



## RESEARCH ARTICLE

## Neural predictors of sensorimotor adaptation rate and savings

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## Abstract

In this study, we investigate whether individual variability in the rate of visuomotor adaptation and multiday savings is associated with differences in regional gray matter volume and resting-state functional connectivity. Thirty-four participants performed a manual adaptation task during two separate test sessions, on average 9 days apart. Functional connectivity strength between sensorimotor, dorsal cingulate, and temporoparietal regions of the brain was found to predict the rate of learning during the early phase of the adaptation task. In contrast, default mode network connectivity strength was found to predict both the rate of learning during the late adaptation phase and savings. As for structural predictors, greater gray matter volume in temporoparietal and occipital regions predicted faster early learning, whereas greater gray matter volume in superior posterior regions of the cerebellum predicted faster late learning. These findings suggest that the offline neural predictors of early adaptation may facilitate the cognitive aspects of sensorimotor adaptation, supported by the involvement of temporoparietal and cingulate networks. The offline neural predictors of late adaptation and savings, including the default mode network and the cerebellum, likely support the storage and modification of newly acquired sensorimotor representations.

## KEYWORDS

functional connectivity, gray matter volume, neural predictors, savings, sensorimotor adaptation

## 1 | INTRODUCTION

Sensorimotor adaptation is a gradual process of adjusting motor representations to remain engaged in goal-directed behavior following changes in the environment, sensory inputs, or body physical characteristics. Such adaptation has been studied by having participants adapt

movements to, for example, visual perturbations (Bock, 1992; Bock & Burghoff, 1997; Clower et al., 1996; Inoue et al., 1997; Ghilardi et al., 2000; Imamizu et al., 2000; Krakauer, Pine, Ghilardi, & Ghez, 2000; Pine, Krakauer, Gordon, & Ghez, 1996) or force field perturbations (Shadmehr & Mussa-Ivaldi, 1994; Shadmehr & Holcomb, 1997). The early phase of sensorimotor adaptation is thought to rely mainly on

cognitive processes, such as working memory, error detection and correction, and attention (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2010; Taylor, Krakauer, & Ivry, 2014). In contrast, the later phase of adaptation is assumed to primarily involve slower and more implicit procedural processes (Seidler, Noll, & Chintalapati, 2006; Smith, Ghazizadeh, & Shadmehr, 2006).

Previous studies have shown that individual differences in the rate of sensorimotor adaptation are associated with variability in task-based brain activation patterns. Specifically, faster learning during the early adaptation phase has been associated with greater activation in the right dorsolateral prefrontal cortex (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2011), and greater activation in cingulate, visual, and parietal cortices (Seidler et al., 2006). In addition to such functional, online predictors of adaptability, offline brain structural properties have also been linked to individual variation in sensorimotor adaptation. Della-Maggiore, Scholz, Johansen-Berg, and Paus (2009) found that the rate of visuomotor adaptation was positively correlated with fractional anisotropy in white-matter tracts connecting the cerebellum with motor and premotor cortices. These studies suggest that individual differences in both functional and structural neural characteristics could serve as predictors of adaptability, and help to identify brain networks involved in adaptation. The adjustment of motor representations following adaptation can lead to motor memories that outlast the training session, as evidenced by observations that participants adapt faster when they have been previously exposed to the same perturbation. Such savings of adaptation have been observed immediately following initial learning (Bédard & Sanes, 2011; Seidler & Noll, 2008; Villalta et al., 2013), one month later (Della-Maggiore & McIntosh, 2005), and even one year after initial learning (Landi, Baguear, & Della-Maggiore, 2011). To date, only few studies have investigated the neural mechanisms underlying multiday savings of adaptation. Landi et al. (2011) explored how structural brain changes contributed to long-term memory of a visuomotor adaptation task. They found that a single week of adaptation training led to an increase in gray matter volume in contralateral primary motor cortex. Interestingly, the extent of this increase was found to predict long-term savings: participants who exhibited a larger increase in gray matter volume after one week of training showed more savings one year later. Della-Maggiore, Landi, and Villalta (2015) found that resting-state functional connectivity within a sensorimotor network, including motor, premotor, and posterior parietal cortices, in addition to cerebellum and putamen, increased after a visuomotor adaptation task. Further, the magnitude of the connectivity increase within this network was found to predict savings 24 h after initial learning. These studies provide evidence that structural and functional changes induced by visuomotor adaptation may have a long-term impact on behavior.

In this study, we evaluated whether offline functional connectivity and structural neural characteristics can serve as predictors of adaptability and multiday savings. In particular, we investigated whether individual differences in the rate of visuomotor adaptation and savings of adaptation over time are associated with differences in resting-state functional connectivity (rs-fcMRI) and regional gray matter volume (using voxel-based morphometry; VBM). Participants performed a

manual adaptation task in which they used a joystick to hit targets presented on a screen. After first performing the task under normal visual feedback, they then adapted to 45° clockwise-rotated feedback. Participants performed the task during two separate test sessions, on average 9 days apart.

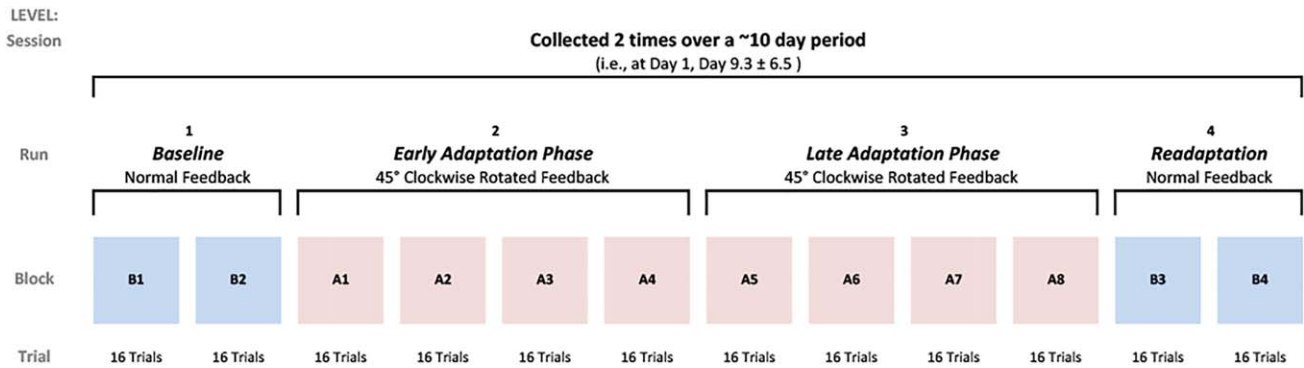
We hypothesized that faster learning during the early phase of adaptation would be predicted by stronger functional connectivity strength between sensorimotor areas within other frontal and parietal regions of the brain (including dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) insula and precuneus cortex) as task-based activation in these regions has previously been shown to predict adaptability (Anguera et al., 2010, 2011; Di Martino et al., 2008). Given the contribution of the superior posterior fissure region of the cerebellum during the late adaptation phase (Flament, 1996; Imamizu et al., 2000; Seidler & Noll, 2008), we further expected that faster learners during this stage would show stronger baseline connectivity between this cerebellar region with motor cortical areas. Based on previously reported associations between structural brain properties and sensorimotor adaptability (Della-Maggiore, 2009), we expected that faster learning during the early adaptation phase would be associated with larger gray matter volume in sensorimotor cortical areas and frontoparietal regions (including DLPFC, ACC, insula, and precuneus cortex). In contrast, we predicted that faster learning during the late adaptation phase would be associated with larger gray matter volume in superior posterior regions of the cerebellum and motor cortical areas.

With respect to multiday savings, we were interested in identifying networks in which connectivity strength was correlated with individual differences in the extent of savings, as well as areas in which gray matter volume was correlated with such differences. Based on the findings from previous studies investigating the neural mechanisms underlying savings (Della-Maggiore et al., 2015; Landi et al., 2011; Seidler & Noll, 2008), we hypothesized that more savings would be predicted by stronger functional connectivity strength between superior posterior regions of the cerebellum with motor cortical areas and larger gray matter volume in these same regions (i.e., overlapping neural predictors between late learning and savings). However, as behavioral evidence has shown that savings is associated with early learning processes (Haith, Huberdeau, & Krakauer, 2015; Morehead, Qasim, Crossley, & Ivry, 2015), we may alternatively observe overlapping neural predictors between early learning and savings.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

This study included 34 healthy participants (30 male, 4 female; age  $35.4 \pm 8.1$  years) who each performed a visuomotor adaptation task at two separate test sessions, completed on average  $9.3 \pm 6.5$  days apart. As 14 participants completed a different experimental protocol during the second session, their data were not included in the analyses that involved savings of adaptation from Session 1 to Session 2. The analyses for test session 2 were thus based on data from 20 participants (16 male, 4 female, age  $36.3 \pm 9.2$ ). All participants were recruited via the



**FIGURE 1** Experimental design. Participants completed the manual adaptation task while lying supine in the MRI scanner on two separate test sessions (top row). The task consisted of 12 blocks of 16 trials each. B refers to baseline blocks involving normal feedback; A refers to adaptation blocks in which feedback was rotated 45° clockwise [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Test Subject Facility at NASA Johnson Space Center and passed a modified Air Force class III physical. The Test Subject Facility at NASA Johnson Space Center (JSC) provides qualified test subjects for ground-based research or microgravity studies. The Test Subject Screening personnel at JSC recruit subjects that include employees from JSC and from outside of JSC. The facility does not select a particular type of subject population; subjects are only required to pass the physical. The modified class III physical is a medical examination that is required to enter the Air Force. All participants at the Test Subject Facility at NASA Johnson Space Center must pass this examination in order to participate in the study. All except four participants were right-handed. They reported average gaming experiences of 1.09 with 0 indicating “none at all” and 4 indicating “extreme” experience. A detailed explanation of the current study was provided to the participants, and all gave written informed consent. The study was approved by the Institutional Review Boards of the University of Michigan, the University of Texas – Medical Branch (UTMB), and NASA Johnson Space Center.

## 2.2 | Experimental design and procedure

The manual sensorimotor adaptation task employed in the current study has been used extensively in previous work from our lab and others (Anguera, Russell, Noll, & Seidler, 2007; Krakauer et al., 2000; Seidler et al., 2006). For this task, participants lay supine in the MRI scanner and controlled a custom-built MRI-compatible dual axis joystick with the thumb and index finger of their right hand to hit targets presented on a screen (viewed via a mirror). Real-time feedback of the joystick location was presented as a cursor on the screen, using a scaling factor of 1. Each movement was initiated from the central position on the screen. A target was presented every 2.5 s, either 4.8 cm to the right, left, above, or below the central position.

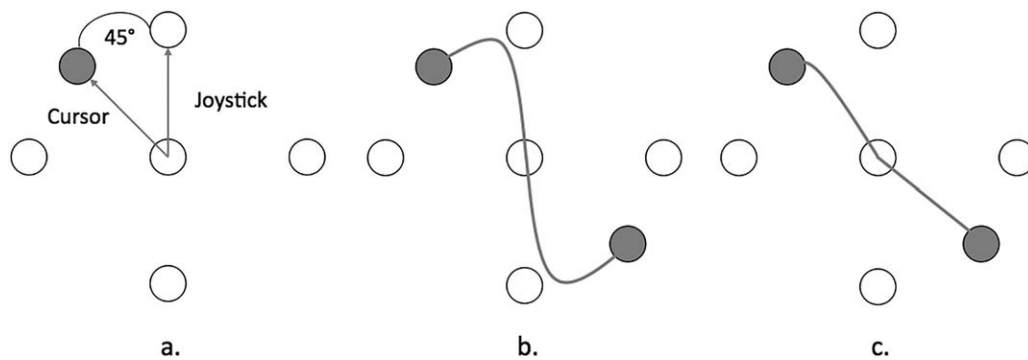
Participants were instructed to move the cursor to the target as quickly as possible by moving the joystick, and to hold the cursor within the target until it disappeared. They were then instructed to release the joystick handle after target disappearance, allowing the spring-loaded joystick to recenter for the next trial. Participants performed four runs of experimental trials. The first run included two

baseline blocks (B1 and B2) of 16 trials each under normal visual feedback. The next two runs included four blocks of 16 trials each under 45° clockwise rotated feedback (blocks A1–A8). The final run (blocks B3 and B4) was identical to the first run, which allowed us to calculate the aftereffects of adaptation, or “readaptation.” Each 16-trial block alternated with 20 s of visual fixation. This block design was repeated at two different test dates, allowing us to evaluate early and late adaptation, the aftereffects of adaptation, and savings of adaptation across days (Figure 1). The second session was completed on average  $9.3 \pm 6.5$  days after the initial session.

## 2.3 | Resting-state fMRI data acquisition

For 18 of the participants, multisequence MRI was acquired using a 3.0 T Siemens Magnetom skyra MRI scanner located at UTMB at Galveston. We used a 3D T1 sagittal MP-RAGE sequence with the following parameters: (TR = 1900 MS, TE = 2.49 MS, flip angle = 9°, FOV = 270 × 270 mm, slice thickness = 0.9 mm, 192 slices; matrix = 288 × 288, voxel size = 0.94 × 0.94 mm, duration = ~4 min). For rs-fcMRI, we used a single-shot gradient-echo (GRE) echo planar imaging (EPI) sequence to acquire 164 T2\*-weighted BOLD images (TR = 3660 MS, TE = 39 MS, flip angle = 90°, FOV = 240 × 240 mm, slice thickness of 4 mm, 1 mm slice gap, matrix = 94 × 94, voxel size = 2.55 × 2.55 × 5.0 mm, 36 axial slices, duration = ~10 min).

For 16 of the participants, fMRI data were collected on a 3.0 T Siemens Magnetom Verio, located at UTMB Victory Lakes. For these participants, we used a 3D T1 sagittal MP-RAGE sequence with the following parameters: (TR = 1900 ms, TE = 2.32 ms, flip angle = 9°, FOV = 250 × 250 mm, slice thickness = 0.9 mm, 192 slices; matrix = 512 × 512, voxel size = 0.49 × 0.49 mm, duration = ~4 min). For T1 pre-processing, the in-plane resolution was down sampled to 0.94 × 0.94 mm. For rs-fcMRI, we used a single-shot gradient-echo (GRE) echo planar imaging (EPI) sequence to acquire 164 T2\*-weighted BOLD images (TR = 3660 MS, TE = 39 MS, flip angle = 90°, FOV = 250 × 250 mm, slice thickness of 4 mm, 1 mm slice gap, matrix = 94 × 94, voxel size = 2.66 × 2.66 × 5.0 mm, 36 axial slices, duration = ~10 min). All participants were instructed to keep their eyes open, to remain awake, and to look at a fixation point while not



**FIGURE 2** Illustration of the visuomotor adaptation task and calculation of direction error (DE). (a) DE was calculated as the angle between the line connecting the start and target positions (in joystick coordinates) and the line connecting the start with the spatial location of the joystick at the time of peak velocity. (b) Illustration of example cursor movement during early phase of adaptation task. (c) Illustration of example cursor movement during late phase of adaptation task

thinking about anything in particular during the resting-state fMRI acquisition. Owing to differential MRI scanners, scanner sequences, and staff, scanner site was used as a covariate in all analyses.

## 2.4 | Behavioral data processing and analyses

Direction error (DE) was measured in order to examine performance during adaptation. This was defined as the angle between the line connecting the start and target positions (in joystick coordinates) and the line connecting the start with the spatial location of the joystick at the time of peak velocity (Figure 2). Trials for which DE deviated more than 2.5 standard deviations from the mean across a test session were replaced by the mean of the directly preceding and succeeding trials. This was computed separately for each of the two sessions per participants and resulted in the replacement of 2.38% of the trials overall. Movement time (MT) and reaction time (RT) were also measured for each trial. MT was defined as the time it took for participants to move the cursor from the start to the target position, whereas RT was defined as the time it took for participants to begin moving the cursor once a new trial began.

A repeated measures analysis of variance (ANOVA) was performed on each outcome measure with session (2), block (12), and trial (16) defined as the within-subject variables. As aforementioned, this analysis was performed on the data from the 20 participants that completed identical protocols on both test sessions. For all ANOVAs, the Huynh-Feldt correction (Huynh & Feldt, 1970) was applied when the assumption of sphericity was not met. The threshold for statistical significance was set at  $p < .05$ .

Each participant's rate of learning during the first test session was determined by computing the exponential decay constant across adaptation trials. We used MATLAB's fit function to fit a single-term exponential model to early learning and late learning data for all participants, with the initial value specified as "[0,0]." All other parameters were default to the function. This decay constant was used as the primary outcome measure for examining functional connectivity predictors of sensorimotor adaptation, with more negative values reflecting faster adaptation. Several previous studies have demonstrated that visuomotor adaptation data are generally well-characterized by exponential

decay functions (Burge, 2008; Flanagan et al., 1999; King et al., 2009; Krakauer et al., 2000, 2005). To confirm that such exponential functions better characterized the present data for early and late learning than linear functions, we measured the  $R^2$  fits using both approaches. Indeed, we found that exponential functions provide significantly better fits than linear functions, for both early and late learning (early:  $t = 6.20$ ,  $p < .001$ ; late:  $t = 5.99$ ,  $p < .001$ ). Example single-subject DE data and exponential decay fits are illustrated in Supporting Information, Figure S1.

We differentiated the rate of learning during the early, late, and post adaptation phases by assigning adaptation blocks A1–A4 as "early," adaptation blocks A5–A8 as "late," and "postadaptation" baseline blocks as B3 and B4. Finally, to assess multiday savings, we computed individual savings scores. Specifically, savings was measured as the difference between a participant's mean DE in the first adaptation block (i.e., the first 16 trials with rotated feedback) on the first test session and the mean DE in that block on the second test session. It should be noted that learning rates and savings scores thus were calculated on an individual basis.

Subsets of these data have already been published in part by Ruitenber et al. (2017) in a comparison of manual and locomotor adaptation. Here, we present the manual adaptation results for a larger group of participants, and for the first time focus on associations between behavior and rs-fcMRI and VBM measures.

## 2.5 | Resting-state fMRI data preprocessing

Rs-fcMRI data were first corrected for slice timing using sinc interpolation and then realigned for head motion correction using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, United Kingdom). To examine outliers due to spiking and movement, we used the Artifact Detection Tool (ART) software package (available on the NITRC website: [http://www.nitrc.org/projects/artifact\\_detect/](http://www.nitrc.org/projects/artifact_detect/)). Next, whole brain rs-fcMRI images were normalized to MNI152 space using a multistep procedure. First, the T1 image was corrected for field inhomogeneities using N4ITK within an intracranial mask that was obtained using FSL's brain extraction tool (BET; Tustison et al., 2010). The bias field

**TABLE 1** Peak coordinates of the regions of interest (ROIs) used for seed-to-voxel functional connectivity analyses

Seed region	MNI coordinates (x,y,z)	References
R Middle frontal gyrus	44, 14, 36	Anguera et al. (2011)
R Inferior parietal lobule	48, -40, 44	Anguera et al. (2010)
L Putamen	26, 6, 0	Di Martino et al. (2008)
L Superior temporal gyrus	-46, -34, 14	Anguera et al. (2010)
L Middle temporal gyrus	-48, -48, 6	Anguera et al. (2010)
R Globus pallidus	20, -6, 0	Della-Maggiore et al. (2005)
L Anterior cingulate cortex	-7, 9, 40	Seidler and Noll (2008)
L Cerebellum lobule V	-11, -56, -13	Seidler and Noll (2008)
L Cerebellum lobule VI	-26, -62, -20	Seidler and Noll (2008)
L Posterior cingulate cortex	-12, -47, 32	Greicius et al. (2003)

Note. Cortical ROIs were defined as 6-mm-radius spheres, and subcortical ROIs were defined as 4-mm-radius spheres around peak coordinates.

corrected and averaged image was skull stripped using FSL's BET using robust brain center estimation and a fractional intensity threshold of 0.1.

SPM8 was used to coregister the skull stripped bias field corrected T1 image to the mean rs-fMRI EPI. The co-registered images were normalized to MNI152 common space using advanced normalization tools (ANTs) with cross correlation as the similarity metric and symmetric normalization as the transformation model (Avants et al., 2011). The resulting warp parameters were applied to the 4D EPI images that were subsequently smoothed with a Gaussian kernel of 4 mm sigma (~9.4 mm FWHM). To maximize cerebellar normalization accuracy, we isolated the cerebellum using the SUIT toolbox and registered the isolated cerebellum to the MNI152 cerebellum that was normalized to SUIT space (Diedrichsen, 2006). The normalization steps for the cerebellum were then identical to the ones for the whole brain described above.

## 2.6 | Functional connectivity analyses

Functional connectivity MRI (fcMRI) analyses were performed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The rs-fcMRI data were filtered using a temporal band-pass filter of .008 to .09 Hz to examine the frequency band of interest and to exclude higher frequency sources of noises such as heart rate and respiration. Linear detrending was used to remove any linear trends within each functional run. For noise reduction, we used an anatomical component-based noise correction method called aCompCor, which models the influence of noise as a voxel-specific linear trend combination of multiple empirically estimated noise sources by extracting principal components from noise regions of interest (ROIs) and including them as nuisance parameters in the general linear models (Behzadi, Restom, Liu, & Liu, 2007).

Specifically, the anatomical images for each participant were segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) masks using the default parameters of the SPM8 Segment function (Ashburner & Friston, 2005). These parameters include a non-linear deformation estimated field that best overlays the tissue

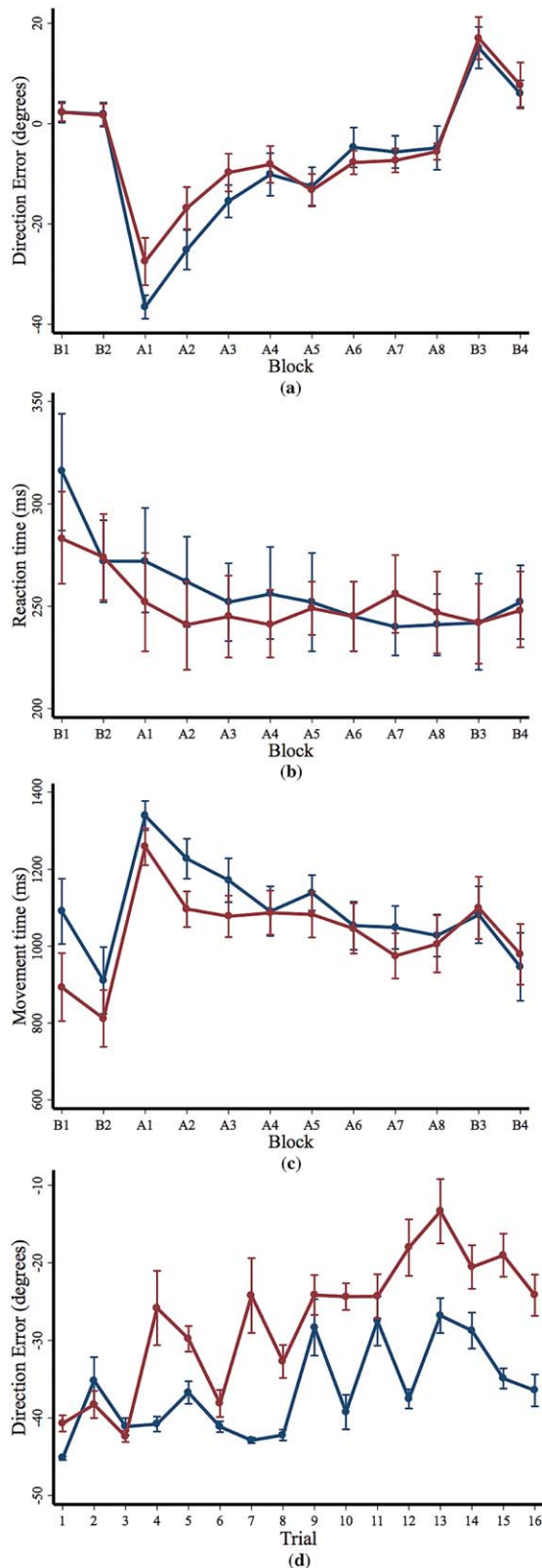
probability maps on each participants' image. The model is further refined by allowing tissue probability maps to be deformed based on a set of estimated parameters. This allows spatial normalization and segmentation to be combined into the same model. This procedure uses a low-dimensional approach, which parameterizes the deformations by a linear combination of about one thousand cosine transform bases.

To reduce partial voluming with GM, the WM and CSF masks were eroded by one voxel. The eroded WM and CSF masks were then used as noise ROIs. Time courses from all ROIs were extracted from the unsmoothed functional volumes to avoid risk of potential "spillage" of the BOLD signal from nearby regions. Residual head motion parameters (three rotations and three translations, in addition to six parameters that represent their first-order temporal derivatives) and signals from WM and CSF were regressed out during the computation of functional connectivity maps.

For statistical analyses, we performed both hypothesis driven (seed-to-voxel) and hypothesis-free (voxel-to-voxel) approaches. For the first-level seed-to-voxel analysis, we selected ten ROIs to examine for brain-behavior associations. These ROIs were based on results from previous studies investigating associations between brain activation and early/late adaptation and savings (Table 1). Cortical ROIs were defined as 6-mm-radius spheres and subcortical ROIs as 4-mm-radius spheres, centered on peak coordinates taken from the literature. The mean time series of each ROI was obtained by averaging the time series of all voxels within that region. Next, Pearson's correlation coefficients were computed between the mean time series of each ROI and the time series of each voxel in a standard *a priori* brain mask. This mask refers to a standard MNI-space brain mask used for voxel-based analyses only, and limits analyses only to voxels within the mask.

First-level voxel-to-voxel analysis included the calculation of voxel-to-voxel functional correlation matrices for each participant. From the residual BOLD time series at each voxel with an *a priori* brain mask, the matrix of voxel-to-voxel bivariate correlation coefficients was computed. From this correlation matrix, the intrinsic connectivity contrast defining the overall strength of the global connectivity patterns (Martuzzi et al., 2011) was computed between each voxel and all other





**FIGURE 3** Mean (a) DE, (b) RT, and (c) MT as a function of block within the adaptation task. (d) Mean DE as a function of trial within block A1. Blue lines represent the data from Session 1; red lines represent the data from Session 2

voxels in the brain. This approach was employed to assess network changes that may not have been identified with our hypothesized ROIs. For both seed-to-voxel and voxel-to-voxel analyses, the correlation coefficients were converted into z-values using Fisher's r-to-z transformation to improve their normality.

Positive and negative associations between voxel-to-voxel fcMRI and behavioral performance were examined using one-sample t-tests in SPM8. In this model, first-level beta maps were included as the main variables of interest. Each participant's rate of early and late learning as well as aftereffects and savings were included as covariates. Statistical significance was determined with a cluster-level FDR  $p < .05$  to correct for multiple comparisons. For the seed-to-voxel second level analysis, one subject-averaged mask was created for the regions correlated with each ROI during session 1 (using a cluster-level FDR  $p < .05$  to correct for multiple comparisons). From these masks, one average functional connectivity measure was extracted for each network and each participant. To examine the relationship between these fcMRI measures and performance, Pearson's correlation coefficient was computed across each participant's average fcMRI measure and their rates of early and late learning, aftereffects, and savings.

### 2.7 | Voxel-based morphometry

Whole-brain VBM analyses were performed using the VBM8 toolbox for SPM8 (<http://dbm.neuro.uni-jena.de/vbm.html>). Cortical thickness analysis can provide additional information to a VBM analysis, and these different measures can be sensitive to different pathologies. However, these measures are correlated (Hutton, Draganski, Ashburner, & Weiskopf, 2009), which is why we chose to report on only one of these two measures. VBM reflects cortical thickness, cortical surface area, and gyral folding, whereas cortical thickness only reflects the thickness (Hutton et al., 2009). Furthermore, cortical thickness analysis excludes the deep gray matter areas, which are important in sensorimotor learning. For these reasons, we selected VBM over cortical thickness analysis.

High-resolution T1-weighted anatomical images were segmented, modulated using the non-linear DARTEL warping parameters from the normalization results, and then smoothed with a standard deviation of 8 mm full-width at half-maximum. Positive and negative associations between gray matter volume and sensorimotor adaptation metrics were evaluated by performing one-sample t-tests in SPM8. Preprocessed gray matter images were included as the main variables of interest, and the various adaptation performance measures were included as covariates. Voxels with an intensity value of  $<0.1$  were excluded from the analysis to account for edge effects. Statistical significance was determined by using a cluster-level FDR  $p < .05$  to correct for multiple comparisons.

## 3 | RESULTS

### 3.1 | Behavioral results

For the manual adaptation task, the repeated measures ANOVA on DE yielded a significant main effect of Block,  $F(11, 209) = 122.89$ ,  $p < .001$ ,  $\eta_p^2 = .87$ . As Figure 3a and Table 2 demonstrate, performance decreased when the rotated feedback was introduced in block

**TABLE 2** Mean and standard error of the mean (SEM) for direction error (DE), movement time (MT), and reaction time (RT) per block during Sessions 1 and 2

Session	Block	DE mean	DE SEM	MT mean	MT SEM	RT mean	RT SEM	
1	B1	2.29	0.99	1091	41	316	14	
	B2	1.88	1.11	911	41	272	9	
	A1	-36.55	1.12	1340	18	272	12	
	A2	-25.16	1.88	1228	25	262	11	
	A3	-15.49	1.55	1172	27	252	9	
	A4	-10.15	2.03	1091	31	256	11	
	A5	-12.51	1.82	1139	22	252	11	
	A6	-4.74	1.90	1054	30	245	8	
	A7	-5.64	1.54	1049	27	240	7	
	A8	-4.83	2.08	1028	26	241	7	
	B3	15.14	1.98	1082	35	242	11	
	B4	5.96	1.27	946	42	252	9	
	2	B1	2.29	0.85	893	42	283	11
		B2	1.68	1.09	812	35	274	10
A1		-27.51	2.25	1259	23	252	12	
A2		-16.84	2.00	1097	22	241	10	
A3		-9.76	1.80	1078	26	245	10	
A4		-8.13	1.75	1087	27	241	8	
A5		-13.27	1.55	1083	28	249	6	
A6		-7.75	1.13	1046	31	245	8	
A7		-7.34	1.13	975	28	256	9	
A8		-5.56	0.78	1006	36	247	10	
B3		17.05	2.01	1100	39	242	9	
B4		7.62	2.18	979	38	248	9	

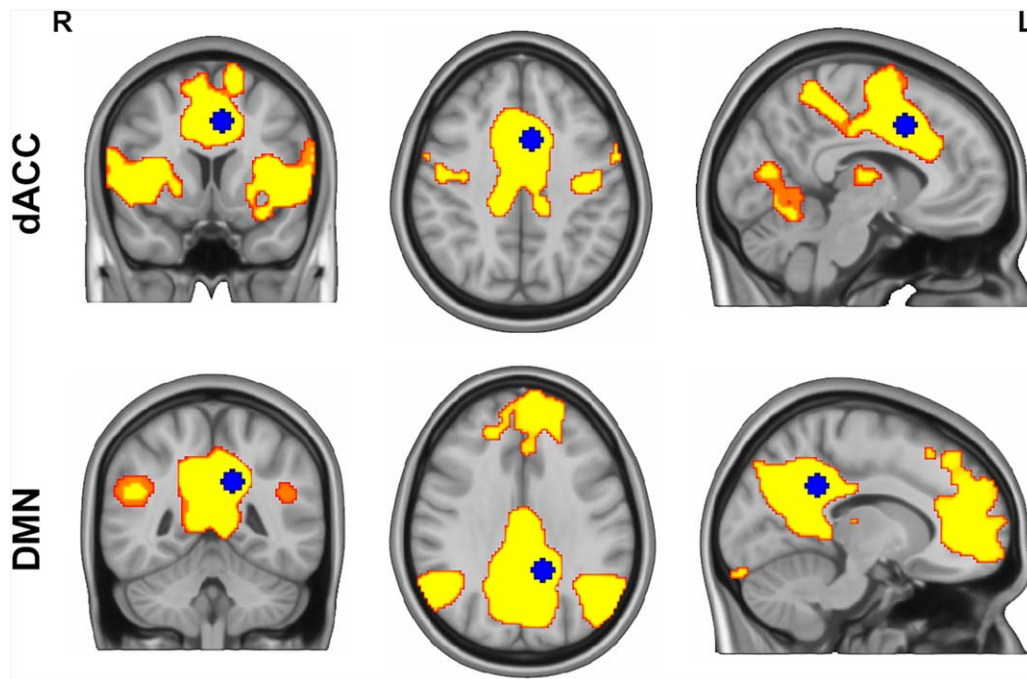
A1, and participants gradually adapted to this rotated feedback across the following blocks. When the rotated feedback was removed in block B3, participants had to readapt to the normal feedback. The results also yielded a significant Block  $\times$  Trial interaction,  $F(165, 3135)=2.19$ ,  $p < .01$ ,  $\eta_p^2 = .10$ . Post-hoc analyses revealed that DE significantly decreased across trials in blocks A1-B3,  $F_s > 1.82$ ,  $p_s < .05$ ,  $\eta_p^2s > .088$ , indicating within-block performance improvements. Additionally, the results revealed a significant Session  $\times$  Block interaction,  $F(11, 209) = 4.91$ ,  $p < .001$ ,  $\eta_p^2 = .21$ . Post-hoc analyses demonstrated that DE differed significantly across sessions 1 and 2 in blocks A1-A3,  $F_s > 9.51$ ,  $p_s < .01$ ,  $\eta_p^2s > .33$ , supporting that savings occurred from Session 1 to Session 2.

For RT, results revealed a significant main effect of Block,  $F(11, 209) = 11.22$ ,  $p < .001$ ,  $\eta_p^2 = .37$ , and a significant Block  $\times$  Trial interaction,  $F(165, 3135) = 1.56$ ,  $p < .01$ ,  $\eta_p^2 = .076$  (Figure 3b and Table 2). However, this interaction was no longer significant after excluding the first block from the analysis ( $p = .08$ ), indicating that RTs decreased more quickly in the first block of the adaptation task than in

the remaining blocks. Results also showed a significant Session  $\times$  Trial interaction,  $F(15, 285) = 3.70$ ,  $p < .001$ ,  $\eta_p^2 = .16$ . However, this interaction was no longer significant after excluding the first trial from each block ( $p = .23$ ).

The results for MT yielded significant main effects of Session,  $F(1, 19) = 27.90$ ,  $p < .001$ ,  $\eta_p^2 = .60$ , Block,  $F(11, 209) = 35.21$ ,  $p < .001$ ,  $\eta_p^2 = .65$ , and Trial,  $F(15, 285) = 12.29$ ,  $p < .001$ ,  $\eta_p^2 = .39$  (Figure 3c and Table 2). Additionally, there was a significant Session  $\times$  Block interaction,  $F(11, 209) = 9.08$ ,  $p < .001$ ,  $\eta_p^2 = .32$ . Post-hoc analyses demonstrated that MT differed significantly between Sessions 1 and 2 within blocks B1-A3, and A5 and A7,  $F_s > 5.67$ ,  $p_s < .05$ ,  $\eta_p^2s > .23$ , suggesting that savings across the two sessions is also reflected in MT in addition to DE.

To examine how well participants remembered the adaptation task from Session 1 to Session 2, we calculated individual saving scores. This score was defined as the difference between a participant's mean DE in the first adaptation block (i.e., the first 16 trials with rotated feedback) on the first session and the mean DE in that block on the



**FIGURE 4** Top row: Greater functional connectivity strength among left dACC seed region (in blue) with SMA, bilateral insula, putamen, and thalamus, and left cerebellar lobule V was associated with faster early adaptation. Bottom row: Greater functional connectivity strength between left posterior cingulate cortex seed region (in blue) with precuneus cortex, bilateral occipital cortices, and superior frontal gyrus (comprising the DMN) was associated with faster late adaptation and more savings [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

second session. Savings scores ranged from  $-35.58^\circ$  to  $6.53^\circ$ , with more negative scores reflecting more savings. To determine whether saving scores were significantly different from zero, we performed a one-sample *t*-test. The results showed that overall participants had significant savings, with a mean score of  $-8.73$ ,  $t(19) = -3.69$ ,  $p < .01$ . Our individual differences measure of savings could comprise both retention and savings effects. To investigate this, we performed a linear contrast to evaluate whether performance changes across trials in block A1 were different for the two test sessions. As illustrated in Figure 3d, results revealed that DE improved significantly faster across trials in the second compared to the first test session,  $F(1,19) = 5.26$ ,  $p < .05$ ,  $\eta_p^2 = .22$ . It is clear from the figure that performance is essentially identical across the first few trials of block A1 for both Sessions 1 and 2, supporting that the session difference in A1 average direction error is based on savings (rate of adaptation) and not retention. However, it is difficult to disentangle the effects of retention from savings; this issue should thus be investigated in future studies.

### 3.2 | Functional connectivity results

For the seed-to-voxel analyses, results revealed that functional connectivity among the left dorsal anterior cingulate cortex (dACC) seed region with supplementary motor area (SMA), bilateral insula, putamen and thalamus and left cerebellar lobule V was predictive of the rate of early adaptation, such that faster learners exhibited greater connectivity strength within this network. In addition, connectivity between left posterior cingulate cortex seed region with precuneus cortex, bilateral occipital cortices, and superior frontal gyrus (comprising the default

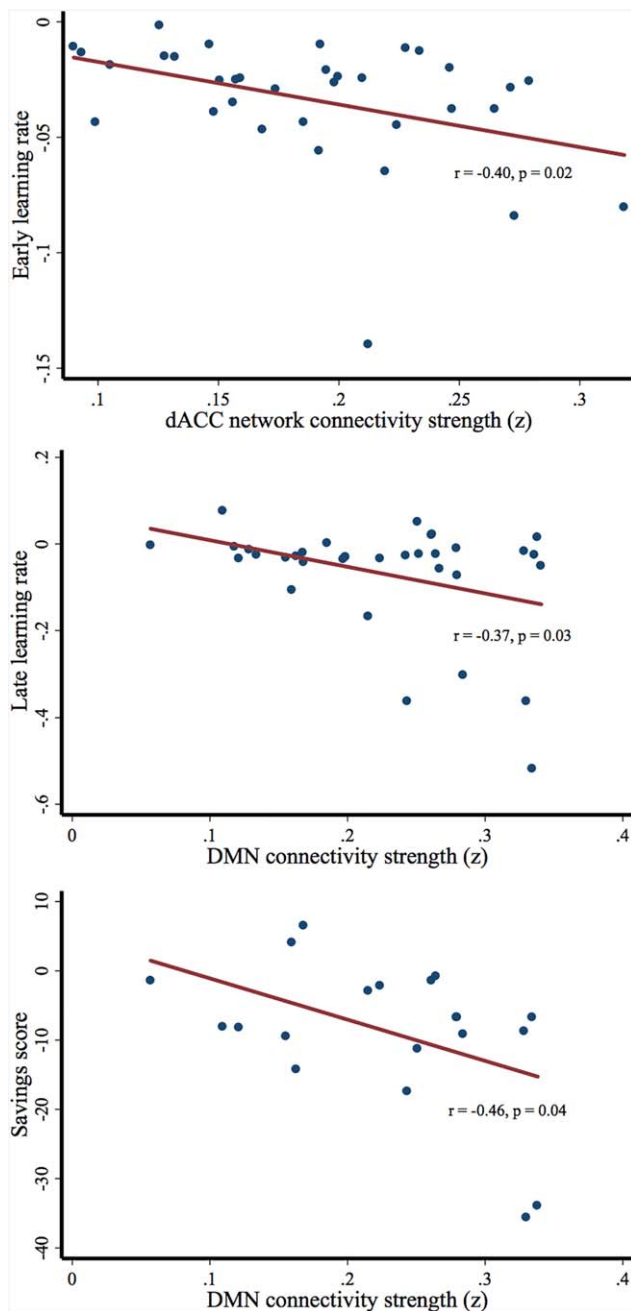
mode network; DMN) was associated with the rate of late adaptation and savings scores. Specifically, we observed that DMN connectivity was stronger in participants who adapted faster during the late phase of the visuomotor adaptation task and for those who showed better savings in the second test session (Figures 4 and 5). The DMN is a set of brain areas that exhibit higher metabolic activity at rest than during performance of externally directed tasks. Important functions attributed to this network are the support of internally directed mental activity (Gusnard & Raichle, 2001; Mason et al., 2007) and memory consolidation (Miall and Robertson, 2006).

Voxel-to-voxel analyses also revealed significant associations between the rate of learning in the early adaptation phase as well as aftereffects with functional connectivity. Specifically, left insular cortex connectivity was correlated with the rate of early adaptation, such that faster learners exhibited greater connectivity strength between left insular cortex with the rest of the brain. Furthermore, we found that connectivity strength between right operculum cortex with the rest of the brain was stronger in individuals who adapted faster to the removal of rotated feedback during the post adaptation blocks (Table 2 and Figure 6). Thus, for both seed-to-voxel and voxel-to-voxel approaches, stronger functional connectivity was always associated with better performance.

### 3.3 | Voxel-based morphometry results

The VBM results showed significant correlations between the rates of early and late adaptation and gray matter volume. Specifically, participants who had faster rates of adaptation during the early phase of the visuomotor adaptation task showed larger gray matter volume in left





**FIGURE 5** Scatterplots illustrating the relationship between dACC network functional connectivity strength and early adaptation rate (top row), DMN connectivity strength and late adaptation rate (middle row), and DMN connectivity strength and savings scores (bottom row). Note that more negative values reflect faster adaptation/more savings [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

central operculum cortex, precuneus cortex, and left postcentral gyrus. In contrast, participants who adapted faster during the late phase of the adaptation task had larger gray matter volume in a cluster including vermis VI and right crus I of the cerebellum (Tables 3 and 4 and Figure 7). There was no association between gray matter volume and aftereffects or savings. Thus, larger gray matter volume was always associated with better performance.

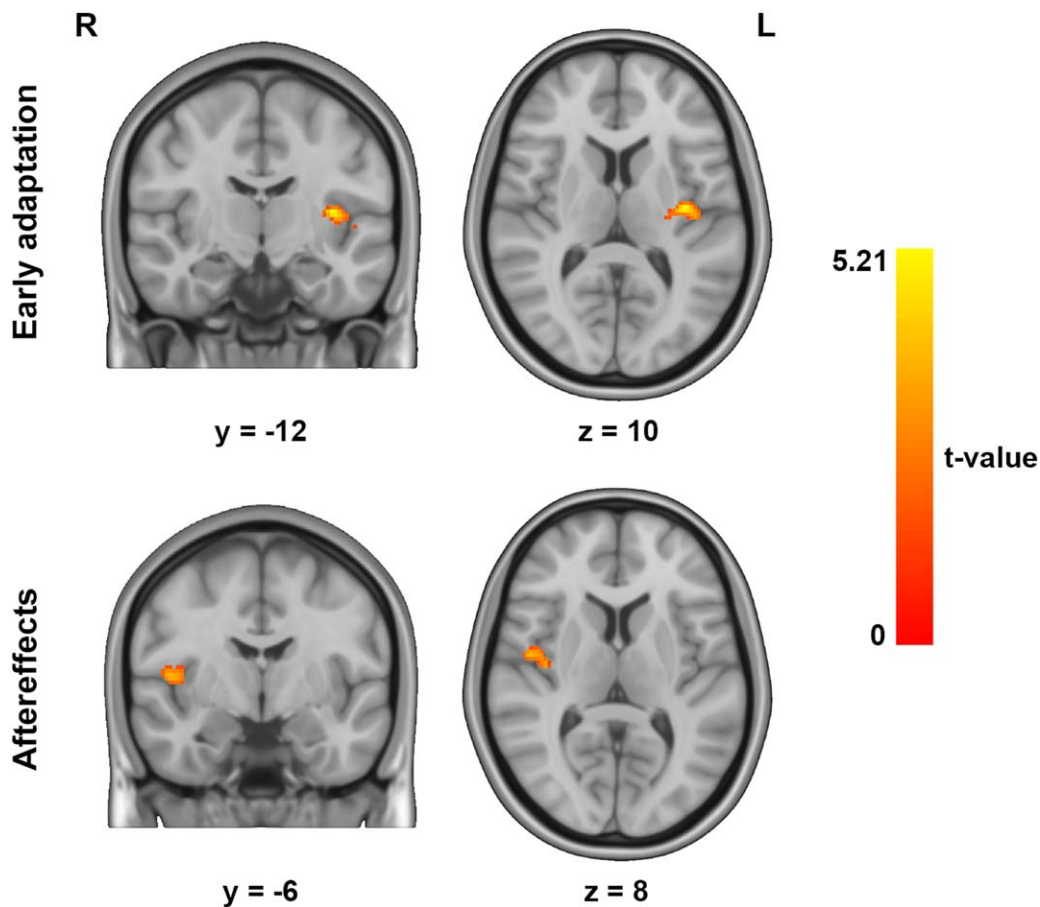
### 3.4 | Relationship between connectivity strength and GM volume

To explore the relationship between GM volume and fcMRI in the overlapping brain regions that showed associations with behavior, we first correlated the neural measures (fcMRI and GM volume) in left temporoparietal cortex (region associated with early adaptation). We found a significant positive relationship between GM volume and fcMRI in this region ( $r = .71$ ;  $p < .0001$ ). Next, we correlated each participant's average DMN connectivity measure and GM volume in Vermis VI of the cerebellum (regions associated with late adaptation), but this relationship was not significant ( $r = -.20$ ;  $p = .26$ ).

To more fully investigate the potential role of fcMRI as a mechanistic link between GM volume and the rate of early/late adaptation, we applied mediation analyses to the VBM, fcMRI, and behavioral data. Mediation analyses examine the mechanism by which two variables are related, and is appropriate when the mediator (M) is the logical effect of one variable (X) and the logical cause of another variable (Y). In this study, fcMRI is the logical effect of GM volume (X) and the logical cause of differences in adaptation rate (Y).

We performed a first mediation analysis using GM volume in temporoparietal cortex as the independent variable (X), fcMRI in temporoparietal cortex as the mediator (M), and early adaptation rate as the outcome variable (Y). In Step 1 of the mediation model, the regression of GM volume on early adaptability, ignoring the mediator (fcMRI) was significant,  $b = -.0001$ ,  $t(32) = -4.09$ ,  $p < .001$ . Step 2 showed that the regression of GM volume on the mediator, fcMRI, was also significant,  $b = .0032$ ,  $t(32) = 5.69$ ,  $p < .0001$ . Step 3 of the mediation process showed that the mediator (fcMRI), controlling for GM volume, was not significant,  $b = -.02$ ,  $t(31) = -1.91$ ,  $p = .07$ . Step 4 of the analyses revealed that, controlling for the mediator (fcMRI), GM volume was not a significant predictor of early adaptability,  $b = -.0001$ ,  $t(31) = -1.65$ ,  $p = .11$ . A Sobel test was then conducted which yielded a non-significant mediation in the model ( $z = -1.78$ ,  $p = .07$ ). Thus, fcMRI did not fully mediate the relationship between GM volume and early adaptability.

We performed a second mediation analysis using GM volume in Vermis VI of the cerebellum as the independent variable (X), fcMRI in DMN as the mediator (M), and late adaptation rate as the outcome variable (Y). Here, too, results showed that the regression of GM volume on late adaptability, ignoring the mediator (fcMRI) was significant,  $b = -.001$ ,  $t(32) = -3.93$ ,  $p < .001$ , while the regression of GM volume on fcMRI was not significant,  $b = -.0002$ ,  $t(32) = -1.16$ ,  $p = .26$ . Step 3 of the mediation process showed that the mediator (fcMRI), controlling for GM volume, was significant,  $b = -.84$ ,  $t(31) = -4.17$ ,  $p < .001$ . Step 4 of the analyses revealed that, controlling for the mediator (fcMRI), GM volume was a significant predictor of late adaptability,  $b = -.0013$ ,  $t(31) = -5.57$ ,  $p < .0001$ . A Sobel test was then conducted which yielded a nonsignificant mediation in the model ( $z = 1.09$ ,  $p = .28$ ). Thus, like above this, analysis showed no indications that fcMRI fully mediated the relationship between GM volume and late adaptability.



**FIGURE 6** Left insular cortex functional connectivity was correlated with the rate of early adaptation, such that faster learners showed greater connectivity strength between left insular cortex with the rest of the brain than slower learners (top row). Functional connectivity strength between right central operculum cortex with the rest of the brain was stronger in individuals who readapted to the visuomotor task faster (bottom row)

## 4 | DISCUSSION

In this study, we evaluated whether individual differences in the rate of visuomotor adaptation and savings magnitude are associated with differences in offline measures of brain structural and functional properties. We observed that specific patterns of resting-state functional connectivity strength and gray matter volume were associated with individual variability in learning rates and multiday savings, suggesting that these patterns represent neural predictors of sensorimotor adaptability and savings. Below, we will first elaborate on our findings regarding predictors of learning rate and then discuss our findings related to multi-day savings in sensorimotor adaptation.

### 4.1 | Predictors of adaptability

While previous investigations have reported associations between the rate of learning during the early adaptation phase and brain structural and online functional measures, the present study is the first to demonstrate that resting-state functional connectivity strength and gray matter volume are associated with the rate of learning during different phases of visuomotor adaptation. For the early phase of adaptation—which we defined here as the first 64 trials with rotated feedback—faster adapters exhibited stronger functional connectivity between dACC, SMA, bilateral insula, putamen and thalamus, and left cerebellar lobule V. In terms of structural predictors, faster adapters exhibited larger gray matter volume in temporoparietal and occipital regions,

**TABLE 3** MNI coordinates of the suprathreshold clusters showing a significant correlation across participants between the intrinsic connectivity contrast and adaptation rate

Phase	Anatomic location	Direction	Coordinates of peak	T value	Cluster size
Early adaptation	L insular cortex	-	-36, -12, 10	5.21	153
Aftereffects	R central operculum	-	48, -6, 8	4.47	96

Note. In the direction column, - denotes that a more negative decay constant (i.e., faster adaptation) was associated with stronger connectivity between the suprathreshold cluster with the rest of the brain.

**TABLE 4** MNI coordinates of the suprathreshold clusters showing a significant correlation across participants between the gray matter volume and adaptation rate

Phase	Anatomic location	Direction	Coordinates of peak	T value	Cluster size
Early adaptation	L central operculum	-	-45, -16, 18	6.43	2135
	Precuneus cortex	-	-4, -79, 39	5.06	1136
	L postcentral gyrus	-	-36, -37, 48	4.65	696
Late adaptation	Cerebellum vermis VI	-	-3, -79, -17	5.30	863

Note. In the direction column, - denotes that a more negative decay constant (i.e., faster adaptation) was associated with larger gray matter volume in the suprathreshold clusters.

partially overlapping with findings from the connectivity analyses. For the late adaptation phase—i.e., the final 64 trials with rotated feedback—faster adapters showed greater connectivity strength between DMN regions and larger gray matter volume in superior posterior regions of the cerebellum. These findings support the existence of differential learning processes contributing to sensorimotor adaptation (Heuer & Hegele, 2015; Smith et al., 2006), with fast explicit, strategic and slower implicit, automated processes jointly contributing to performance throughout the task but dominating at different time courses (Taylor et al., 2014).

Consistent with our hypotheses, participants with stronger resting-state functional connectivity between dACC seed region with SMA, insula, putamen, thalamus, and cerebellum adapted faster during the early phase of the adaptation task. Neuroimaging studies suggest that the dACC plays a critical role in the cognitive aspect of movement generation, that is, intentional motor control (Hoffstaedter, Grefkes, Zilles, & Eickhoff, 2013; Hoffstaedter et al., 2014). In particular, this region is known to be involved in evaluating and assigning values to actions based on relevant feedback (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2003). According to this view, successful movements (i.e., those that are correct for counteracting the perturbation in a sensorimotor adaptation task) get assigned higher value and thus are more likely to be repeated than unsuccessful ones.

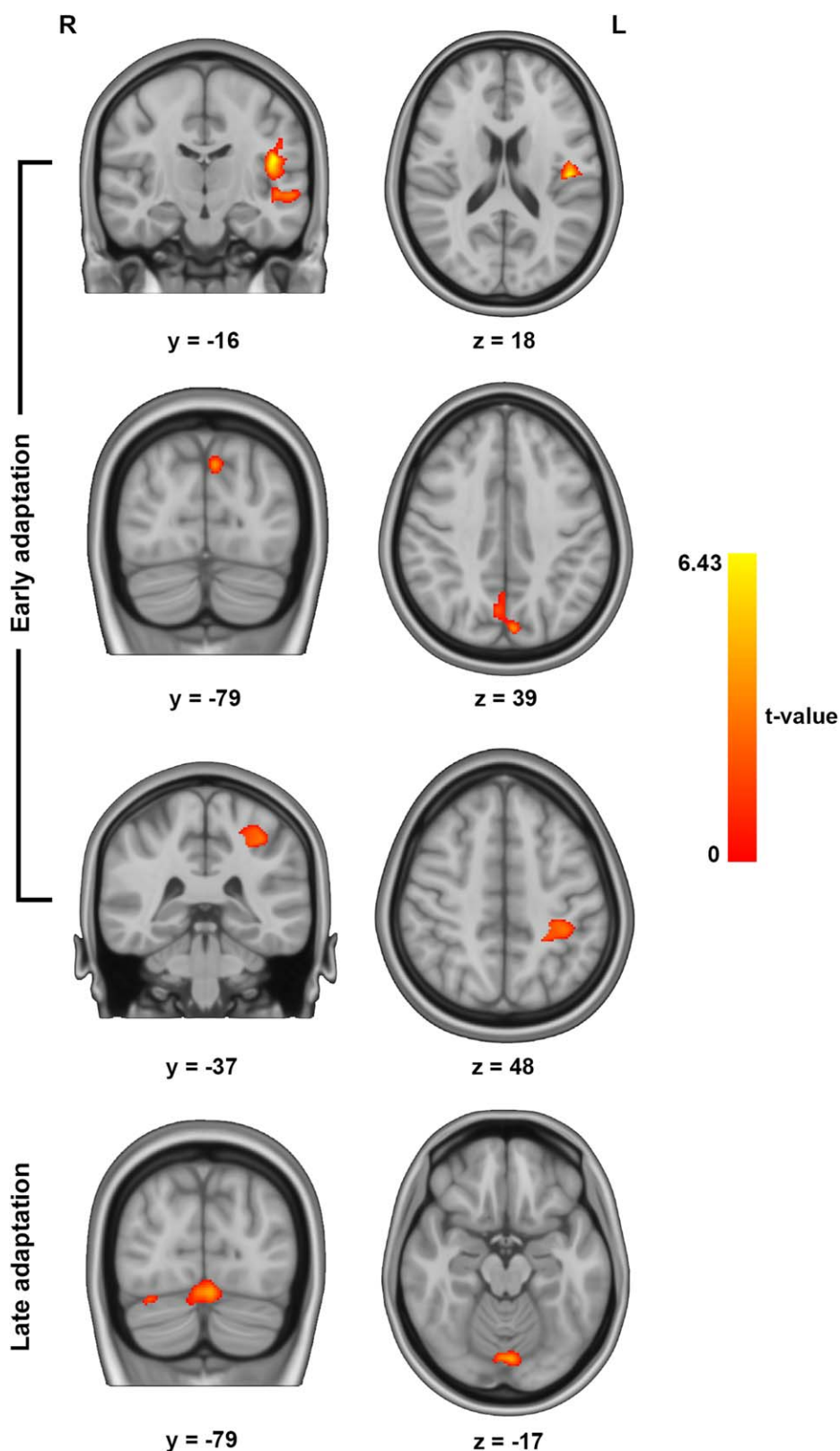
In addition, our previous work has found an association between functional activity in the dorsal ACC and conditions of high task difficulty, in which motor errors were relatively large and movements were slow (Seidler, Noll, & Thiers, 2004). This suggests that participants who are better at error detection and correction may garner their advantage at skill learning by utilizing the dACC network during the early phase of adaptation. Functional neuroimaging evidence links the dACC with prefrontal, premotor, parietal, and insular regions and the basal ganglia, thalamus, and cerebellum forming a core network for the internal generation of movement (Hoffstaedter et al., 2014). One interpretation of our results is that high functional connectivity at rest within this network may facilitate the early, more cognitively demanding phase of sensorimotor adaptation.

Also consistent with our hypotheses, faster adapters during the early phase of the task showed greater functional connectivity strength between left insular cortex with the rest of the brain. Furthermore, connectivity strength between right insular cortex with the rest of the brain was stronger in participants who readapted to the normal feedback faster. The insular cortex plays an important role in the integration

of multimodal sensorimotor and cognitive functions such as error detection, salience, attention to behaviorally relevant stimuli, anticipation, and decision making (Taylor, Seminowicz, & Davis, 2009). Previous studies using resting-state fMRI have identified this region as part of an intrinsic task-positive network or “salience network” along with other areas such as DLPFC, SMA, inferior parietal sulcus and frontal eye fields (Fox et al., 2005; Taylor et al., 2009). This intrinsic network could thus be a general salience and action system involved in environmental monitoring, response selection, and other attentional processes required during visuomotor adaptation.

Interestingly, we observed converging results between functional connectivity and gray matter volume as neural predictors of sensorimotor adaptation. Both analyses indicated a prominent role of left temporoparietal regions in explaining individual variation in early adaptability to the visuomotor task. These findings are in line with previous studies that have explored the neural correlates of sensorimotor adaptation. For instance, Mutha et al. (2011) reported that left parietal regions are crucial for adaptive visuomotor control. They proposed that this region is important for forming and maintaining internal representations of the relationship between motor commands and limb and environmental state. Additionally, Danckert, Ferber, and Goodale (2008) used event-related fMRI to examine the dynamic effects of prisms lenses on manual pointing. Their results demonstrated that activity in anterior cingulate and intraparietal regions were higher during early compared to late adaptation, suggesting that an extensive network of cingulate and temporoparietal regions is involved in recalibrating visuomotor commands in the face of perturbed visual input.

Another converging finding from multiple imaging modalities within this study was the role of the posterior region of the cerebellum in explaining individual variability in late adaptation. According to the functional network parcellation of the cerebellum, this region is located within the DMN area of the cerebellum (Buckner, 2011). Results from both our functional connectivity and VBM analyses indicate that this network can be considered a neural predictor of late adaptation. Overall, these results demonstrate that both temporoparietal and cerebellar regions are associated with faster initial adaptation, whereas only the cerebellum is associated with faster adaptation during the late phase. Results of our mediation analyses showed no significant indications that gray volume and connectivity strength jointly contribute to individual differences in adaptability. Future studies should aim to investigate the relationship between measures from multiple imaging modalities and sensorimotor adaptability and savings.



**FIGURE 7** Gray matter volume in left central operculum cortex (first row), precuneus cortex (second row), and left postcentral gyrus (third row) was correlated with the rate of early adaptation, in which faster learners exhibited higher gray matter volume in these regions than slower learners. Gray matter volume in vermis VI and right crus I of the cerebellum (fourth row) was higher in participants that showed faster rates of adaptation during the late phase of the task

## 4.2 | Predictors of savings

We found behavioral evidence for multiday savings in sensorimotor adaptation from the first to the second test session. Participants were less perturbed when the rotated feedback was introduced during the second test session compared to the first, indicating that they showed savings of what they learned during their previous experience with the task. At the neural level, we observed that the amount of savings was associated with the degree of resting-state functional connectivity among default mode regions of the brain. Specifically, stronger DMN connectivity was associated with more savings. Consistent with some previous studies, these results also demonstrate that the neural correlates associated with savings are similar to those for late learning (Kojima, Iwamoto, & Yoshida, 2004; Medina, Garcia, & Mauk, 2001; Seidler & Noll, 2008; Smith et al., 2006). For instance, Seidler and Noll (2008) found that better generalization of adaptation was correlated with higher activity in brain regions that play a role in late adaptation, including the superior posterior fissure of the cerebellum. These findings suggest that savings is less cognitively demanding than acquisition, and further, that stronger DMN resting-state connectivity may facilitate the later, more procedural stages of sensorimotor adaptation as well as better savings of the task.

Although we found evidence for overlapping neural processes between late adaptation and savings, there are reports in the literature supporting that savings is more associated with early learning cognitive/strategic processes (Haith et al., 2015; Morehead et al., 2015; Seidler, Gluskin, & Greeley, 2017). One potential explanation for these differential findings is that these previous studies were based on behavioral measures of adaptation (Haith et al., 2015; Morehead et al., 2015; Seidler et al., 2017). In contrast, this study examined offline neural predictors of performance, or the baseline state that participants bring to the adaptation process. In particular, offline neural predictors reveal individual differences in system configuration that are more likely to facilitate subsequent dynamic states.

A novel and somewhat unexpected finding of this study is the association between DMN connectivity strength with learning rate during the late adaptation phase and with savings from the first to the second test session. The DMN consists of a set of brain areas that show highly correlated activity and high metabolic demands at rest (Raichle et al., 2001). An important function of this network is to support internally directed mental activity (Gusnard & Raichle, 2001; Mason et al., 2007). The DMN may also make a crucial contribution to the offline processing and consolidation of memories (Miall and Robertson, 2006). Memory consolidation can be defined behaviorally as performance becoming less susceptible to interference (Brashers-Krug, Shadmehr, & Bizzi, 1996) or as performance that improves over time in the absence of further practice (Robertson, Pascual-Leone, & Press, 2004a; Robertson, Pascual-Leone, & Miall, 2004b). Thus, the DMN may play a role in the reprocessing of past experiences to support memory consolidation during the late phase of sensorimotor adaptation, as well as savings of the task. The DMN is considered to be anticorrelated with brain regions involved in cognitive control (Seeley et al., 2007) such as the dACC network, which we found to be associated with early adaptation.

The dynamic opposition between these two networks may therefore be important for regulating attentional and goal-directed demands, and potentially coordinating the interplay between internally and externally directed thought (Raichle, 2010). Our results demonstrate that DMN functional connectivity strength is a predictor of the later, more procedural stages of sensorimotor adaptation and savings, potentially allowing better consolidation of the adapted state.

## 4.3 | Limitations

One limitation of this study is that neuroimaging data were collected on different scanners at different sites (i.e., different scanner sequences and staff), which may have affected the results. However, we used scanner site as a nuisance covariate in all analyses to control for this potential confound. Another limitation is that in contrast to the voxel-to-voxel functional connectivity analyses, seed-to-voxel analyses were not corrected for the number of correlations performed, and therefore should be interpreted with caution. However, the magnitude of these correlations is still moderate and therefore provides useful information about the neural predictors of sensorimotor adaptability and savings. It should further be noted that the subject-averaged mask created during the seed-to-voxel analyses was corrected for multiple comparisons.

Last, this study is limited by the unequal distribution of males and females (30 males; 4 females). Men and women differ in many sensory systems, neural anatomy, and functional responses (Mark et al., 2014). For instance, Moreno-Briseño, Díaz, Campos-Romo, and Fernandez-Ruiz (2010) investigated gender differences in a prism adaptation throwing task. They found that males had significantly higher throwing accuracies, although there were no adaptation differences between genders. In contrast, females showed significantly larger negative after-effects, which could be explained by a larger contribution of spatial alignment. The unequal gender distribution in the present study may thus have prevented us from identifying additional brain-behavior associations. Using gender as a covariate yielded very similar results for our brain-behavior analyses; however, the association between GM volume in the cerebellum and late adaptation was no longer significant ( $p = .12$ ) and the association between voxel-to-voxel functional connectivity in right central operculum cortex and the behavioral after-effects was no longer significant ( $p = .07$ ). With our current sample size, it is difficult to say whether this should be interpreted as evidence for gender differences in adaptability, or simply as a reduction of power due to the addition of gender as a covariate in the model. Future studies should aim to include equal distributions of males and females to test this hypothesis and to be more representative of the population.

## 5 | CONCLUSION

To summarize, we found that functional connectivity strength within a salience network is predictive of the rate of learning during the early phase of a sensorimotor adaptation task. In contrast, DMN functional connectivity strength predicts late learning and multiday savings, such that faster learners during the late phase and individuals with better



savings of the task showed greater connectivity strength within this network.

In terms of structural predictors, gray matter volume in temporoparietal regions was correlated with the rate of early adaptation, whereas gray matter volume in superior posterior cerebellum was associated with the rate of learning during the late phase of the visuomotor task. We propose that the functional and structural correlates of early adaptation likely support cognitive components of the visuomotor task, such as working memory, error detection and correction, and attention. In contrast, the neural correlates of late performance likely support the storage and modification of newly acquired sensorimotor representations.

Better multiday savings was associated with stronger resting-state functional connectivity in the same network involved in late adaptation, suggesting overlapping neural processes between these two phases of sensorimotor adaptation. Ultimately, being able to identify people who are slower adapters could have important implications for developing targeted training programs that enhance adaptation learning, for example, with respect to spaceflight (Bloomberg, Peters, Cohen, & Mulavara, 2015; Seidler, Mulavara, Bloomberg, & Peters, 2015) or rehabilitation (Bastian, 2008).

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#### SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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