Thinking About a Task Is Associated with Increased Connectivity in Regions Activated by Task Performance

Michael D. Gregory,[1–3,*] Edwin M. Robertson,[4] Dara S. Manoach,[2,3,5] and Robert Stickgold[3,6]

Abstract

We investigated whether functional neuroimaging of quiet "rest" can reveal the neural correlates of conscious thought. Using resting-state functional MRI, we measured functional connectivity during a resting scan that immediately followed performance of a finger tapping motor sequence task. Self-reports of the amount of time spent thinking about the task during the resting scan correlated with connectivity between regions of the motor network activated during task performance. Thus, thinking about a task is associated with coordinated activity in brain regions responsible for that task's performance. More generally, this study demonstrates the feasibility of using the combination of functional connectivity MRI and self-reports to examine the neural correlates of thought.

Key words: conscious thought; functional connectivity; resting state; unconstrained thought

Introduction

AN ESSENTIAL GOAL of neuroscience is to understand how thinking is represented in the brain. Functional neuroimaging during wakeful rest has shown that brain activity is organized across multiple networks (Smith et al., 2009). The occurrence of spontaneous undirected thought is reflected in the activation of subsystems of the default network (Christoff et al., 2009). However, regions not thought to be part of the default network have also been associated with undirected thought, suggesting that examinations limited to the default network alone are not sufficient to capture the neurobiological underpinnings of thought (Fox et al., 2015). It has also been shown that the resting brain connectivity of task-specific networks is both modulated by learning (Albert et al., 2009; Stevens et al., 2010; Tambini et al., 2010) and associated with memory consolidation (Deuker et al., 2013) of the respective task. To our knowledge, however, no studies have attempted to identify the neural correlates of specific thoughts during wakeful rest. In this study, we used a postscan mentation questionnaire and functional connectivity MRI (Biswal et al., 1995) to examine the neural correlates of thinking about a just-completed task.

We previously reported that increased resting-state connectivity in the motor network, measured immediately after learning a finger tapping motor sequence task (MST) (Karni et al., 1998), predicts sleep-dependent performance improvement measured the following day (Gregory et al., 2014). Using the same data set, we now demonstrate that self-reports of the amount of time spent spontaneously thinking about the task during this post-training rest correlates with connectivity between a different set of brain regions—those that were activated during task training.

Materials and Methods

The study design and experimental methods are detailed in our previous publication (Gregory et al., 2014) and are summarized here. Fourteen healthy participants (age 24.6 ± 1.8 years, six males) provided written informed consent and completed the study. The study was approved by the Partners Human Research Committee. Participants completed a resting functional MRI (fMRI) scan immediately before and after training on the MST. The MST involves repeatedly typing a five-digit sequence displayed on the screen, with the fingers of the left hand, as quickly and as accurately as possible, for twelve 30-sec trials, separated by 30-sec rest periods (Walker et al., 2002). Immediately after the post-task rest scan, participants were informed as follows: "We'd like to

[1]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
[2]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts.
[3]Harvard Medical School, Boston, Massachusetts.
[4]Centre for Cognitive Neuroimaging, Institute of Neuroscience & Psychology, Glasgow, United Kingdom.
[5]Department of Psychiatry, Massachusetts General Hospital, Charlestown, Massachusetts.
[6]Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
*Present address: Section on Integrative Neuroimaging, Clinical and Translational Neurosciences Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

ask you a few questions about what you were thinking during the last scan, so take a few moments now to try and remember what you were thinking.'' After they were removed from the scanner, they were asked to divide a pie chart into a maximum of five slices to indicate the proportion of time during the post-MST rest scan they had spent thinking about (1) the past, (2) the future, (3) the MST, (4) other things, and (5) nothing. The percentage of the pie chart allocated to the ''MST'' was taken as the percentage of time spent thinking about the task.

Image acquisition

Participants were scanned using a Siemens 3T Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) and a 12-channel head coil. We first acquired a high-resolution structural scan using a 3D rf-spoiled magnetization prepared rapid gradient echo (MP-RAGE) sequence acquired in the sagittal plane (TR/TE/Flip = 2530 msec/1.64 msec/7°; FOV = 256 mm, 176 – 1 mm isotropic slices). This was followed by three functional scans—rest, task performance, and rest—that used gradient echo T2* weighted sequences and contiguous slices parallel to the intercommissural plane. Rest scans took 6′12″ each (TR/TE/Flip = 3000 msec/30 msec/85°; FOV = 216 mm; 47 – 3 mm isotropic slices, acquired interleaved). The task performance scan took 12′42″ (TR/TE/Flip = 3000 msec/30 msec/77°; FOV = 190 mm; 47 – 3 mm isotropic slices, acquired interleaved) and included prospective acquisition correction for head motion (Thesen et al., 2000).

Functional image preprocessing

All analyses were conducted using AFNI (Cox, 1996). The first four images of each functional run were removed, and the remaining images were slice time corrected and corrected for residual motion. Each participant's functional images were aligned to their MP-RAGE scan and transformed to Montreal Neurological Institute (MNI) space. Functional data were spatially smoothed (6 mm FWHM), and a temporal band-pass filter was applied (0.008–0.10 Hz).

MST analysis and identification of the seed region for functional connectivity analyses

We used activation during the task scan to identify the seed region for functional connectivity analyses. Task activation was identified using a regression on the spatially normalized, averaged group data with condition (typing vs. rest) as the regressor of interest and the six directions of residual head motion from AFNI as nuisance regressors. The statistical map of task activation was corrected for multiple comparisons using a false discovery rate (Genovese et al., 2002) corrected threshold that set the overall probability to $p < 0.01$. The cortical voxel with the maximum T-statistic in the comparison of typing versus rest in the hand area of M1 on the right precentral gyrus, contralateral to the hand, used to perform the task. MNI coordinates (51, −24, 63) were used as the center of a 6 mm diameter spherical seed for resting-state functional connectivity analyses.

Resting-state functional connectivity analyses

Artifact Detection Tools (www.nitrc.org/projects/artifact_detect) were used to exclude time points corrupted by motion or other sources of spurious signal (Whitfield-Gabrieli and

Nieto-Castanon, 2012), and anatomic component-based noise correction (Behzadi et al., 2007; Chai et al., 2012) was used to correct for spurious correlations in the data. Voxel-wise connectivity maps for each participant were derived from the post-training resting scan by computing Pearson correlations between the signal averaged over the motor seed region and the signal at each voxel in the entire brain. Correlation coefficients were transformed to z-score connectivity maps. The resulting connectivity maps were correlated with each participant's report of the percent of time spent thinking about the MST.

Correction for multiple comparisons used a cluster threshold based on 10^6 Monte Carlo simulations of synthesized white Gaussian noise with the smoothing and resampling parameters of the functional analyses and an uncorrected threshold of $p < 0.01$ (Nichols, 2012). This determined the likelihood that a cluster of a given size would be found by chance. A cluster threshold of 38 voxels set the corrected threshold to $p \leq 0.05$ in the entire brain.

Results

MST performance was associated with activation in motor areas, including the bilateral cerebellum, bilateral pre- and postcentral gyri, and bilateral basal ganglia, consistent with prior reports of motor learning (Fig. 1 yellow areas and Table 1) (Hanakawa et al., 2003). The peak cortical activation region (right M1) was used as the center of a seed region for functional connectivity analyses.

Participants reported thinking about the MST during the postperformance resting-state scan 16% ± 21% (SD) of the time. This percentage significantly correlated with the strength of resting-state connectivity between the right M1 seed region and other motor regions activated by MST performance, including the bilateral cerebellum (lobes V and VIIIa), bilateral frontal operculum, bilateral supplementary motor area (SMA), and the left precentral gyrus (Fig. 1 green areas and Table 2). In addition, the right lingual gyrus (Fig. 1 blue area), which is not a motor region and did not show significant task-related changes in activation, was inversely correlated with time spent thinking about the MST.

TABLE 1. CLUSTERS SHOWING SIGNIFICANT TASK ACTIVATION DURING THE MOTOR SEQUENCE TASK

Location of maxima	x	y	z	T-stat
Left cerebellum (lobe V)	−21	−51	−21	21.0
Right precentral gyrus (BA 4)	51	−24	63	14.6
Left SMA (BA 6)	−6	6	54	16.1
Right putamen	36	3	12	16.9
Right cerebellum (lobe VIIIb)	24	−57	−21	14.2
Left thalamus	−15	−12	12	11.0
Left putamen	−24	0	12	8.8
Left middle frontal gyrus (BA 46)	−27	42	21	5.0
Left middle temporal gyrus (BA 37)	−48	−66	12	4.4

List of maxima locations, MNI coordinates and peak T-score for clusters with false discovery rate probability values $q < 0.01$.

MNI, Montreal Neurological Institute; SMA, supplementary motor area.
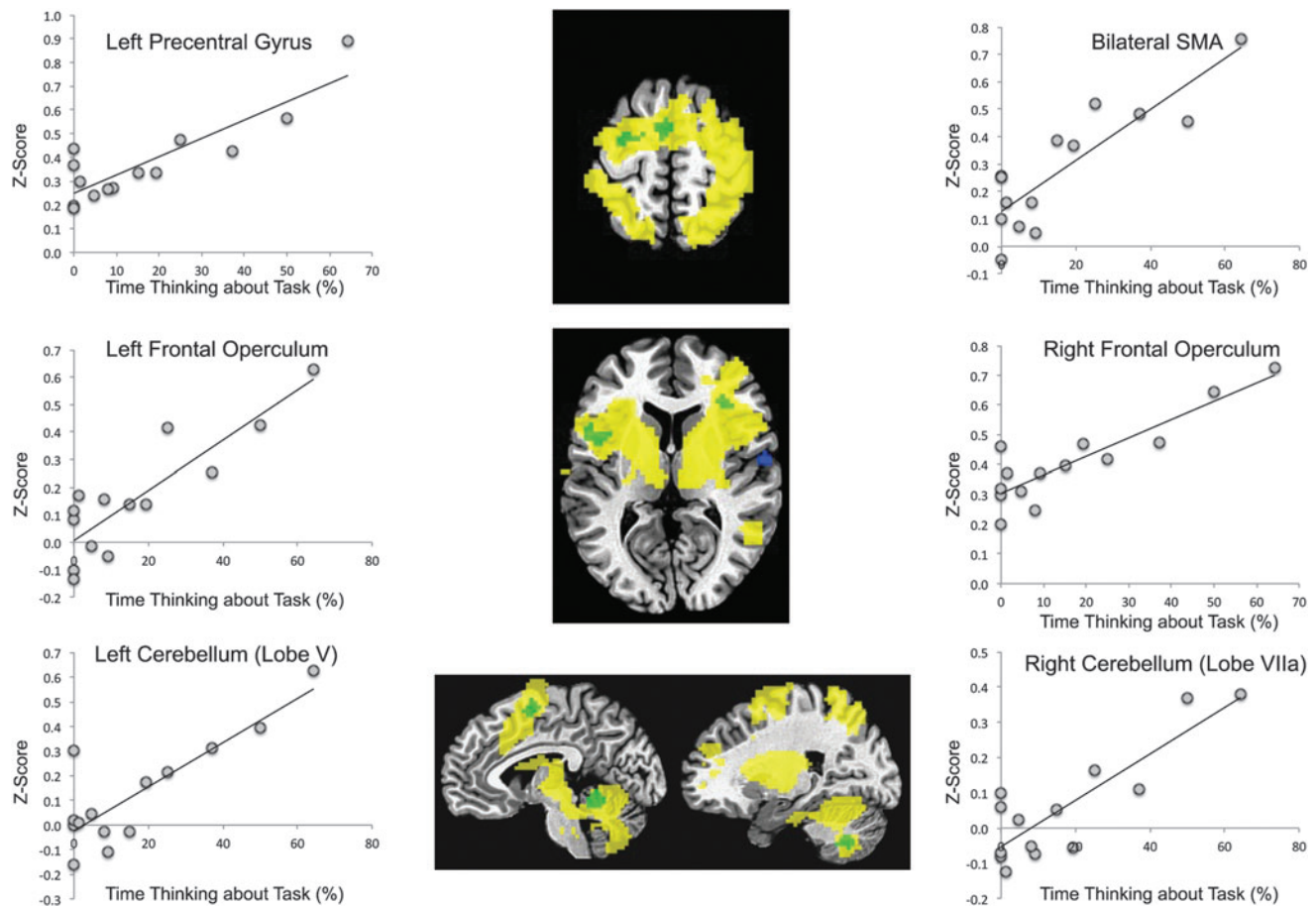
FIG. 1. Motor sequence task (MST) activation and its overlap with regions in which connectivity correlated with mentation. Graphs show the percentage of time spent thinking about the MST during the post-task resting scan plotted against connectivity at the peak voxel within each correlated region. Brain slices show MST activation (yellow), the overlap of activation with regions in which connectivity correlated with task-related mentation (green), and a region inversely correlated with mentation that was not activated by the MST (blue).

Correlations of task-related post-training thought with connectivity in task-activated regions were seen only in the post-task resting scan. No such correlations were found between task-related thought and connectivity in task-related regions during the pretask scan, suggesting that the correlations with thinking about the task do not reflect trait-like patterns of functional connectivity. We have previously shown that connectivity of these regions did not correlate with learning of the task, as measured by either MST performance improvement during training or subsequent sleep-dependent improvement (Gregory et al., 2014). Post-training thought also did not correlate with task-related activation seen during MST training, either in any of the significant regions identified in the primary analysis (Fig. 1, green) or in the MST seed region (all p's > 0.1).

Discussion

In conclusion, thinking about a recently learned motor task was associated with increased functional connectivity between motor brain areas that were activated during training. Control analyses demonstrated that there was no correlation (1) between post-training thought and either pretraining resting-state connectivity, task-related fMRI activation, or training task performance or (2) between the post-training connectivity of these regions and subsequent sleep-dependent task improvement.

Hence, the association of this connectivity pattern and thinking about the task are unlikely to be secondary to (1) a trait-like pattern of connectivity, (2) simple maintenance of connectivity patterns present during task training, or (3) tagging of the memory for subsequent sleep-dependent task improvement.

TABLE 2. REGIONS IN WHICH M1 CONNECTIVITY
IS SIGNIFICANTLY AND POSITIVELY ASSOCIATED
WITH THINKING ABOUT THE TASK

Region	No. of voxels	x	y	z	T-stat
Left cerebellum (lobe V)	99	−12	−45	−18	5.29
Right frontal operculum (BA 44)	76	39	27	12	5.32
Left precentral gyrus (BA 6)	71	−30	−6	63	6.02
Left frontal operculum (BA 44)	58	−51	9	3	6.07
Right frontal operculum (BA 4)	58	57	−9	15	6.45
Bilateral SMA (BA 6)	58	−6	0	60	5.85
Right cerebellum (lobe VIIIa)	45	15	−69	−45	5.67

Note that all regions show overlap with task-activation.

Several of the regions identified in our primary analysis play important roles in the conscious control of hand movements: the SMA (Roland et al., 1980) and frontal operculum (Tunik et al., 2008) are involved in planning of hand movements and the frontal operculum is involved in ''mental ownership'' in the rubber hand illusion (Ehrsson et al., 2004). In addition, the cerebellar regions (areas V and area VIIIa) are involved in sensorimotor processing (Stoodley and Schmahmann, 2009). The SMA is also involved in the temporal sequencing of hand movements (Roland et al., 1980; Shima and Tanji, 1998). Together, these earlier findings offer face validity for the conclusion that connectivity within this network can reflect thinking about the MST.

Obviously, thinking about any topic must be reflected in specific brain activity. However, it has been unclear how such activity can be measured. One approach has been through multivoxel pattern recognition (Norman et al., 2006), in which the subject consciously attends to specific sensory stimuli presented repeatedly. Our findings suggest another possible approach, as spontaneously thinking about prior actions is reflected in measurable changes in patterns of brain activity, specifically altering functional connectivity within circuits critical to the performance of those actions. Furthermore, they demonstrate that resting-state functional connectivity can be combined with a self-reported mentation questionnaire to investigate how thoughts alter activity in specific circuits within the human brain.

In this study, we used a remarkably simple self-report technique to probe conscious thought. The self-reporting occurred after the resting scan, and participants were not aware of the self-report requirement during the scanning session. We chose to collect the reports retrospectively, to avoid confounds associated with participants reporting their thoughts during scanning. Such reporting would also introduce a metacognitive task and thereby further alter patterns of brain connectivity.

In summary, we identified brain regions active during training on a motor task whose functional connectivity during a subsequent period of quiet rest correlated with retrospective self-reports of thinking about the task during that rest. This demonstrates the feasibility of using a combination of self-reports and functional connectivity analyses to study neural correlates of conscious thought.

Future work could apply a similar methodology to other domains, to determine patterns of functional connectivity associated with thinking about a wide range of cognitive and affective tasks. This may bring us closer to understanding the neural representations of conscious thought, both in experimental settings and in the natural environment.

References

Albert NB, Robertson EM, Miall RC. 2009. The resting human brain and motor learning. Curr Biol 19:1023–1027.

Behzadi Y, Restom K, Liau J, Liu TT. 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37:90–101.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537–541.

Chai XJ, Castanon AN, Ongur D, Whitfield-Gabrieli S. 2012. Anticorrelations in resting state networks without global signal regression. Neuroimage 59:1420–1428.

Christoff K, Gordon AM, Smallwood J, Smith R, Schooler JW. 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proc Natl Acad Sci U S A 106:8719–8724.

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

Deuker L, Olligs J, Fell J, Kranz TA, Mormann F, Montag C, et al. 2013. Memory consolidation by replay of stimulus-specific neural activity. J Neurosci 33:19373–19383.

Ehrsson HH, Spence C, Passingham RE. 2004. That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. Science 305:875–877.

Fox KC, Spreng RN, Ellamil M, Andrews-Hanna JR, Christoff K. 2015. The wandering brain: meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. Neuroimage 111:611–621.

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878.

Gregory MD, Agam Y, Selvadurai C, Nagy A, Vangel M, Tucker M, et al. 2014. Resting state connectivity immediately following learning correlates with subsequent sleep-dependent enhancement of motor task performance. Neuroimage 102 Pt 2:666–673.

Hanakawa T, Immisch I, Toma K, Dimyan MA, Van Gelderen P, Hallett M. 2003. Functional properties of brain areas associated with motor execution and imagery. J Neurophysiol 89:989–1002.

Karni A, Meyer G, Rey-Hipolito C, Jezzard P, Adams MM, Turner R, et al. 1998. The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. Proc Natl Acad Sci U S A 95:861–868.

Nichols TE. 2012. Multiple testing corrections, nonparametric methods, and random field theory. Neuroimage 62:811–815.

Norman KA, Polyn SM, Detre GJ, Haxby JV. 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn Sci 10:424–430.

Roland PE, Larsen B, Lassen NA, Skinhoj E. 1980. Supplementary motor area and other cortical areas in organization of voluntary movements in man. J Neurophysiol 43:118–136.

Shima K, Tanji J. 1998. Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. J Neurophysiol 80:3247–3260.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. 2009. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 106:13040–13045.

Stevens WD, Buckner RL, Schacter DL. 2010. Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cereb Cortex 20:1997–2006.

Stoodley CJ, Schmahmann JD. 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44:489–501.

Tambini A, Ketz N, Davachi L. 2010. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 65:280–290.

Thesen S, Heid O, Mueller E, Schad LR. 2000. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. Magn Reson Med 44:457–465.

Tunik E, Lo OY, Adamovich SV. 2008. Transcranial magnetic stimulation to the frontal operculum and supramarginal gyrus disrupts planning of outcome-based hand-object interactions. J Neurosci 28:14422–14427.

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. 2002. Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211.

Whitfield-Gabrieli S, Nieto-Castanon A. 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2:125–141.

Address correspondence to:
Michael D. Gregory
Section on Integrative Neuroimaging
Clinical and Translational Neurosciences Branch
National Institute of Mental Health
National Institutes of Health
10 Center Drive Room 3C-216
Bethesda, MD 20892

E-mail: gregorymd@mail.nih.gov