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Decoupling of Reaction Time-Related Default Mode Network Activity with Cognitive Demand

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Reaction Time (RT) is associated with increased amplitude of the Blood Oxygen-Level Dependent (BOLD) response in task positive regions (Carp et al., 2010; Grinband et al., 2011; Neta et al., 2014; Prado et al., 2011; Weissman and Carp, 2013; Yarkoni et al., 2009). Few studies have focused on whether opposing RT-related suppression of task activity also occurs. The current study used two Go/No-go tasks with different cognitive demands to examine regions that showed greater BOLD suppression for longer RT trials. These RT-related suppression effects occurred within the DMN and were task-specific, localizing to separate regions for the two tasks. In the task requiring working memory, RT-related decoupling of the DMN occurred. This was reflected by opposing RT-BOLD effects for different DMN regions, as well as by reduced positive RT-related Psycho-Physiological Interaction (PPI) connectivity within the DMN and a lack of negative RT-related PPI connectivity between DMN and task positive regions. The results suggest that RT-related DMN suppression is task-specific. RT-related decoupling of the DMN with more complex task demands may contribute to lapses of attention and performance decrements that occur during cognitively-demanding tasks.

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Background

The default mode network (DMN) was originally characterized as a distributed set of brain regions in which activity is commonly suppressed during goal-directed behavior, but is predominant during rest (Raichle et al., 2001). This set of regions is involved in internally-directed or self-reflective thought (Buckner et al., 2008; Andrews-Hanna et al., 2010a) and therefore, suppression of activity during effortful, externally-directed tasks reflects the inhibition of self-reflective thought during goal-directed behavior. Fox and colleagues (2005) noted that key regions of the DMN, which show suppression during attention and working memory tasks, are also intrinsically anti-correlated with a set of regions involved in cognitive control functions at rest. The DMN is therefore often referred to as the “task negative” network, while anti-correlated behavioral regions are often referred to as the “task positive” network or networks. This antagonistic relationship suggests that the internally-directed functions performed by the DMN are intrinsically-opposing to the externally-directed functions performed by “task positive” network regions. Further evidence for this opposing relationship comes from studies of attentionally-demanding and working memory tasks in which both the amount of task-evoked activity in task positive regions and the amount of task-evoked suppression in DMN regions is parametrically-related to the degree of task difficulty (Fox et al., 2005; McKiernan et al., 2003).

Although this antagonistic relationship between “task positive” network regions and DMN network regions has been well-characterized, no studies to date have focused on Reaction Time (RT)-related suppression of DMN activity. RT-related activity, in which activity increases as RTs become slower, has been found across an extensive set of “task positive” regions for a number of studies and task designs (Carp et al., 2010; Grinband et al., 2011; Neta et al., 2014; Prado et al., 2011; Weissman and Carp, 2013; Yarkoni et al., 2009). Due to the intrinsically-opposing nature of task positive activity and DMN activity, it follows that task positive activity that is RT-related would likewise be opposing to DMN activity that is also RT-related. If such RT-related DMN suppression occurs, this suggests that the RT on any given trial is a by-product of on-going network dynamics.

Although RT-related DMN suppression during task has not been well-studied, intrinsic DMN anti-correlation is associated with summary measures of RT-related trait behavior. The relationship between individual differences in RT variability and DMN anti-correlation has been found in a number of resting-state (Kelly et al., 2008; Barber et al., 2015) and task studies (Kelly et al., 2008; Fassbender et al., 2009). Individuals with a greater degree of antagonistic DMN-task positive network connectivity tend to have reduced RT variability. In addition, antagonistic DMN connectivity is altered in individuals with Attention Deficit Hyperactivity Disorder (ADHD) (Castellanos et al., 2005; Castellanos and Tannock, 2002; Barber et al., 2015; Fassbender et al., 2009), a population that has consistently elevated RT variability (Castellanos and Tannock, 2002; Castellanos et al., 2005). These studies provide consistent evidence that DMN antagonism is related to RT variability; however, few studies have examined task-evoked RT-related DMN effects. One task fMRI study found that stronger connectivity between the prefrontal cortex and the DMN was associated with slower RTs on the current trial, but faster RTs on the previous trial (Prado and Weissman, 2011). Other studies have examined RT variability during task, or the degree to which a

given trial deviates from the mean RT (Esterman et al., 2013; Rosenberg et al., 2015). These studies have all implicated DMN regions; however, this task-evoked RT-variability measure does not index RT-related activity directly and, in many cases, RT-related activity is regressed out (Esterman et al., 2013; Rosenberg et al., 2015). More DMN activity is found during periods of low RT variability, but the relationship between DMN activity and attention state is nuanced (Esterman et al., 2013; Johnson et al., 2015). Esterman and colleagues (2013) found that DMN activity during attention lapses was very different during periods of low and high RT variability. While the current study expected to find greater DMN suppression with slower RTs, previous findings have been mixed and no studies have focused on RT-related DMN suppression.

The current study examined RT-BOLD suppression using two Go/No-go tasks with differing cognitive demands to determine whether RT-BOLD suppression occurred in DMN regions and whether this suppression depended on the particular demands of the task. The Simple task required a perceptual decision (green=Go, red=No-go), while the Repeat task required working memory to guide the decision (color change=Go, color repeat=No-go). In addition to these negative RT-BOLD effects, RT-related connectivity was examined for the medial prefrontal cortex (MPFC), the anterior node of the DMN, to determine whether “task positive” network-DMN antagonism increases as RTs become slower.

Methods

Participants

22 healthy, right-handed adults (10 males), aged 20 – 40 years (mean = 28.97, SD = 5.22) participated in the study. Participants were recruited through local advertisements and had no history of mental illness or substance abuse. The study was approved by the Johns Hopkins Medicine Institutional Review Board. Informed consent was signed before task participation.

Procedure

Two Go/No-go tasks (Barber et al., 2013; Barber et al., 2016) were performed by all participants. For each trial, spaceship stimuli were presented for 300 milliseconds followed by a 1500 millisecond inter-stimulus interval. 10 second blocks of rest occurred at the beginning, end, and four times throughout each run. Separation of hemodynamic events was achieved through the use of a trial epoch (1.8 seconds) that was not a multiple of the TR (2.5 seconds) and through the use of the occasional rest blocks. The use of incoherent trial and TR epochs is an effective alternative to jittering the interval between trials and allows the BOLD response to be sampled at different intervals from trial onset for each trial (Henson, 2007).

The proportion of Go:No-go trials was 3:1, with 78 Go trials and 26 No-go trials occurring in each run. Participants performed two runs each of the two Go/No-go tasks. Each run was preceded by instructions and 20 practice trials. Half of the participants performed the two Simple runs first and the other half performed the two Repeat runs first.

For the Simple task paradigm, stimulus-response associations were well-ingrained and easy to remember. Go stimuli were green while No-go stimuli were red. For the Repeat task, a more complex task rule that required working memory was used. Participants were required to remember the color of the previous stimulus. A change in the stimulus color signaled a Go trial, while a repetition of the stimulus color signaled a No-go trial. For this task, 50% of stimuli were blue and 50% of stimuli were yellow.

Imaging data were acquired on a Philips 3T scanner. This included a high-resolution anatomical scan (MPRAGE, 8-channel head coil, TR = 7.99 milliseconds, TE = 3.76 milliseconds, Flip angle = 8°, voxel-size = 1 mm³) for image coregistration, segmentation and normalization processing steps. The behavioral task was performed during four fMRI runs (2D SENSE EPI, 8-channel head coil, TR = 2500 milliseconds, TE = 30 milliseconds, Flip angle = 70°, voxel-size = ~3 mm³). Each run was 4 minutes and 5 seconds in duration.

Preprocessing of functional data was performed using SPM8 and included: slice time correction, motion correction, co-registration of the first functional image in the run to the MPRAGE image, segmentation of gray matter, white matter and cerebrospinal fluid (CSF) using SPM probabilistic tissue priors, normalization to standard MNI space, resampling of voxels to 2 mm³, and 8mm full width at half maximum spatial smoothing.

The current study used the same data set as a previous examination of RT-related activity in Go and No-go trials (Barber et al., 2016); however, new general linear models were created in SPM8 in order to examine negative RT effects in the two tasks. First-level models included up to seven condition trial onset regressors (Post-Rest Go, Go, Negative Go RT, No-go, Commission Error, Omission Error, and Anticipatory Error Trials on which the RT was less than 200 msec). Since Post-Rest Go trials were significantly slower than other Go trials, these trials were included as a separate regressor and were not examined in group contrasts. RT on Go trials was modeled as a parametric modulation regressor in which the Go regressor was scaled by RT, mean-centered, divided by the RT standard deviation of each block, and then multiplied by -1 (to reflect greater suppression of activity as RTs increased). All regressors included 0-duration impulse functions at event onset, which were then convolved with the canonical hemodynamic response function (HRF), and its temporal and dispersion derivatives. In addition, each functional run included nuisance regressors (six motion parameters, mean white matter, mean CSF, mean whole-brain time-courses) and a block regressor.

First-level analyses were performed for the Negative Go RT regressors, which reflects the RT regressor multiplied by -1. These analyses tested for voxels in which activity was associated with the negative RT regressor. Second-level one-sample t-tests were performed to determine those regions in which the RT association was significantly different from zero. Go RT contrast maps were thresholded at a voxel-wise p-value of 0.01 and were multiple-comparisons corrected at a cluster-level p-value of 0.05 (Worsley et al., 1996).

Follow-up analyses were performed to examine task differences in the RT regressors (i.e. whether there was an interaction between the RT regressors for the two tasks). This was done to determine whether any RT-related activity was significantly different for the two

tasks. At the second-level, these analyses were thresholded in the same manner as the primary RT analyses.

To determine whether RT-related suppression was confined to the DMN, a previous resting-state parcellation scheme (Yeo et al., 2011) was applied to each contrast. This parcellation scheme was consistent across different samples of subjects and was similar to that found in other studies examining full-brain resting-state parcellation (Power et al., 2011). The parcellation divided the brain into 7 total networks. These included the DMN and 6 task-positive networks: Visual, Somatomotor (SM), Dorsal Attention Network (DAN), Ventral Attention Network (VAN), which included both the Ventral Attention and Cingulo-Opercular sub-networks (Power et al., 2011), Limbic, and Frontoparietal Network (FPN). The parcellation mask was resampled to the same space as the functional preprocessed images. The overlap between the significant voxels in each contrast map and the 7 networks was determined. For each contrast, the total number of significant voxels in each sub-network and the proportion of significant voxels in each sub-network out of the total number of significant voxels were computed.

For the analyses examining task differences in RT effects, a conjunction with the Yeo DMN parcel was performed. This was done to determine whether task differences in RT-related suppression were confined to the DMN.

Psycho-Physiological Interaction (PPI) models were created to determine regions that change their connectivity with the MPFC for Go events as a function of RT. PPI assesses the degree to which connectivity changes as a function of task demands (Friston et al., 1997; O'Reilly et al., 2012). For the current study, we examined the degree to which connectivity with the MPFC changed as a function of RT. The MPFC, a node of the Default Mode Network (DMN), was chosen as the seed region because it was consistently related to RT in both tasks, but showed differential peak localization for the two tasks. In the Simple task, RT-related suppression localized to the dorsal MPFC (dMPFC), while in the Repeat task RT-related suppression localized to the ventral MPFC (vMPFC). Both of these MPFC regions were examined to determine whether they show differential RT-related PPI connectivity for the two tasks.

To construct the PPI regressor, Go RTs in each run were first converted to a proportion value ranging from 0.01 to 1.01 by subtracting the absolute value of the minimum RT and dividing by the RT range. The resulting scaled-RT values were proportional to the original RT values with the fastest RT in a run being 0.01 and the slowest RT in a run being 1.01. These values were then multiplied by the Go onset regressor to create a new parametric modulation regressor that reflected the RT proportion for that run. This Go RT proportion regressor was then multiplied by the deconvolved MPFC timecourse to create the PPI regressor. To extract the MPFC timecourse, two 9-mm MPFC seeds were created at the following MNI coordinates: dMPFC: 0 58 36, and vMPFC: 0 56 -4. For each seed, the timecourse was the first eigenvariate time-course across those voxels that showed an association with the convolved Go RT regressor (MPFC-BOLD). Go RT activity was deconvolved from the MPFC-BOLD timecourse, prewhitened, and multiplied by the Go RT Proportion trial onset regressor (Gitelman et al., 2003). This PPI timecourse was then convolved with the

canonical HRF and its temporal and dispersion derivatives to create the PPI regressors. Two first-level PPI models were created for the two MPFC seeds. These models contained the PPI regressors and the MPFC-BOLD time course, in addition to all other regressors included in the first-level Go RT analysis (McLaren et al., 2012; O'Reilly et al., 2012).

Second-level, one-sample t-tests were performed to evaluate the significance of the PPI regressor. These contrasts tested for regions with increased and decreased MPFC connectivity with slower RT. The PPI contrasts were thresholded in the same manner as the Go RT second-level contrasts.

To determine whether task differences existed in RT-related PPI connectivity, the PPI regressors for the two tasks were directly contrasted to test for an interaction between the two tasks. At the second level, this analysis was thresholded in the same manner as all previous analyses. The RT-related task differences were then compared to RT-related suppression as well as RT-related activation to better understand the effects in the two individual tasks.

Results

Figure 1 and Table 1 display the regions with significant negative RT-related activity in the two tasks. This activity occurred almost entirely within the DMN for both tasks (Figure S1, top panels), consistent with predictions that greater suppression of DMN activity occurs for slower RT trials. Although the significant voxels were largely confined to the DMN for both tasks, peak activity localized to different regions for the two tasks. For the Simple task, negative RT-related activity occurred in the dMPFC and bilateral angular gyrus; while for the Repeat task, this occurred in the vMPFC and hippocampus. In addition, regions with significant positive RT-related activity were examined to determine whether any positive RT-related activity occurred in the DMN. Positive RT-related activity was mostly confined to task positive network regions in both tasks. Very few DMN voxels showed positive RT-related activity for the Simple task; however, for the Repeat task, there was a sizeable number of DMN voxels showing this type of activity. While the majority of positive RT-related activity still occurred within task positive regions, the results reveal an unexpected finding that different DMN regions show opposing RT-related effects.

Follow-up examination of task differences in RT-related activity revealed that there was more suppression in the Simple task than the Repeat task (i.e. Repeat RT > Simple RT) for a distributed set of DMN regions (Figure S2, Table S1). While the regions showing the RT-related task differences were primarily within the DMN, they were not strictly confined to this network and also included adjacent regions (Figure S2 and S3) that formed part of neighboring task positive networks. The significant differences in RT-related activity for the two tasks are presented in Table S1.

To investigate this further, the regions showing RT-related task differences were masked by those voxels showing RT-related effects in each of the individual tasks. A large number of those voxels that showed task differences (Repeat RT > Simple RT) had greater RT-related suppression in the Simple task (932 voxels); however, a large number also had RT-related

positive activation in Repeat task (1710 voxels). Therefore, task differences were driven by both greater RT-related suppression in the Simple task, but also greater RT-related activation in the Repeat task. In addition, the majority of those voxels with greater RT-related suppression in the Simple task occurred in the DMN (823 voxels), and a sizable number of those voxels showing positive RT-related activation in the Repeat task also overlapped with the DMN (773 voxels). Therefore, these task differences were due not just to greater RT-related suppression of DMN regions in the Simple task, but also greater positive RT-related activation of DMN regions in the Repeat task.

Table S3 shows that the opposite pattern of RT-related task differences (i.e. greater RT-related suppression in the Repeat task or Simple RT > Repeat RT) occurred for very few isolated DMN voxels (Figures S2 and S3, Table S1). Further, examination revealed that this type of task difference effect was entirely driven by greater RT-related positive activity in the Simple task rather than any RT-related suppression.

Positive RT-related PPI connectivity examined regions that are more connected as RTs become slower. For both of the MPFC seeds, such positive RT-related PPI connectivity occurred across a distributed set of DMN regions (Figure 2-5 and Tables 2 and 3). For the Simple task, both the ventral and dorsal MPFC regions had increasing connectivity with the DMN as RTs became slower. Both of these MPFC regions also showed corresponding negative RT-related PPI connectivity (i.e. decreases in connectivity, or in this case, greater anti-correlation as RTs become slower) across a number of task positive networks, particularly within the Visual network, DAN, VAN, and FPN (Figure S4).

For the Repeat task, positive RT-related PPI connectivity with both MPFC seeds occurred with a local region of the MPFC and not across the more distributed set of DMN regions that were found for the Simple task PPI connectivity. Negative RT-related PPI connectivity for the two MPFC seeds was not significant for any region within the task positive networks or elsewhere. Therefore, RT-related PPI connectivity was not dependent on the particular MPFC seed that was chosen but was dependent on task demands.

To further examine task differences in RT-related PPI connectivity for the two MPFC seeds, task interaction effects were examined. No regions showed significantly greater RT-related PPI connectivity for either task, suggesting that the weak PPI connectivity in the Repeat task may have been due to subthreshold estimates. To determine whether this was the case, RT-related PPI connectivity was re-examined for the Repeat task using a more liberal voxel-level threshold ($p < 0.05$). A distributed set of DMN regions was found however, most of these regions remained subthreshold at the cluster-level (i.e. all except the MPFC for both seeds). Likewise, for the negative connectivity, the reduced threshold resulted in a distributed set of task-positive regions; however, the connectivity was much less extensive and was mostly sub-threshold. For the dMPFC seed, one region did survive multiple-comparisons correction. This was a large area of the posterior parietal cortex (i.e. 6775 voxels), which mainly overlapped with the DMN. Therefore, although task differences in RT-related connectivity were not significant, the results suggest that RT-related connectivity in the Repeat task is much weaker and less-extensive.

Discussion

The current study found that RT-related suppression of task activity occurred within DMN regions. This was expected given previous findings that activity in task positive regions show both intrinsic and task-related antagonism with the DMN (Fox et al., 2005; Barber et al., 2013). These findings suggest that RT on any given trial is related to on-going intrinsic network dynamics. The particular DMN regions that showed this RT-related suppression differed for the two tasks. In the Simple task, RT-related suppression occurred in the dMPFC and bilateral angular gyrus. For the Repeat task, it was confined to the vMPFC. Task differences in RT-related activity revealed that, in the Repeat task, a number of DMN regions showed positive RT modulation and further that these regions were modulated along with adjacent task positive regions (see Figure S2). Therefore, a functional decoupling, or break-down of the functional-relatedness, of the DMN occurred during the cognitively-demanding Repeat task. Some DMN regions (i.e. the vMPFC) showed the expected pattern of RT-related suppression, while other DMN regions (i.e. parts of the middle frontal and angular gyrus) showed RT-related activation. RT-related connectivity results corroborated this DMN decoupling. For the Simple task, RT-slowness was associated with increased connectivity between the MPFC and the rest of the DMN and was associated with increased antagonistic connectivity between the MPFC and an extensive set of task positive regions. For the Repeat task, however, RT-slowness was only associated with increased MPFC connectivity within a local area and did not result in increased positive connectivity with the rest of the DMN or antagonistic connectivity for any task positive regions. Examination of task-differences in RT-related connectivity yielded no significant differences, and follow-up examination revealed that RT-related PPI connectivity was subthreshold and much less extensive in the Repeat task.

The DMN is involved in introspective, self-reflective, or future-directed thought (Buckner, Andrews-Hanna, and Schachter, 2008) and has a well-known antagonistic relationship with task positive networks, in particular the dorsal attention network (Fox et al., 2005). This antagonism is thought to sub-serve goal-directed behavior that requires externally-directed attention through the suppression of internally-directed thoughts. RT-related suppression of the DMN was thereby expected given that RT-related positive activation of task positive regions has previously been reported in a number of studies (Carp et al., 2010; Grinband et al., 2011; Neta et al., 2014; Prado et al., 2011; Weissman and Carp, 2013; Yarkoni et al., 2009). Increased DMN suppression for slower RT trials may therefore be related to on-going intrinsic dynamics between task-positive and DMN regions (Fox et al., 2005).

This RT-related DMN-task positive antagonism was also corroborated by the PPI-connectivity findings in which the MPFC, the anterior-most part of the DMN, becomes more positively connected with the rest of the DMN, and becomes more negatively connected with task positive regions, as RTs become slower. Within the Simple task, these connectivity results spanned broad distributed regions of the DMN. Likewise, negative RT-related MPFC connectivity for the Simple task occurred for a broad, distributed set of task positive regions. This RT-related MPFC anti-correlation occurred across most of the task positive networks with robust, significant effects in the Visual, Somatomotor, Dorsal Attention, Ventral Attention, and Fronto-Parietal Networks. Therefore, evidence of RT-related DMN-task

positive antagonism was found in both the task-evoked activity, as well as the PPI connectivity findings. This is in-line with previous findings that task-evoked antagonism with the DMN is related to intrinsic network relationships (Fox et al., 2005) and further suggests that the RT on any given trial may reflect these on-going dynamics. This is not surprising given that a number of studies have found associations between RT-related trait behavior and the degree to which the DMN and task positive networks are anti-correlated (Barber et al., 2015; Fassbender et al., 2009; Kelly et al., 2008). However, future research is needed to understand the relationship between RT-related suppression in the DMN and task-evoked RT-variability that has been examined in previous studies (Esterman et al., 2013; Johnson et al., 2015; Rosenberg et al., 2015). The DMN has likewise been implicated in RT-variability during task; in which DMN activity is higher during periods of RT stability (Esterman et al., 2013; Johnson et al., 2015). It may be that the DMN is less anti-correlated with task positive regions during these periods.

Although RT-related suppression was confined to the DMN for both tasks, it occurred in different DMN regions for the two tasks. For the Simple task, greater suppression of activity for slower RT trials occurred in the dMPFC and bilateral angular gyrus; whereas, for the Repeat task, this effect occurred only in the vMPFC. This difference may be due to task-specific antagonism between task positive sub-networks and the DMN. RT-related positive activity occurs in distinct task positive networks for the two tasks (Barber et al., 2016), which may lead to task-specific RT-related suppression. The distinct set of DMN regions showing RT-related suppression for the two tasks is in-line with previous findings that there may be distinct functional sub-networks within the DMN (Andrews-Hanna et al., 2010b).

RT-related PPI connectivity, on the other hand, was not confined to the same network sub-regions for the two tasks. The two MPFC seeds: dorsal and ventral, were chosen because of their respective negative RT effects for the Simple and Repeat tasks. However, both the ventral and dorsal seeds showed similar patterns of connectivity and antagonism.

Although RT-related suppression was almost-entirely confined within the DMN, follow up examination of RT-related positive activity found that, for the Repeat task, a number of DMN regions showed this unexpected pattern of activity. This occurred in a spatially-distinct set of DMN regions from those showing the expected RT-related suppression. This finding suggests that RT-slowness in the cognitively-demanding Repeat task leads to a de-coupling of the DMN. VMPFC became more suppressed with longer RTs; while, parts of middle frontal cortex and the angular gyri became more strongly active, along with task-positive regions.

There are a couple of potential mechanisms that could account for the observed RT-related de-coupling of the DMN in the Repeat task. The first is that continual DMN suppression over the course of the Repeat task could be an unstable state which results in inadequate suppression of parts of the DMN for slower RT trials. We previously found that DMN activity is more suppressed for Repeat Go than Simple Go trials (Barber et al., 2013). It may be that continual suppression of the DMN as observed in the Repeat task, results in DMN instability and greater DMN interference on slow RT trials. Another possibility is that part of the DMN participates in cognitive processes, along with task positive regions, on slower RT

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trials. This possibility is supported by previous findings that the DMN, under certain task conditions, affiliates with cognitive control regions (Spreng et al., 2010). This is further supported by the current findings that some of the regions showing RT-related task differences (Repeat RT > Simple RT), overlapped with the DMN and showed, not only RT-related suppression during the Simple task, but also RT-related positive activation along with adjacent fronto-parietal regions during the Repeat task. Therefore, in the Repeat task, some DMN regions are showing the expected pattern of RT-related suppression, while other regions are showing positive RT-related activity. We previously reported RT-related positive activity in cognitive control regions (Barber et al., 2016). Follow-up examination of those findings revealed that positive RT-related activity for the Repeat task occurred primarily in fronto-parietal regions; however, this effect also occurred in parts of the DMN that were adjacent to the fronto-parietal network (i.e. both middle frontal and angular gyrus regions). This finding is consistent with the interpretation that portions of the frontoparietal network and DMN show RT-related functional coupling under certain task demands. It may be that for cognitively demanding tasks, part of the DMN shows greater participation in cognitive control functions as RTs become slower.

DMN de-coupling during the Repeat task was further supported by findings that RT-related PPI connectivity of the DMN breaks down during the Repeat task. In the Simple task, the DMN becomes more connected with a distributed set of DMN regions as RTs become slower (Figure 2 and 3). Likewise, the DMN becomes more antagonistic with a distributed set of task positive regions as RTs become slower. This effect occurred across a number of task positive sub-networks (Figure 2 and 3) and was not dependent on which MPFC region was examined. Therefore, for the Simple task, increased RT-related connectivity for slower RT trials was a system-wide effect. In the Repeat task, however, RT-related increases in DMN connectivity only occurred around a local MPFC region for both the dorsal and ventral MPFC seeds, and showed a lack of RT-related antagonism in task positive regions. The results support the finding that RT-related functional integrity of the DMN breaks down during the cognitively-demanding task. This corroborates the findings of a previous study in which the inter-subject association between mean RTs and connectivity in DMN regions shows state-dependent de-coupling (Gao et al., 2013). This is also supported by a study that found that DMN-task positive network connectivity was associated both with RT on the current and subsequent trial (Prado and Weissman, 2011). Further research is necessary to better understand whether RT-related DMN de-coupling occurs with the recruitment of specific cognitive control processes (e.g. working memory) or whether it occurs, more generally, with increased cognitive demand.

Conclusions

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Across two Go/No-go tasks, longer RTs were associated with increased suppression in the DMN; however, the localization of RT effects differed for the two tasks. For the cognitively-demanding task, RT-related de-coupling of the DMN occurred. Some DMN regions showed the expected finding of more suppressed activity for slower RT trials; while other DMN regions showed increased activity for slower RT trials along with task positive regions. This de-coupling of the DMN was likewise reflected in the absence of system-wide RT-related coordination of the DMN, which was found in the perceptual decision task. RT-related de-

coupling of the DMN during cognitively-demanding tasks may contribute to performance decrements and may inform the understanding of disorders involving inattention (e.g. attention deficit hyperactivity disorder).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Regions showing a negative effect of RT in the Simple Task and in the Repeat Task. The color bars represent the T-values for significant voxels.

Figure 2. Regions showing positive and negative RT-related PPI connectivity with the dMPFC in the Simple Task. The PPI seed is in black. The color bars represent the T-values for significant voxels.

Figure 3.

Regions showing positive and negative RT-related PPI connectivity with the vMPFC in the Simple Task. The PPI seed is in black. The color bars represent the T-values for significant voxels.

Figure 4. Regions showing positive and negative RT-related PPI connectivity with the dMPFC in the Repeat Task. The PPI seed is in black. The color bars represent the T-values for significant voxels.

Figure 5. Regions showing positive and negative RT-related PPI connectivity with the vMPFC in the Repeat Task. The PPI seed is in black. The color bars represent the T-values for significant voxels.

Table 1

Regions with Significant RT-related Decreases in Activation. The size of each region represents the number of significant voxels.

Negative Simple RT								
region	side	BA	significance	size	peak T	x	y	z
Superior Medial Frontal Gyrus/Superior Frontal Gyrus	B	9/10/8	<0.001	4075	4.48	-2	42	54
Anterior Cingulate Gyrus/Medial Orbital Frontal		32/6			4.32	18	38	54
Middle Frontal Gyrus					4.02	10	64	0
Angular Gyrus/Middle Temporal Gyrus	L	39	0.038	526	4.39	-46	-58	32
Angular Gyrus/Inferior Parietal Lobule	R	40	0.052	490	3.7	58	-56	34
					3.38	46	-58	38
					3.32	52	-70	32
Negative Repeat RT								
region	side	BA	significance	size	peak T	x	y	z
Precentral Gyrus/Postcentral Gyrus	B	6/4/3/2/32	<0.001	5141	9	0	6	56
Superior Medial Frontal Gyrus					4.46	-8	46	-2
					2.68	10	40	-2
Hippocampus/Putamen/Parahippocampal Gyrus	L		0.05	476	3.55	-22	-10	-20
					3.38	-28	4	-8

Table 2

Regions with Significant RT-related PPI connectivity with the vMPFC. The size of each region represents the number of significant voxels.

vMPFC Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
Superior Medial Frontal/Superior Frontal Gyrus/	B	10/8/9/32	<0.001	11271	15.90	4	60	-4	
Middle Frontal Gyrus/Anterior Cingulate Cortex		6/24/11			14.55	-6	50	-6	
Medial Orbital Frontal/Superior Orbital Frontal					13.68	2	48	-2	
Supplementary Motor Area									
Precuneus/Middle Cingulate Cortex	B	31/7/23	<0.001	5021	10.50	-8	-48	32	
Posterior Cingulate Cortex/Calcarine Sulcus/Cuneus		30/29			9.09	6	-54	20	
Lingual Gyrus					8.99	-4	-58	26	
Angular Gyrus/Middle Temporal Gyrus	L	39/19/7	<0.001	1570	9.19	-46	-66	26	
Middle Occipital Gyrus/Inferior Parietal Lobule									
Angular Gyrus/Middle Temporal/Middle Occipital	R	39/40	0.001	982	7.64	50	-62	26	
Middle Temporal Gyrus/Inferior Temporal Gyrus	L	21	0.024	582	4.87	-58	-14	-12	
					4.57	-48	2	-32	
					4.36	-60	-6	-16	
vMPFC Negative Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
Supramarginal Gyrus/Inferior Parietal Lobule/Lingual Gyrus	B	40/7/18/19	<0.001	20808	7.67	50	-36	56	
Superior Parietal Lobule/Calcarine Sulcus		2/17/6/22			7.47	-58	-44	34	
Superior Temporal Gyrus/Precuneus		9/5/42/3/			7.43	62	-34	46	
Middle Occipital Gyrus/Postcentral Gyrus		37/44/1							
Superior Occipital Gyrus/Middle Temporal Gyrus		13/30/23/4							
Precentral Gyrus/6th Cerebellar Lobule									
Inferior Frontal Operculum/Fusiform Gyrus									
Cuneus/Inferior Temporal Gyrus/Insula									
Rolandic Operculum/6th Cerebellar Lobule/Angular Gyrus									
Crus I Cerebellum/Superior Temporal Pole									
Inferior Occipital Gyrus/Inferior Frontal Trigeminal									

vMPFC Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
7th Vermis Cerebellum									
Middle Frontal Gyrus/Inferior Frontal Operculum	R	9/6/10/46	<0.001	5750	6.58	40	34	38	
Inferior Frontal Trigeminal/Insula/Precentral Gyrus		13/44/47			5.85	54	14	0	
Superior Frontal Gyrus/Superior Temporal Pole		45/22/8							
Rolandic Operculum/Inferior Frontal Orbital					5.54	48	40	8	
Middle Frontal Gyrus/Inferior Frontal Trigeminal	L	10/9/46	0.001	958	5.50	-34	46	32	
					5.07	-42	48	18	
					4.77	-38	36	38	
vMPFC Repeat RT									
region	side	BA	significance	size	Peak T	x	y	z	
Medial Orbital Frontal/Superior Medial Frontal	B	10/32/11	<0.001	1280	5.15	-4	56	-4	
Anterior Cingulate Cortex					4.20	6	50	-4	
					4.13	0	50	4	
vMPFC Negative Repeat RT									
region	side	BA	significance	size	Peak T	x	y	z	
No Significant Findings									

Table 3

Regions with Significant RT-related PPI connectivity with the dMPFC. The size of each region represents the number of significant voxels.

dMPFC Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
Superior Medial Frontal/ Superior Frontal Gyrus/	B	10/8/9/32	<0.001	10335	14.21	2	56	38	
Middle Frontal Gyrus/ Anterior Cingulate Cortex		6/11/24			9.99	-4	44	54	
Medial Orbital Frontal/ Supplementary Motor Area					8.71	0	48	20	
Superior Orbital Frontal									
Angular Gyrus/ Middle Temporal Gyrus	L	39/40/19	<0.001	1451	9.26	-48	-64	28	
Middle Occipital Gyrus/ Inferior Parietal Lobule					5.90	-42	-70	42	
Precuneus/ Posterior Cingulate Cortex	B	31/7/23/30	<0.001	2182	8.27	-6	-52	28	
Middle Cingulate Cortex		30/29							
Middle Temporal Gyrus/ Middle Temporal Pole	R	21/38	0.002	883	6.42	62	-4	-20	
Superior Temporal Pole/ Superior Temporal Gyrus					6.06	46	16	-30	
Inferior Temporal Gyrus					4.16	54	0	-32	
Angular Gyrus/ Middle Temporal Gyrus	R	39/40	0.010	658	6.04	48	-60	30	
Inferior Frontal Orbital/ Inferior Frontal Trigeminal	L	47/45	0.001	982	5.10	-46	28	-10	
					3.86	-52	22	10	
					3.35	-34	42	-8	
Middle Temporal Gyrus/ Inferior Temporal Gyrus	L	21	<0.001	1059	5.00	-50	-8	-24	
Superior Temporal Pole/ Middle Temporal Pole					4.81	-42	6	-32	
					4.80	-56	-16	-12	
dMPFC Negative Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
Supramarginal Gyrus/ Inferior Parietal Lobule	B	40/7/18/19	<0.001	23566	7.25	48	-38	58	
Superior Temporal Gyrus/ Postcentral Gyrus/ Precuneus		2/13/22/17			6.46	40	-50	56	
Superior Parietal Lobule/ Middle Occipital Gyrus		3/5/42/6			6.20	-34	-52	54	
Calcarine Sulcus/ Lingual Gyrus/ Superior Occipital Gyrus		30/41/31/4							
Cuneus/ Middle Temporal Gyrus/ Insula		9/1/43/39/							
Rolandic Operculum/ Precentral Gyrus/ Fusiform Gyrus		44/23/37							

dMPFC Simple RT									
region	side	BA	significance	size	Peak T	x	y	z	
Inferior Frontal Operculum/Angular Gyrus/Heschl's Gyrus									
Superior Temporal Pole/Precentral Gyrus									
Middle Cingulate Cortex/Inferior Occipital Gyrus									
Paracentral Lobule/4th, 5th, & 6th Cerebellar Lobule									
Middle Frontal Gyrus/Insula/Superior Frontal Gyrus	R	6/9/10	<0.001	4065	5.60	58	10	6	
Inferior Frontal Operculum/Inferior Frontal Trigeminal		13/46/44			5.57	40	42	30	
Precentral Gyrus/Rolandic Operculum		22/47/45			5.34	36	0	58	
Superior Temporal Pole/Supplementary Motor Area									
Middle Frontal Gyrus/Inferior Frontal Trigeminal	L	10/46/9	0.010	667	4.82	-40	44	30	
					4.07	-42	52	18	
					3.68	-48	38	24	
dMPFC Repeat RT									
region	side	BA	significance	size	Peak T	x	y	z	
Superior Medial Frontal/Superior Frontal Gyrus	B	10/9/8	<0.001	3788	4.93	-6	60	28	
Medial Orbital Frontal/Anterior Cingulate Cortex		32/6/11			4.72	0	58	38	
					4.68	-6	64	18	
dMPFC Negative Repeat RT									
region	side	BA	significance	size	Peak T	x	y	z	
No Significant Findings									