, were complying with task demands, we varied the modality of stimulus presentation- visual or auditory -allowing for specific a priori hypotheses regarding the patterns of brain activity that would indicate compliance with task demands.

Contrasts across these four conditions can help to isolate the neural substrates that support specific operations for removing information from working memory, indicating which mechanisms are common across conditions and which are unique. As shown in the first row of Table 1, replacing the contents of WM or clearing it (either in a targeted manner or globally) requires the current item to be removed from working memory, which is not the case when an item must be maintained in WM. We predict that shifting focus away from the current item in working memory is likely to activate parietal regions that are engaged in shifts of attention between items in working memory (e.g., Tamber-Rosenau et al., 2011; Nee and Brown, 2013; Nee et al., 2013). These regions may be more medial as compared to those more lateral areas that have been suggested to aid in maintaining information in working memory (e.g., McNab and Klingberg, 2008). As shown in the second row, clearing the contents of WM (either in a targeted manner or globally) requires the present information in WM to be emptied. Based on previous research showing that inhibition of memory processes requires cognitive control (Anderson et al., 2004; Depue et al., 2007), we predict greater activity in portions of the fronto-parietal executive network for the two conditions requiring information to be cleared from WM compared to either maintaining or replacing its contents. As shown in the third row, only a global clearing of WM requires that *all* thought be cleared. In the motor domain, neural control mechanisms for global stopping, which is the cessation of all motor responding, are partially distinct from those required to stop a specific motor response (Aron and Verbruggen, 2008; Majid et al., 2012). Analogously, we predict that while some regions required for each of these distinct ways in which information is cleared from working memory will overlap, at least some will also be distinct.
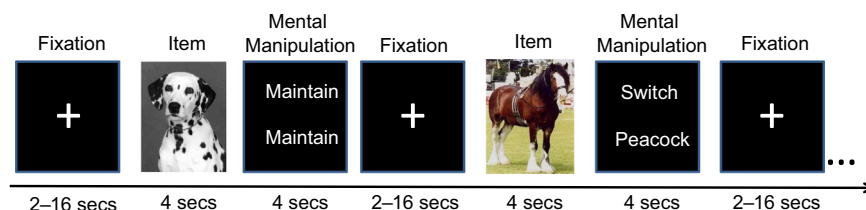

Fig. 1. *The experimental paradigm.* Individuals either heard or saw an item for 4 s and then immediately afterwards were asked to perform a mental manipulation on that item (Maintain, Replace, Targeted Clear, or Global Clear) for the next 4 s. Fixation trials were distributed logarithmically between these 8-s epochs to provide a baseline for comparison.

Table 1
Contrasts of major interest in the current study and unique operations indexed by each condition. The contrasts in Rows 1–3 can be conceptualized as a hierarchy of control operations, from more general to more specific, that are involved in removing the current item from working memory. First row: The Replace and both Clear conditions require the current item to be removed, whereas the Maintain condition does not. Second Row: Emptying the contents of working memory is required for each of the two Clear conditions, but not the Maintain and Replace conditions. Third Row: The Global Clear condition uniquely indexes the clearing of all information from working memory, whereas the other conditions do not. The contrasts in Row 3–6 isolate those processes that are uniquely indexed by each of the given condition compared to the other three.

Operation	Maintain	Replace	Targeted Clear	Global Clear
Removing the current item from working memory	No	Yes	Yes	Yes
Emptying the contents of working memory	No	No	Yes	Yes
Clearing working memory of all thought	No	No	No	Yes
Retaining the current item	Yes	No	No	No
Updating with a new item	No	Yes	No	No
Clearing a targeted item	No	No	Yes	No

In addition, as shown in rows 3 to 6 of Table 1, each of these conditions can also be conceptualized as uniquely indexing a particular operation on information in working memory. As such, this design also allows us to address a contentious issue – specifically how individual representations are inhibited in memory. Some researchers have argued that one can suppress thinking about a specific item by replacing it with another thought or even action (Tomlinson et al., 2009). This perspective would predict that no brain regions should be uniquely activated by a targeted clear of the contents of WM other than those observed when information in WM is replaced, as a targeted clearing would simply occur via replacement with another item. On the other hand, if specific mechanisms exist to directly inhibit specific representations in working memory, they should be uniquely active in a targeted clear of WM.

In conjunction with the previous analyses, we examined whether brain regions involved in cognitive control (e.g., mid-DLPFC) that are co-activated across conditions (e.g., during both a targeted and global clearing of WM) exhibit differential patterns of connectivity for each of the conditions that activated them. These analyses were motivated by research suggesting that cognitive control regions can exert their influence by modulating activity in distinct brain regions depending on task demands (e.g., Zanto et al., 2010). As such, we wished to explore whether such a mechanism is also used to aid in the removal of information from working memory.

A final goal of the current study was to examine whether the degree of difficulty an individual has in controlling his or her internal thoughts covaries with the neural mechanisms engaged for removing information from working memory. To do so, we administered self-report questionnaires measuring such difficulty: the White Bear Suppression inventory (Wegner and Zanakos, 1994), the Ruminative Response Scale (Nolen-Hoeksema and Morrow, 1991), and the Penn State Worry Questionnaire (Meyer et al., 1990). We predicted that greater difficulty in controlling internal thought would be associated not only with a poorer ability to reduce activation in regions supporting the memory representations to be removed but also altered activation in cognitive control regions required to remove such thoughts.

2. Material and methods

2.1. Participants

19 healthy individuals (9 women, 10 men; age $M=21.58$, $SD=2.91$) served as participants. All were right-handed and reported no history of brain injury or neurological disease, psychiatric disorder, or MR contraindication. Three male and 1 female participant were dropped from subsequent analyses, two due to technical difficulties and two due to excessive movement during data acquisition, resulting in a final sample of 15 participants (8 women, 7 men; age $M=21.07$, $SD=2.80$). All participants gave informed, written consent and were compensated monetarily. The study was approved by the Colorado Multiple Institutional Review Board at the University of Colorado.

2.2. Questionnaires regarding control of thought

To examine individual differences in the difficulty of controlling internal thought, three self-report questionnaires were administered. As all measures were highly correlated ($r > .50$), each scale was Z-scored and then averaged to provide a covariate that was then entered into the GLM for fMRI analyses (see below).

a. White Bear Suppression Inventory (Wegner and Zanakos, 1994) – This 15 item inventory measures the presence of intrusive thoughts and the degree to which individuals attempt to suppress thoughts.
b. Ruminative Response Scale (Nolen-Hoeksema and Morrow, 1991) – This 22 item questionnaire assesses the degree to which people tend to ruminate when they are feeling down, sad, or depressed.
c. Penn State Worry Questionnaire (PSWQ: Meyer et al., 1990) – This 16-item questionnaire measures excessive and uncontrollable worry.

2.3. fMRI paradigm

Prior to entering the MRI scanner, participants were shown a series of pictures and listened to a series of melodies. There were a total of 16 familiar, emotionally neutral pictures, half black and white (e.g., Dalmatian, penguin) and half color (e.g., peacock, Statue of Liberty). Additionally, there were 16 familiar, neutral melodies with words (e.g., "Happy Birthday," "Twinkle, Twinkle Little Star"). Participants learned a word for each stimulus (e.g., picture of a peacock paired with the word "peacock"), and were tested on these paired associations until they correctly recognized all 32 word–stimulus pairs. This procedure ensured that individuals knew which item to "switch" to for trials in the Replace condition (see below).

Participants were told that in the scanning session, they would see a picture or hear a melody (accompanied by a black screen). Afterwards a prompt would indicate which of four operations was to be performed on that item. In the Maintain condition, they were to maintain the image of the picture or the melody in their mind (e.g., seeing a picture of a peacock, and then keeping that image in mind). In the Replace condition, they were to replace the current image or melody with the item associated with the word presented on the screen (e.g., after viewing a picture of a horse and seeing the word "peacock," bring the image of the peacock to mind). In the Targeted Clear, they were to suppress just the image or melody they had recently seen or heard, whereas in the Global Clear condition, they were to clear their mind of everything. These two conditions were further delineated to participants through instructions: In the Targeted Clear condition, you are to suppress

the particular image or melody "like you would suppress a cough", whereas in the Global Clear condition you are clearing your mind of "not only that image or melody, but everything". Participants were also informed that in between trials they would see white fixation crosses for variable lengths of time and to fixate on them until the next trial.

The procedure during scanning was as follows (see Fig. 1). After fixation, a picture or melody was presented for four seconds, followed by a black screen with two words indicating the instructions for the next four seconds. For the Replace condition, the word "Switch" and a word describing a specific stimulus were presented. For the Maintain, Targeted Clear and Global Clear conditions, two identical words were presented (e.g., "Maintain Maintain"; "Suppress Suppress"; "Clear Clear," respectively).

Each stimulus was presented once per condition, for a total of 128 experimental trials. There were 64 fixation trials (a white cross centered on a black screen), ranging in duration from 2 to 16 seconds, logarithmically and randomly distributed. Trial and fixation order was optimized using OptSeq2 (Dale, 1999). There were 20 seconds of fixation baseline at the beginning of the scan.

Stimuli were programmed using E-Prime software (Psychology Software Tools, Inc.). Visual stimuli were presented via stereoscopic goggles and auditory stimuli were presented via headphones. Stimuli were administered in one functional run comprised of 686 volumes, lasting approximately 23 min. Seven fixation volumes were dropped from the beginning of the run to ensure steady-state magnetization, resulting in a total of 679 volumes. An air pillow was inflated around each participant's head in order to minimize movement.

2.4. fMRI data acquisition

Functional images were acquired with a GE (Waukesha, Wisconsin) Signa 3T MRI scanner with a T2*-weighted gradient-echo, echo-planar imaging (TR=2000 ms, TE=32 ms, flip angle=77°, 29 Axial slices, thickness=4 mm, gap=0 mm, 64 × 64 in-plane resolution, in-plane FOV=22 cm). A high-resolution T1-weighted anatomical scan was collected for each participant to localize functional activity.

2.5. Image preprocessing

Image preprocessing was conducted with the FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Images were motion corrected with MCFLIRT, and brain tissue was extracted with BET to remove all non-brain tissue from the images. Prior to statistical analysis, images were spatially smoothed with a Gaussian kernel (FWHM=8 mm), mean-based intensity normalized, high-pass temporal filtered with a cut-off period of 125 s to remove low-frequency noise, and intensity-normalized to allow valid analyses across participants.

2.6. Statistical analyses

2.6.1. General linear models
Statistical analyses were conducted with FMRIB's improved linear model. Analyses on the blood oxygen level dependent (BOLD) time series were performed separately for each individual participant using event-related analyses, convolved using a double-gamma hemodynamic response function. For comparisons across individuals, parameter and variance estimates for each participant were registered to Montreal Neurological Institute standard stereotaxic space (MNI152) with the two-stage registration procedure implemented in FMRIB's Linear Image Registration Tool. The FMRIB's Local Analysis of Mixed Effects (FLAME) was used to model the mixed-effects variance for each contrast of interest, taking into account both fixed effects and random effects.

Separate General Linear Models (GLMs) were run to examine compliance with instructions and study hypotheses. In the GLM we modeled the 4-s stimulus (i.e., picture/melody) period as a nuisance regressor separately from the 4-s manipulation period, which was the focus of our analyses. As each stimulus was followed exactly once by each condition, we expected that the effect of stimulus on the manipulation period would be minimal due to this counterbalancing. Nonetheless, to ensure that activation occurring during the manipulation period was not reflecting activation in the prior stimulus presentation period, we ran a different set of models using a single EV to characterize the entire 8-s trial period (i.e., presentation of the stimulus item plus mental manipulation), so that we had just four EVs (Maintain, Replace, Targeted Clear, Global Clear). Consistent with our assumption that modeling the stimulus period as a nuisance regressor did not unduly influence our results, the results with the 8-s EVs were highly similar (i.e., the same main clusters and extent were revealed in both analyses). Hence, we present the data from the model in which the stimulus period is modeled separately from the manipulation period.

To test for compliance with task demands, these GLMs were run separately for visual and auditory stimuli, as distinct regions were expected to show the effect of interest. These analyses employed a two-step process. First FEAT was used to identify clusters that exhibited significantly greater activation for the contrast of Maintain and Replace > Targeted Clear and Global Clear. Correction for multiple comparisons was conducted via Monte Carlo simulations using AlphaSim within Analysis of Functional NeuroImages (AFNI; Cox, 1996). Clusters were considered significant, corrected for a whole-brain error rate of $p < 0.05$, if they exceeded a voxel-wise threshold of $p < 0.0025$ ($Z=3.02$) and consisted of at least 73 contiguous voxels.

For each of these clusters, featquery was used to extract the mean activity of a 5-voxel sphere (10 mm diameter) around the cluster's peak for each condition individually relative to baseline. If participants are complying with task demands, then activity for each of the Maintain and Replace conditions individually should be significantly above baseline ($p < .05$) because an item is being held in working memory, but should not reach a statistically significant level of activity relative to baseline ($p > .05$) for either of the two Clear conditions individually.

The second set of GLMs averaged over the auditory and visual conditions to test specific contrasts. To identify regions of interest, a cluster-wise whole-brain threshold of $p < .05$ (single-voxel threshold of $p < 0.0025$ with at least 73 contiguous voxels) was used for each contrast. Again, a two-step process was applied to ensure that clusters (averaged across a 5 voxel (10 mm) sphere at their peak) showed significant activation ($p < .05$) relative to fixation baseline for the conditions of interest and non-significant activation for the conditions to which they were contrasted ($p > .05$). Only clusters meeting this two-step criterion are reported in Table 2.

While Table 1 presented a logical hierarchy characterizing the four conditions on each of three operations (i.e., removing the current item from working memory, emptying the contents of working memory and clearing working memory of all thought), one might consider an alternative conceptualization for the Replace condition. More specifically, the Replace condition might involve two phases- a clearing of working memory followed by the maintenance of a new item. In such a case, the hemodynamic response on these trials might look like the Clear conditions initially and then later look like that of the Maintain condition.

To address this possibility, we examined the time course of activity in the major clusters identified as described above, focusing specifically on those clusters in brain regions involved in

cognitive control. More specifically, we examined the time course of activity during an 8-s time period covering both the item presentation and mental manipulation. We used the 8-s EV for this analysis because it also allowed us to verify that there were no significant differences across conditions during the 4 s in which the stimulus item was presented. To determine the time course, we identified the peak of a cognitive control region for a particular contrast of interest (e.g., Global Clear > All Others, $x=8$, $y=4$, $z=42$), and created an ROI, which was a 10 mm diameter sphere (5 voxel width) around that peak, projected back into each subject's native space. FSLmeants was used to extract the average percentage signal change for each condition (i.e., Global Clear, Targeted Clear, Replace, Maintain) for each participant for the 12 s following the trial onset. These percentage signal change values were then averaged across participants for each TR. To preview, these plots (presented in Fig. 4) are inconsistent with the notion that the Replace condition is an amalgam of an early clear response followed by a later maintain response.

2.6.2. Functional connectivity analyses

We used the clusters that met our two-step criterion described above as seed ROIs for whole brain connectivity analyses. First, after motion correction, slice timing correction, and high pass filtering, an initial analysis was run using FEAT to covary a set of nuisance regressors (i.e., ventricles, white matter, and whole brain signal) from each participant's time course. Second, the average time course was extracted separately for each seed ROI using fslmeants and explanatory variable (EV) filtering (i.e., average time course multiplied by EV) was applied to extract individual time courses for the experimental conditions – Maintain, Replace, Targeted Clear, Global Clear. Third, these conditional time courses were used as predictors in a group-level GLM to identify brain regions in a whole-brain search that covaried across participants with activation of a given seed ROI.

We classified regions as showing task-related connectivity when two conditions were met: (1) the relationship with the seed ROI across participants differed between task conditions, and (2) the region exhibited a pattern of activity for one of those conditions that differed significantly from the fixation condition. This latter criterion was included to ensure that patterns of functional connectivity reflect changes that occur as a result of task demands. A cluster-wise whole-brain threshold of $p < .05$ (single-voxel threshold of $p < 0.005$ with at least 103 contiguous voxels) was used to correct for multiple comparisons.

2.6.3. Individual differences

The composite Z-score from the three self-report questionnaires (White Bear Suppression Inventory, Ruminative Response Scale, and Penn State Worry Questionnaire) was entered as a covariate into FEAT for the six main contrasts of interest (refer back to Table 1). A cluster-wise whole-brain threshold of $p < .05$ (single-voxel threshold of $p < 0.005$ with at least 103 contiguous voxels) was used to identify those regions that yielded a significant relationship with the composite score (see Table 3). For contrasts that yielded significant associations with the self-reported questionnaires, we created a 10 mm diameter sphere (5 voxel width) centered at the peak of significant clusters. These spheres were then projected back into subject-specific space. Featquery was used to obtain an average percentage signal change for each peak for each participant. This information was used to generate the scatterplots in Fig. 6 indicating the relationship across individuals between the composite Z-score measure from the self-report questionnaires and percentage signal change as extracted from peaks of interest for the contrast of Targeted Clear and Global Clear > Maintain and Replace.

3. Results

3.1. Compliance with task demands (Maintain and Replace > Targeted Clear and Global Clear in sensory processing regions)

As outlined above, these analyses used a two-step criterion to determine whether individuals as a group complied with task demands. First, significantly greater activity should be observed in regions supporting a memory representation when individuals must keep a representation in mind (Replace and Maintain) as compared to when they must clear their memory (Targeted Clear and Global Clear). Furthermore, activation for each of the former two conditions should be significantly above a fixation baseline, while each of the latter two should not. For the visual modality, two regions bilaterally in the ventral visual stream met this two-step criterion (see Fig. 2a). For auditory stimuli, the left middle temporal gyrus (BA 21) showed activity that approached significance for the Maintain and Replace conditions, and below baseline activity for both Clear conditions, although only that of the Global Clear reached significance (see Table 2 and Fig. 2b).

3.2. Operations on items in working memory

In these and all subsequent analyses data are reported for contrasts collapsed across modalities, as they did not differ significantly.

3.2.1. Removing the current item from working memory (Replace and Targeted Clear and Global Clear > Maintain)
3.2.1.1. Activation. All conditions except the Maintain condition yielded significant activation for a large area of BA 7 bilaterally, portions of BA 6, as well as the medial dorsal nucleus of the thalamus. (See Table 2 and Fig. 3A). Moreover, all three of these conditions exhibited higher activation as compared to the Maintain condition across the entire time course (see Fig. 4A).

3.2.1.2. Connectivity. There was no evidence that this region of BA 7 or BA 6 exhibited differential connectivity across the three conditions that activated it-Replace, Targeted Clear and Global Clear.

3.2.2. Emptying working memory > working memory occupied (Targeted Clear and Global Clear > Maintain and Replace)
3.2.2.1 Activation. This contrast was designed to reveal those brain regions responsible for emptying the contents of working memory, either by specifically inhibiting the current item or by clearing all information from working memory. Regions that exhibited greater activation for this contrast are those that have been previously identified as being involved in cognitive control (see Table 2 and Fig. 3B), including an anterior portion of BA 9 bilaterally, the cuneus bilaterally that extended both dorsally and ventrally in the left hemisphere, and the SMA. Activation was also noted in the globus pallidus bilaterally. It should be noted that activation in this condition, while including portions of area 18, was much more dorsal than that observed for the reverse contrast of Maintain and Replace > Targeted Clear and Global Clear. While the time course of activation for the SMA/ACC showed a clear differentiation between the two Clear conditions compared to the Maintain and Replace condition, a more graded response was observed for the DLPFC bilaterally (see Fig. 4B).

3.2.2.2. Connectivity. Differential connectivity for the two Clear conditions was observed for each of the left and right precuneus peaks. In all cases, connectivity for the Global Clear condition was similar to fixation, with that of the Targeted Clear condition being

Table 2
Areas of significant brain activation for the contrasts of interest.

Region	BA	Max Z	No. of voxels	x	y	z
Compliance with Task Demands: Maintain & Replace > Targeted Clear & Global Clear						
Visual regions						
Fusiform Gyrus (R)	37	4.71	1830	56	−52	−18
Occipital/Temporal Junction (R)		4.33	537	30	−60	26
Auditory regions						
Middle_Temporal_Gyrus(L)	21	4.37	498	−66	−32	−6
Removing Information from Working Memory: Replace & Targeted Clear & Global Clear > Maintain						
Cuneus/Precuneus (L)	7	4.85	2776	−4	−72	36
Precentral Gyrus	6	3.97	132	−34	−8	48
Thalamus (L)		3.04		−12	−22	10
Thalamus (R)		3.18		10	−14	4
Emptying the Contents of Working Memory: Targeted Clear & Global Clear > Maintain & Replace						
SMA/ACC (R)	6	4.52	872	16	8	64
Cuneus (L)	18	4.52	788	−12	−80	20
Middle Frontal Gyrus (R)	9	4.16	640	28	42	18
Middle Frontal Gyrus (L)	9	4.18	201	−30	36	24
Middle Frontal Gyrus (R)	6	3.74	184	26	−4	50
Cerebellum		3.46	128	−12	−72	−20
Cuneus (R)	18	3.77	79	6	−80	34
Globus Pallidus (L)		3.16		−18	−4	−6
Globus Pallidus (R)		3.22		18	0	−4
Clearing Working Memory of All Thought: Global Clear > All Others						
SMA/Cingulate Gyrus (R)	24	4.93	1325	8	4	42
Insula (R)	13	4.35	580	40	4	8
Supramarginal gyrus/Inferior_Parietal_Lobule (R)	40	4.56	553	66	−40	28
Middle Frontal Gyrus (R)	10	4.81	470	32	44	20
Not Clearing Working Memory of All Thought: All Others > Global Clear						
Superior Occipital Gyrus	19	4.71	878	−38	−76	36
Inferior Frontal Gyrus (L)	47	3.85	772	−50	20	−16
Fusiform/Inferior Temporal Gyrus (R)	20	3.79	296	60	−34	−16
Precentral Gyrus (L)	6	3.70	271	−48	4	36
Superior Frontal Gyrus (L)	8	3.63	249	−10	36	46
Middle Frontal Gyrus (L)	46	3.45	168	−44	20	22
Inferior Frontal Gyrus (R)	47	4.19	167	34	32	−14
Retaining the Current Item in Working Memory: Maintain > All Others						
Inferior Parietal Lobule (R)	40	3.49	75	56	−44	48
Updating a New Item: Replace > Others						
Fusiform Gyrus (L)	37	5.04	4153	−46	−60	−22
Inferior Occipital Gyrus	18	4.98	3108	42	−84	−8
Superior Lateral Occipital Cortex (L)		4.34	1297	−34	−74	24
Lingual Gyrus (R)	19	4.52	835	10	−60	0
Superior Lateral Occipital Cortex (R)		4.42	775	38	−68	26
Clearing a Targeted Item: Targeted Clear > Others						
Superior Frontal Gyrus (L)	9	3.76	417	−22	48	26
Cuneus (L)	18	3.56	100	−4	−70	18

BA refers to the Brodmann area in which the peak resides. Max Z is the maximum Z value of the cluster. No. of voxels is the number of voxels that comprise the cluster, followed by the MNI coordinates of the cluster's peak. All regions except subcortical regions met a voxelwise threshold of Z=3.02, p < .0025, with a clusterwise correction of p < .05, 73 voxel extent. In addition, all clusters met a more stringent requirement of significant activity (Z=1.96, p < .05) relative to fixation for the condition(s) of interest, as well as non-significant activity (p > .05) for the comparison condition(s). For example, the regions listed for the contrast of Maintain & Replace > Targeted Clear & Global Clear met a voxelwise threshold of Z=3.02, p < .0025, with a clusterwise correction of p < .05, 75 voxels. In addition, activity was significantly above fixation for each of the Maintain and Replace conditions, which was not the case for each of the other conditions (i.e., Targeted Clear, Global Clear).

distinct. More specifically, the more superior portion of the left precuneus ($x = -12, y = -80, z = 20$) showed a significant positive correlation for the Global Clear but not the Targeted Clear condition with a portion of BA 18 (14, −80, −14), and a significant negative correlation for the Targeted Clear condition but not the Global Clear condition with a portion of lateral occipital cortex (LOC) ($x = 50, y = -4, z = -26$). Both of these regions of visual cortex exhibited more activation for Maintain and Replace conditions than either of the Clear conditions. For the right precuneus ($x = 6, y = -80, z = 34$ all conditions (including fixation) had a significant negative correlation with the left inferior frontal cortex (BA 44: $x = -48, y = 18, z = 8$), an effect not observed for the Targeted Clear condition. While the underlying mechanism that drives these specific patterns of connectivity may not be certain, the overall pattern nonetheless suggests that the cuneus and precuneus are important loci of control in clearing information

from working memory and play distinct roles for a targeted versus a global clearing of such information.

3.2.3. Clearing all thought (Global Clear > Maintain and Replace and Targeted Clear)

3.2.3.1. Activation. Clearing all thought from working memory activates a network of regions that varies drastically from the other conditions. Most notable among the components of this network is a region of the cingulate proper above the mid-body of the corpus callosum that spans into the SMA, an extensive portion of the right insula, portions of the right supramarginal gyrus and frontopolar cortex (BA 10) (see Fig. 3C). The cingulate/SMA activity is in the opposite hemisphere and more ventral than that observed in the Targeted Clear condition (see Table 2). Moreover, the time course of activation for the Global Clear condition in this region is clearly distinct from that of the other three conditions (See Fig. 4C).

The reverse contrast (Maintain and Replace and Targeted Clear > Global Clear; see Table 2), yielded activation above baseline activity for all conditions but the Global Clear in a large extent of left lateral frontal cortex, extending from the superior to inferior frontal gyri along a posterior to anterior gradient (see Fig. 5D). Activity in the right fusiform gyrus was also significant for all conditions but the Global Clear condition.

3.2.3.2. Connectivity. The right middle frontal gyrus (BA 10) yielded a significant positive correlation with activity in the right mid-insula (BA 13) ($x = 34$, $y = -6$, $z = 10$) for the Global Clear condition, but none of the others, consistent with the concept that unique processes are implemented in the Global Clear condition.

3.3. Activation unique to a given condition

In these analyses we determined which brain regions were uniquely activated for a specific condition as compared to all others (See Table 2). As discussed in the methods section, determination of unique activation occurred via a two-step process in which (a) brain regions had to exhibit significant activation above baseline for the condition of interest (e.g., Maintain), and (b) *not* exhibit significant activation above baseline for each of the remaining conditions (e.g., Replace, Targeted Clear, Global Clear).

3.3.1. Maintain specific – holding onto the current item. Portions of BA 40 (supramarginal gyrus) showed more activity for the Maintain condition than all others (See Fig. 5E). The reverse contrast-regions that showed more activity for all conditions compared to the Maintain condition-was discussed above.

3.3.2. Replace specific – updating with a new item. A number of regions in both the inferior and superior portions of the ventral processing stream were activated for the Replace condition but not the others (See Fig. 5A–C). Of note, activation extended into the parahippocampal gyrus, which has been shown previously to become active when information must be retrieved again from memory in the face of other information having just been in working memory (Sakai et al., 2002). Although one cannot make definitive conclusions based on a null result, it is worth noting that no frontal region is activated more for Replace than other conditions (see Fig. 5). With regard to the reverse contrast, there was no region that showed less activity for Replace than all the other conditions.

3.3.3. Targeted clear – clearing a specific item. The targeted clearing of a specific representation uniquely engaged regions of left anterior BA 9 (see Fig. 5C). With regard to the reverse contrast, there was no region that showed less activity for Targeted Clear than all the other conditions.

3.3.4. Global Clear – Clearing All Thought.
The findings for this condition are discussed above in the section entitled "Clearing All Thought (Global Clear > Maintain and Replace and Targeted Clear)". To reiterate, activation was observed in a region of the cingulate proper above the mid-body of the corpus callosum that spans into the SMA, an extensive portion of the right insula, portions of the right supramarginal gyrus and frontopolar cortex (BA10).

3.4. Individual differences

This set of analyses examined whether individual differences in the difficulty of controlling internal thought, as indexed by the composite scores from the questionnaires (White Bear Suppression Inventory, Ruminative Response Scale, and Penn State Worry Questionnaire) covaried with activation across the different contrasts relevant to our task. Two general trends emerged (see Table 3). First, greater difficulty in controlling internal thought was associated with increased activity in brain regions that are likely to help generate and maintain internal thought. Notably, these regions were not significantly activated for the group as a whole, suggesting that activation is contingent on individual differences. The regions so activated included left ventral lateral prefrontal cortex (BA 44), which is associated with inner speech, portions of the fusiform gyrus that would support internal images, and portions of the middle temporal gyrus associated with semantic processing (e.g., Whitney et al., 2011).

Second, greater difficulty in controlling internal thought was associated with increased activity in cognitive control regions. These included the medial prefrontal cortex (BA 6/32), which was activated by conditions requiring the removal of information in working memory (e.g., all conditions but the Maintain condition), as well as the right pregenual region of the ACC, a region associated with monitoring one's actions (e.g., Rollnik et al., 2004). A scatterplot of the relationship between the percentage signal change in these two main regions along with individual scores on the composite measure of difficulty in controlling internal thought is shown in Fig. 6.

Table 3
Regions that show a significant relationship with individual differences in difficulty in controlling internal thought.

Region	BA	Max Z	No. of vox	x	y	z
Targeted Clear & Global Clear > Maintain & Replace						
Precentral Gyrus (L)	44	3.56	301	−50	8	8
Medial_Frontal_Gyrus (L)	**32**	**3.58**	**181**	**−18**	**8**	**50**
Precuneus (L)	**19**	**3.68**	**177**	**−30**	**−78**	**38**
All Others > Maintain						
Inferior Frontal Gyrus (L)	44	3.68	1021	−54	6	14
Medial_Frontal_Gyrus (L)	**6**	**3.28**	**289**	**−18**	**4**	**52**
Targeted Clear > All Others						
Middle Temporal Gyrus (L)	39	3.66	271	−58	−64	12
Others > Global Clear						
Medial Frontal Gyrus (R)	9	3.16	165	16	42	18

BA refers to the Brodmann area in which the peak resides. Max Z is the maximum Z value of the cluster. No. of voxels is the number of voxels that comprise the cluster, followed by the MNI coordinates of the cluster's peak. All regions except subcortical regions met a voxelwise threshold of $Z = 3.02$, $p < .0025$, with a clusterwise correction of $p < .05$, 73 voxels. Regions shown in bold are also activated for the basic contrasts (e.g., without a covariate). In all cases, greater activity for the contrast is associated with a greater degree of difficulty in controlling internal thought.
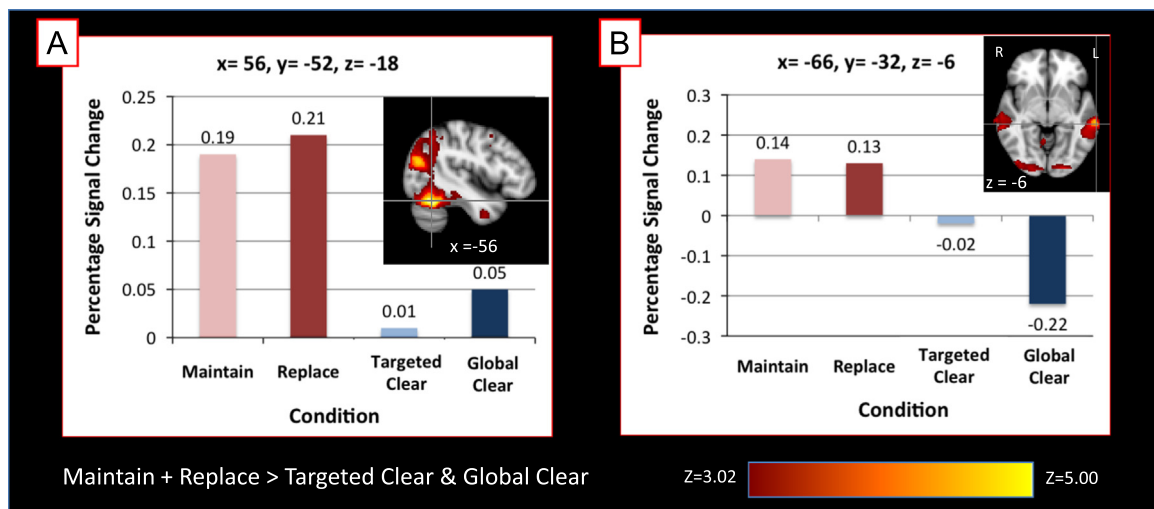
Fig. 2. *Activity in sensory regions confirming individuals' compliance with task demands.* (A) Activity in the ventral visual processing stream during visual trials only. (B) Activity in temporal cortex during auditory trials only. In both cases the bar graphs represent the percentage signal change for each condition individually for the peak of activation relative to a fixation baseline (refer back to Table 2).
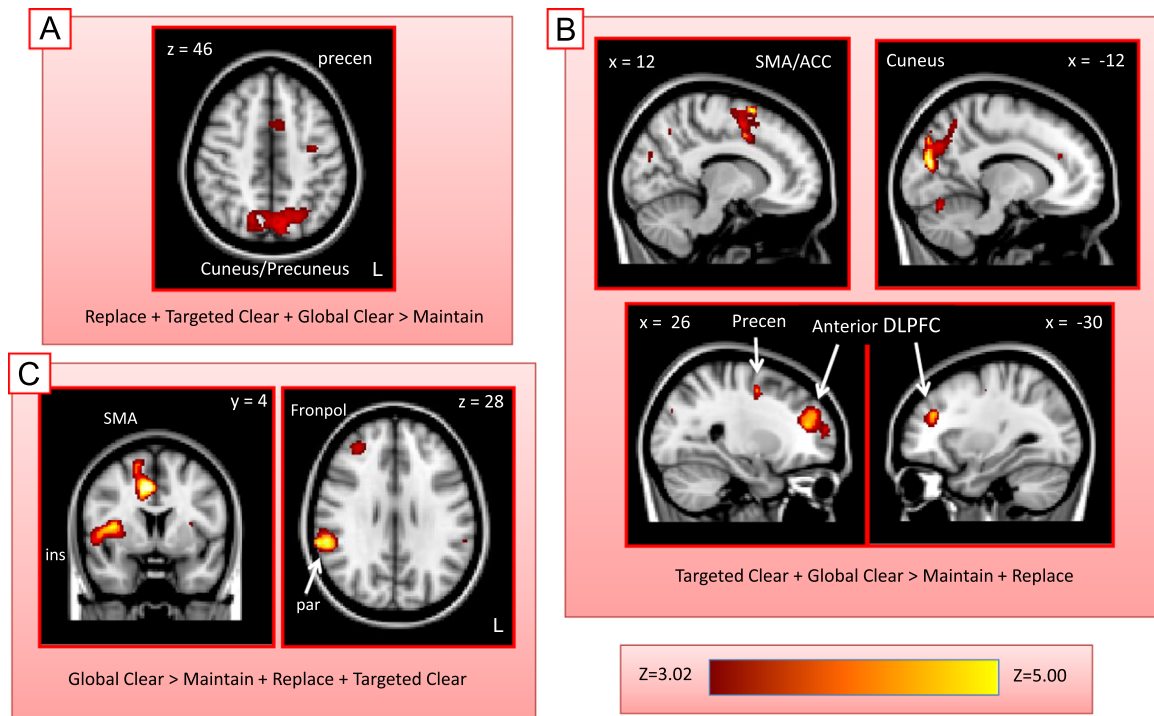

Fig. 3. *Regions involved in cognitive control over items in working memory.* (A) Those involved in removing the current contents of working memory. (B) Those involved when information in working memory must be cleared. (C) Those involved in a Global Clearing of working memory. In all cases regions labeled are those, which on average, show activation above baseline for the condition(s) of interest and non-significant activity for the contrasted conditions. ACC=anterior cingulate cortex, DLPFC=dorsolateral prefrontal cortex, Fronpol=frontopolar, ins=insula, par=parietal, Precen=precentral, SMA=supplementary motor area.

4. Discussion

The present study used the power of neuroimaging to attempt to identify the neural systems that serve to remove information from working memory. One vexing problem in addressing this issue has been the difficulty in verifying that individuals are indeed removing information from working memory. In the current study, the pattern of activity in regions of posterior cortex that support a memory representation was used to demonstrate that, as a group, individuals complied with task demands. Moreover, they did so differentially depending on the manner by which information was removed- by replacing it with some other thought,

by specifically inhibiting it, or by removing it through a global clearing of all thought.

4.1. Distinct neural systems for distinct means of removing information from working memory

Our results indicated that somewhat distinct neural systems are involved in each of the separate methods of removing information from working memory. Of importance, the separate neural systems engaged by the Replace condition as compared to the Targeted Clear condition shed light on a debate surrounding how information may be controlled in memory. By some accounts,
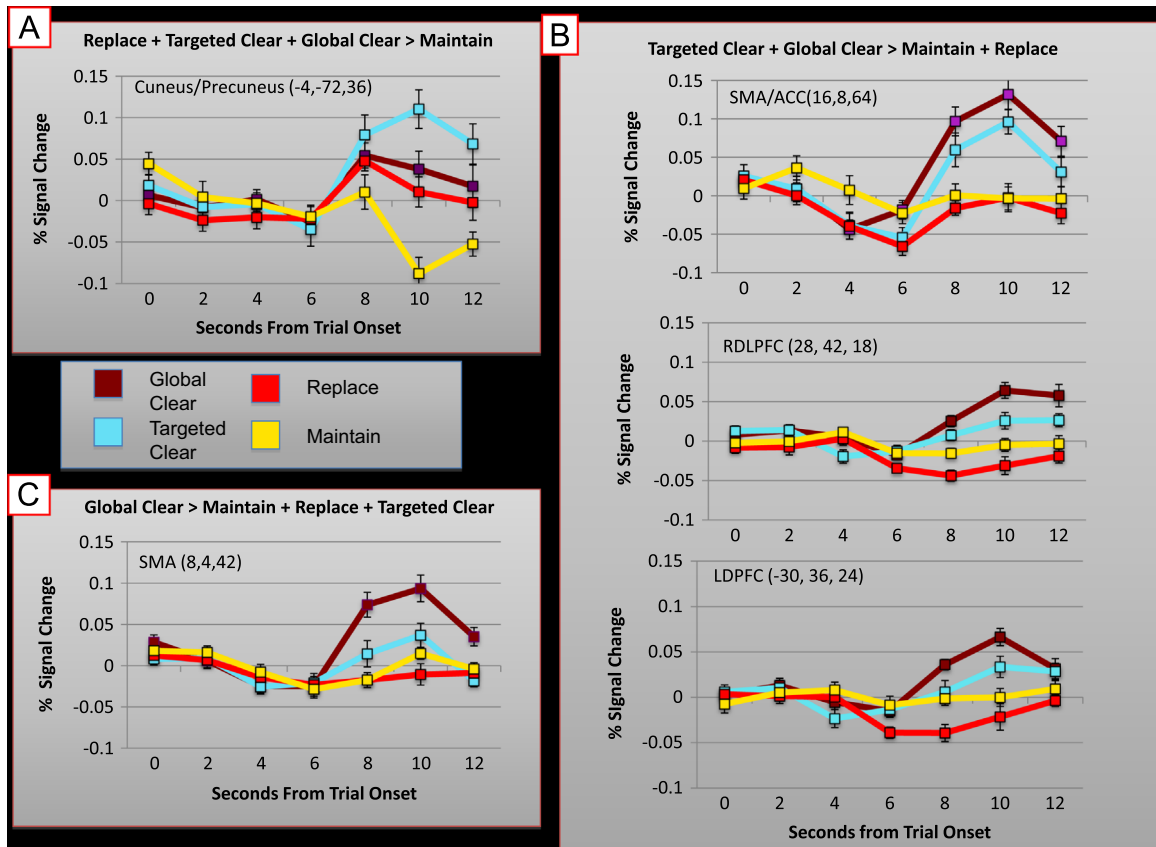
Fig. 4. The time course of activity in regions involved in cognitive control over items in working memory. Shown here is the percentage signal change for regions of interests (refer back to Fig. 3). (A) Those involved in removing the current contents of working memory. (B) Those involved when information in working memory must be cleared. (C) Those involved in a Global Clearing of working memory. In all cases regions labeled are those, which on average, show activation above baseline for the condition(s) of interest and non-significant activity for the contrasted conditions.

information that appears to be "inhibited" behaviorally results not from control over that specific item, but rather from interference generated by a new and distinct item, such as thinking about something else, or even engaging in a motoric action (Tomlinson et al., 2009). Were that the case, the brain regions activated by the Targeted Clear condition should have been isomorphic with those of the Replace condition. According to this proposal a Targeted Clear would be implemented by simply replacing the current thought with some other thought, rather than by trying to exert control over the specific item to be cleared. However, the results of the current study provide strong evidence against such a proposition, as distinct patterns of activity and functional connectivity over both posterior and prefrontal cortex distinguished these two conditions.

First, posterior brain regions involved in supporting a mental representation were uniquely activated in the Replace condition but not in other conditions, including the Targeted Clear condition (see Table 2 and Fig. 5B). Whereas the Replace condition engaged a large region of ventral visual cortex extending into parahippocampal gyrus, suggesting an active representation of information, activity in this same region for the Targeted Clear condition was not significantly above baseline. Conversely, the Targeted Clear condition uniquely engaged additional neural systems above and beyond those of all other conditions, including the Replace condition (see Fig. 5), in a region of frontopolar cortex. As this frontopolar region is just anterior to the DLPFC area activated by both Clear conditions, it may represent a more extensive activation of the neural system required to clear the contents of working memory. Finally, because of our two-step criteriion for

determining regions for our contrasts of interest, greater activation in the SMA and the middle frontal gyrus bilaterally indicates a clear differentiation between the neural systems involved in the Replace and Targeted Clear conditions.

Similarly, there are well-defined distinctions in activation between the Targeted Clear condition and the Global Clear condition. In fact, the Global Clear condition showed what is perhaps the most unique pattern of activation across all the conditions. Unlike the other conditions, it did not engage a large portion of lateral prefrontal cortex involved in executive functioning, most notably BA 46 (see Fig. 5D). Hence, the brain imaging data provide support for the idea that no specific working memory representation is being selected or manipulated in the Global Clear condition.

The Global Clear condition also was distinguished from the Targeted Clear condition by activity in the medial prefrontal cortex. Both Clear conditions engaged the SMA, which has been associated with the inhibition or cessation of movement (e.g., Dinomais et al., 2009; Milham and Banich, 2005; Toxopeus et al., 2007), and may be associated with the "cessation" of retaining an item in WM or within the focus of attention. In contrast, the Global Clear condition yielded activation more ventrally in the vicinity of and below the cingulate gyrus. This region of the ACC is one that has been recently implicated in evaluating the effectiveness of a response (Jahn et al., 2014). It may become activated when additional evaluation is required to ensure that all information has indeed been removed from WM.

Finally, although both Clear conditions activated a region of the cuneus involved in executive control and with strong connectivity to DLPFC, as evidenced by studies both in monkeys and humans
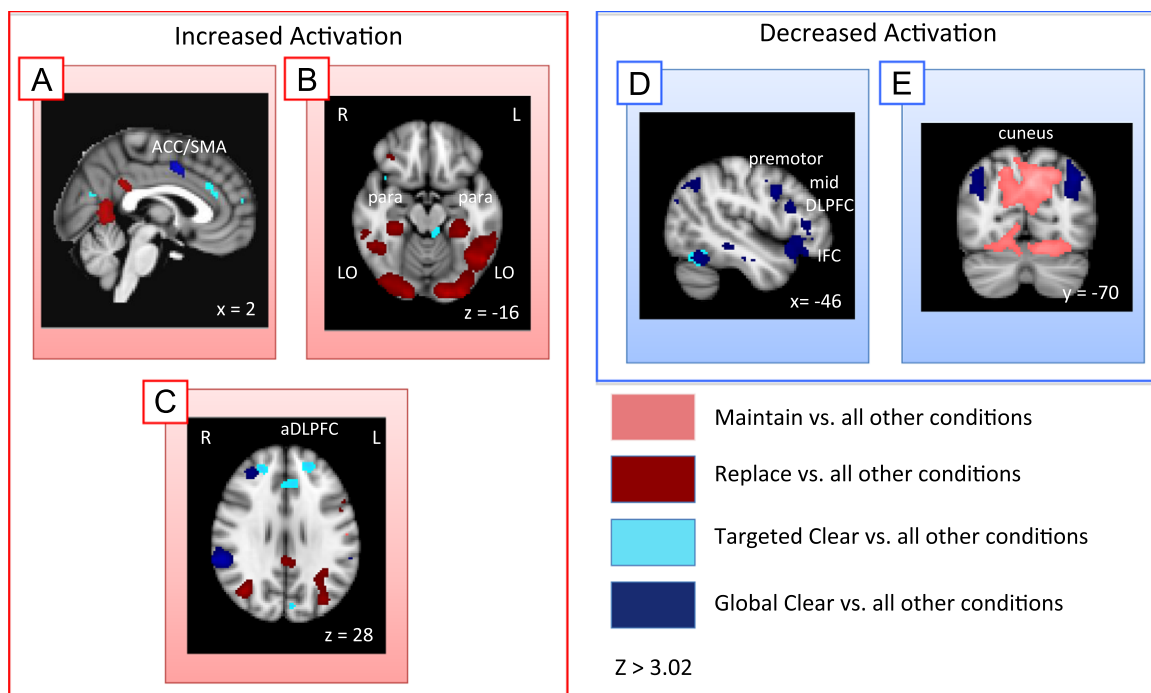
Fig. 5. (A–C) *The extent of regions showing significantly greater activity for one condition than the others.* If the region passed a more stringent requirement that activity must be significantly above fixation baseline for a given condition ($p < .05$) and not for each of the others, it is labeled in the figure. (D–E) The extent of regions showing significantly less activity for a given condition compared to all others. If the region passed a more stringent requirement that activity must not reach significance for a given condition but be significantly above baseline for each of the other conditions ($p < .05$), it is labeled in the figure. (A) The Global Clear condition uniquely activates a region of the ACC extending up into the supplementary motor area (SMA). (B) Much of the ventral visual processing stream, including the lateral occipital (LO) area as well as the para-hippocampus (para) are uniquely activated bilaterally by the Replace condition. (C) The Targeted Clear condition uniquely activates anterior DLPFC (aDLPFC) bilaterally. (D) Whereas all other conditions activated regions of lateral DLPFC from inferior frontal cortex (IFC) to premotor cortex, the Global Clear condition did not. (E) All other conditions but the Maintain condition significantly activated the cuneus.

([Margulies et al., 2009](#)), the pattern of connectivity with visual processing regions was distinct for the Targeted Clear versus Global Clear condition.

In summary, our data provide strong evidence that there are a variety of ways in which current information can be removed from working memory, and that each of these operations engages somewhat dissociable brain systems.

4.2. A hierarchy of common neural systems for removing information from working memory

Despite the differential engagement of distinct brain regions for different methods of removing information from working memory, common mechanisms are also engaged. Our results suggest that these common mechanisms are organized in a hierarchy.

At the most basic level, all methods of removing information from working memory activated the cuneus, the thalamus, and a portion of lateral BA 6. At its simplest, replacing an item in working memory does not appear to require the mid-DLPFC regions that are generally considered to be involved in executive functions over working memory (e.g., [Bunge et al., 2001](#); [Sandrini et al., 2008](#)). Rather, the largest area of activation was in BA 7 (cuneus and precuneus). Patients with damage to this region have difficulty in manipulating information being held in working memory, but not on working memory tasks requiring only rehearsal and retrieval ([Koenigs et al., 2009](#)). Moreover, patients with damage to this region exhibit deficits on memory tasks requiring attentional strategies ([Berryhill et al., 2011](#)). Neuroimaging implicates this region in shifting attention in general, whether between spatial locations or between items held in working memory ([Tamber-Rosenau et al., 2011](#)). Hence, the medial parietal activation in the current study may be associated with a shift of

attention away from the currently held item in working memory to something different.

At the next level, clearing information from working memory, whether through a Targeted Clear or a Global Clear, engages anterior and superior regions of prefrontal cortex (e.g., BA 9). This region has been implicated in goal-directed behavior, such as task switching ([Cutini et al., 2008](#)), the creation of goals ([Majdandzić et al., 2007](#)) and task sets (e.g., [Bengtsson et al., 2009](#); [Stelzel et al., 2008](#)), as well as shifts in attention ([Tamber-Rosenau et al., 2011](#)). From this perspective, the critical operation required by the Targeted Clear and Global Clear conditions that distinguish them from the Maintain and Replace conditions may be the requirement to shift from paying attention to something in working memory to having nothing in WM or having a new abstract goal (e.g., clearing your thoughts). Also activated was a broad region of medial frontal cortex, extending from the SMA into the cingulate (BA 6). This portion of the SMA has been implicated in imposition of a task set (e.g., [Crone et al., 2006](#); [Dosenbach et al., 2008](#)). Hence, its activity in the Clear conditions may occur because individuals are monitoring or evaluating whether they are indeed "responding" appropriately by clearing the current item out of working memory or removing it from the focus of attention. Finally, both Clear conditions, but not the Maintain and Replace conditions, activated the globus pallidus bilaterally. This portion of the basal ganglia is thought to aid in updating the contents of working memory. More specifically, via its connections to prefrontal cortex, it has been suggested to flexibly control the ability to open a gate that allows for the updating of information to be maintained in working memory ([Hazy et al., 2007](#); [O'Reilly and Frank, 2006](#)). Indeed, there is increased activity in the basal ganglia, including the globus pallidus, when higher-order task goals must be updated ([Nee and Brown, 2013](#)). Moreover, the greater the activity of the globus
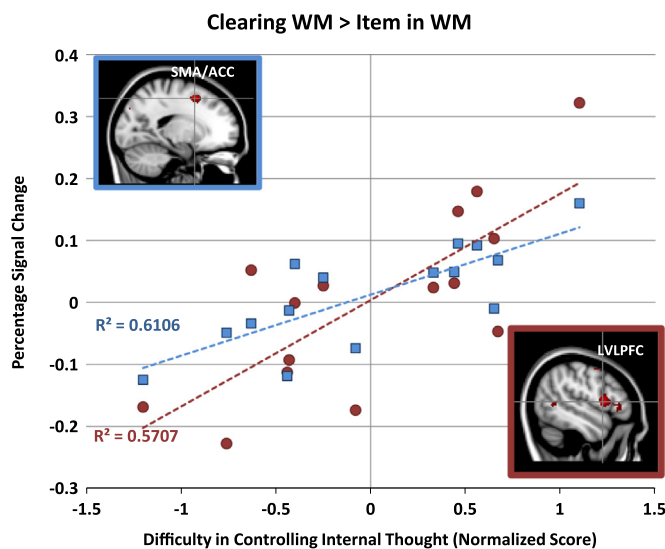
Fig. 6. *Two brain regions that show activity related to individual differences in the tendency towards difficulty in controlling internal thought.* The *y*-axis indicates percentage signal change for the contrast of conditions in which information should be removed from working memory (Targeted Clear and Global Clear) as compared to when it need not (Maintain and Replace). Individuals whose composite score (on the *x*-axis) indicated greater difficulty in controlling internal thought showed greater activation both in cognitive control regions (SMA/ACC) plotted in blue, as well as in regions related to inner speech (left ventrolateral prefrontal cortex: LVLPFC), shown in maroon. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

pallidus during encoding of higher-level task goals, the less distracting and irrelevant information is able to gain access to working memory (McNab and Klingberg, 2008). For both Clear conditions, the updating would involve switching from maintaining a specific representation in working memory to having nothing being maintained. In sum, large portions of the frontal–parietal executive system were activated when individuals needed to clear the contents of working memory.

Also of interest are regions not activated by the two Clear conditions. A priori one might have thought that the Targeted Clear and Global Clear conditions (and perhaps the Replace condition as well) would require inhibition of the current item in working memory. Yet no activation was observed in regions typically associated with inhibitory control, such as the right inferior frontal gyrus (e.g., Goghari and MacDonald, 2009; Jahfari et al., 2011). As such, these findings are consistent with theoretical models (O'Reilly and Frank, 2006) arguing that "inhibition" can occur by simply opening a gate that allows one item to be displaced by something else (for a longer discussion of different models of inhibitory control see Munakata et al., 2011).

At the highest level, the Global Clear condition, as discussed above, engaged additional regions not observed for any other condition- a more frontopolar region (BA 10), portions of the ACC, the insula and the inferior parietal lobe (BA 40). Frontopolar regions help maintain the abstract goal or idea (e.g., Christoff et al., 2009), while ACC activity may indicate the need to suppress any plans or future thoughts about items in memory. The location of activity in the insula is in a region associated with interoception (Craig, 2011). As such, this activation may reflect individuals turning attention inwards to focus on bodily states as a way not to engage in thought (Hölzel et al., 2007), very much akin to what has been reported with meditation (Baer, 2003). Consistent with this speculation, activation in the inferior parietal lobe likely indicates attention to bottom-up information (e.g., Cabeza et al., 2008), which in this case could be bodily states.

4.3. Individual differences

Our study also demonstrated that engagement of the cortical networks recruited when one must remove the contents of working memory is influenced by the degree to which individuals have difficulty controlling internal thought. The larger the degree of self-reported difficulty in controlling internal thought, the greater the activation in BA 6. Whether this activity reflects that individuals have task un-related thoughts that need to be controlled or whether these individuals require more effort to control task-related information in working memory is not clear. Greater difficulty in controlling internal thought was also associated with greater activity in the pregenual region of the cingulate cortex. This relationship suggests that the more an individual has difficulty controlling internal thoughts, the more this region is engaged in monitoring processes either because such thoughts are not being controlled in line with task demands or because one must work hard to ensure that those thoughts are indeed being correctly controlled.

These findings corroborated the validity of the self-rated measures of difficulty in controlling internal thought. The higher the rating of difficulty in controlling internal thought, the greater the activation in a variety of brain regions that would appear to support such thoughts, such as BA 44, semantic processing regions of the temporal lobe and visual cortex. Notably the area of left inferior frontal cortex that shows a relationship with difficulty in controlling internal thought is near the region commonly referred to as Broca's area (which would aid in generating internal thought) and is independent from regions both more dorsal and lateral that have been identified in a meta-analysis as preventing irrelevant memories from intruding into working memory (Nee et al., 2013). Given the sensitivity of our brain-imaging paradigm to index individual differences in controlling internal thought, we believe it may be especially helpful for use with psychiatric populations who may have difficulty controlling thought. We are currently investigating this possibility.

4.4. Limitations and caveats

One of the major limitations of the current study is that it relies on reverse inference with regards to cognitive states on the basis of brain data. As has been clearly articulated by Poldrack (2006, 2011) reverse inference can be problematic. In particular, it is difficult to know whether distinctions in patterns of activation across conditions truly represent distinct cognitive processes, or whether conditions vary in complexity or demand (see also Christoff and Owen, 2006). In such cases, greater activation for a given condition could simply reflect greater usage of some more general process, such as attention, effort, or time on task (e.g., Grinband et al., 2011). Given that we have not utilized a method that can speak more directly to the representation that underlies brain activation, such as multivariate pattern analysis (see reviews by Tong and Pratte, 2012; Serences and Saproo, 2012), our results must be considered in that light.

Nonetheless, there are a number of aspects of the results suggesting that indeed the neural systems underlying the processes we outline in Table 1 are distinct. Most suggestive is that patterns of brain activation across the six different contrasts of interest showed important dissociations in terms regional distribution. First, we found patterns of activation specific to only one of the four conditions (see Fig. 5). The specificity of these different regional patterns of activation across conditions is inconsistent with the idea that the activation in these regions is just reflecting some general process (e.g., attention) that is invoked to varying degrees across conditions. If that were the case, then one would have anticipated varying degrees of activation within the same brain

regions across conditions. Rather, we see clear spatial dissociations in activation across conditions. For example the Global Clear condition uniquely activates the right insula and the Targeted Clear condition uniquely activates the superior frontal gyrus, according to the strict two-step criterion that we employed (i.e., activation must be significantly above zero for the conditions of interest (e.g., Global Clear) and insignificant for all other conditions).

Second, for some regions that exhibited co-activation across conditions (e.g., left precuneus for the Targeted Clear and Global Clear conditions), there was evidence from the connectivity analysis that this activation was not reflecting the same process. Rather, for some regions that co-activated across conditions, the *pattern* of co-activation of this region with other brain regions was distinct across conditions.

While we cannot say exactly what type of process is being invoked by these brain regions because of the problem of reverse inference, nonetheless, we are able to say that there appear to be distinctions between the neural systems involved in removing information from working memory. On the whole, the evidence we provide is strongest for suggesting a distinction between mechanisms involved in a Targeted Clear as compared to a Global Clear. What our results cannot address is the nature of the representations that are being removed or manipulated in working memory. Answering such a question will rely on brain decoding methods, using multivariate pattern analysis or similar approaches, which we are currently pursuing.

It should also be noted that while we speak of the "maintenance" in and "removal" of information from WM, at least some recent research has suggested that information may not be "maintained" in an active state during delay periods but rather be placed outside the focus of attention. According to this evidence, levels of activation of the BOLD signal, at least as assessed via the GLM, may be an insensitive and non-specific measure of memory maintenance (e.g., Lewis-Peacock and Postle, 2012; LaRocque et al., 2013; for review see Postle, in press). While these evolving viewpoints regarding the maintenance of information in working memory are very intriguing, they are unlikely to make the current pattern of results uninterpretable. The logic of our experiment does not rest solely on the idea that information must be maintained in an active state as classically described by Goldman-Rakic, amongst others (e.g., Funahashi et al., 1993), in our Maintain and Replace conditions, but not our Global Clear and Targeted Clear conditions. Even if information is not always actively maintained in the Maintain and Replace condition, the important contrast for our purposes is that the information is maintained to a lesser degree or pushed out of the focus of attention for the Clear conditions. Unlike MVPA approaches that are designed to examine the representations or *contents* of working memory, our initial investigation is designed to focus more on the neural systems that must be engaged to perform *operations* on those representations. Our subsequent work, which is in progress, is designed to examine more carefully what types of representations are held (or not held) during these various operations.

5. Conclusions

The current study identified cognitive control mechanisms that are involved in removing the current contents of working memory. Not surprisingly, these operations engaged the fronto-parietal network, which has been implicated in executive control. Notable, however, is the finding of a hierarchy of control mechanisms engaged depending on the manner in which an item is removed. Replacing one item with another mainly engaged parietal regions and BA 6. Clearing the contents of working memory, whether specifically or generally, required involvement of more anterior regions of BA 9, bordering on BA 10. Globally clearing the contents of working memory engaged additional portions of lateral and prefrontal cortex involved in cognitive control, along with a concomitant shift towards activation in the insula and inferior parietal regions, consistent with a turn of focus towards the body and oneself as a way to avoid thinking about items in working memory.

Activation of these mechanisms was also shown to vary with individual differences in difficulty in controlling internal thought. More specifically, greater difficulty in such control was associated with increased activation of BA 6, consistent with the notion that this region plays an important role in controlling removal of the contents of working memory. As such, the current study not only informs neural models of executive control over working memory but also lays the groundwork for understanding how these various functions may be influenced by variation in both neurologically-normal and clinical populations.

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