Altered Motor and Motor Perceptual Cognitive Imagery Task–Related Activation in Diabetic Peripheral Neuropathy: Insights From Functional MRI

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OBJECTIVE

To compare central nervous system (CNS) activation in patients with and without diabetic peripheral neuropathy (DPN) during motor and motor imagery tasks and to correlate activation with functional performance.

RESEARCH DESIGN AND METHODS

Twenty-six participants (13 with DPN, 13 without DPN) underwent functional MRI during three tasks: ankle dorsi plantar flexion (motor task [MT]) and motor imagery tasks of walking on a smooth surface (SMIT) and rough surface (RMIT). Functional assessment included gait analysis, ankle muscle strength, and ankle range of motion.

RESULTS

The tasks activated the sensorimotor, motor preparation, visual processing, and decision-making regions. Activation was significantly lower in patients with DPN than in those without DPN during MT and SMIT but not RMIT. Poor functional performance in patients with DPN was associated with greater activation in motor preparation regions.

CONCLUSIONS

In patients with DPN, CNS responses appear muted compared with patients without DPN, but they remain capable of enhancing CNS activation when tasks are more challenging or when functional deficits are substantial.

Functional deficits, including impaired balance, altered gait, and a higher risk of falls, are key consequences of diabetic peripheral neuropathy (DPN) (1); however, central nervous system (CNS) responses that compensate or contribute to these deficits have not yet been studied. Emerging evidence suggests that DPN may also involve alterations in the CNS (2–5); therefore, we examined CNS activation in patients with DPN during motor and motor perceptual cognitive imagery tasks compared with patients without DPN and correlated activation patterns to functional performance outside the scanner.

RESEARCH DESIGN AND METHODS

Study Design

This study was approved by the National Healthcare Group Domain Specific Review Board, Singapore. Participants were recruited from a larger study on patients with

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physician-diagnosed type 2 diabetes (6), and written informed consent was obtained. Neuropathy status was assessed by monofilament and/or neurothesiometer testing and confirmed by bilateral sural nerve conduction testing.

Functional Status Assessment

Participants underwent gait analysis at the Motion and Gait Analysis Laboratory at National University Hospital (Supplementary Data). Muscle strength at the ankle and big toe and range of motion at the ankle (microFET2; Hoggan Scientific, Salt Lake City, UT), mobility (timed up and go [TUG] test [7]), and balance confidence (Activities-Specific Balance Confidence (ABC) Scale [8]) were also assessed.

Imaging Paradigms and Procedures

We devised three tasks to assess and compare CNS activation in patients with and without DPN: ankle dorsi plantar flexion (motor task [MT]) and motor imagery tasks of walking on a smooth surface (SMIT) and rough surface (RMIT) (9,10) (Supplementary Fig. 1 and Supplementary Data). Participants were trained on all three tasks before scanning.

Magnetic resonance scans were performed on a 3T Tim Trio scanner (Siemens, Munich, Germany) with a 32-channel head array coil. A T1-weighted anatomical image was acquired with a magnetization-prepared rapid gradient-echo sequence (repetition time/echo time 2,000/35 ms, resolution $1 \times 1 \times 1$ mm^3, matrix $256 \times 256 \times 150$). Functional MRI (fMRI) data were acquired using gradient-echo echo-planar sequence (repetition time/echo time 2,000/35 ms, flip angle 90°, voxel size $2.875 \times 2.875 \times 2.5$ mm, 200 volume, matrix $80 \times 80 \times 35$).

fMRI Image Analysis

Preprocessing and statistical analyses of fMRI data were performed using FMRIB's Software Library (11) (FSL 5.0.6, 2012; Analysis Group, FMRIB, Oxford, U.K.), Analysis of Functional NeuroImages (12) (2011, National Institute of Mental Health, Bethesda, MD), and FreeSurfer (Martinos Center for Biomedical Imaging, Laboratory for Computational Neuroimaging, Boston, MA) software.

Statistical Analysis

A general linear model was applied to generate voxelwise statistical parametric maps of brain activation for each participant and task, adjusted for the matrix of parameters, including task estimated time course, and using the six rigid parameters of motion artifacts, average time course of the white matter, and average time course of cerebral spinal fluid as confounding effects. Mixed-effects models (FLAME 1+2, Feat, FSL) were performed to compare blood oxygenation level–dependent (BOLD) signal intensities between patients with and without DPN and to locate the regions of interest. All statistical maps were corrected for multiple comparisons using cluster-forming threshold at $P < 0.05$, $Z > 2.3$, and cluster size $\geq$40 voxels. A spherical region of interest with radius of 5 mm was used to extract activity levels during each task.

Associations between DPN status and BOLD signal intensities were examined using bivariate and multivariable linear regression. BOLD signal intensities and functional measures among patients with DPN were compared using Pearson correlation (statistical environment R 3.1.2 software; R Development Core Team, Vienna, Austria).

RESULTS

Demographics

Of the 31 participants (15 with DPN and 16 without DPN) enrolled in the study, 5 without complete data were excluded, leaving 26 participants (13 with DPN and 13 without DPN) for analysis (Supplementary Table 1).

Brain Activation Patterns in Response to Different Paradigms

All tasks activated the somatosensory and motor regions corresponding to the foot in patients with and without DPN (Supplementary Figs. 2 and 3). During the imagery tasks, motor and sensory regions corresponding to the hand and face were also activated in patients with DPN but not in those without DPN.

During MT, patients with DPN had significantly lower activation in the right-side (r.) superior parietal lobe, r. lingual gyrus (BA17), r. cerebellar tonsil, and bilateral precuneus (left-sided dorsiflexion movement) and left-side (l.) middle frontal gyrus (BA11), l. inferior frontal gyrus (BA47), bilateral lingual gyrus (BA17), l. cerebellar tonsil, l. declive, and r. inferior semilunar lobule (right-sided dorsiflexion movement) (Table 1 and Supplementary Fig. 2). The bilateral lingual gyrus (BA18, BA19), cuneus, posterior cingulate cortex, l. superior frontal gyrus (premotor, BA6), l. middle temporal gyrus (BA39), bilateral cerebellar tonsil, and r. inferior semilunar lobule exhibited significantly lower activation among patients with DPN during SMIT (Table 1 and Supplementary Fig. 3). During RMIT, only the bilateral lingual gyrus (BA17, BA18) showed lower activation in patients with DPN compared with patients without DPN.

When comparing BOLD activation in RMIT with SMIT, there was increased activity at most regions among patients with DPN during RMIT (Supplementary Fig. 4). A similar comparison in patients without DPN showed increased activity at the bilateral occipital pole and lingual gyrus during RMIT.

Correlation of Brain Activation Patterns With Functional Characteristics Outside the Scanner in Patients With DPN

R. precuneus activation during MT was negatively correlated with pain and discomfort among patients with DPN (Supplementary Table 2). Inferior frontal gyrus activation was positively correlated with total ABC score and negatively with TUG time. Muscle strength and range of motion were inversely associated with activation in the superior parietal lobule, cerebellar tonsil, and declive.

Increased inferior semilunar lobule activation during SMIT was associated with lower cadence, walking velocity, step and stride length, greater step width, and longer TUG time, while increased cerebellar tonsil activation was associated with lower self-care and ankle range of motion (Supplementary Table 3). Similar correlations were observed between premotor cortex activation and walking velocity, stride length, and TUG. Greater activation at the lingual gyrus and cuneus was correlated with greater pain and discomfort, while greater l. middle temporal gyrus activation was correlated with more problems in self-care and longer TUG time. RMIT activation was not significantly correlated with functional characteristics (Supplementary Table 4).

CONCLUSIONS

This study explored differences in brain activation in response to motor and motor

Table 1—Associations between BOLD signal in selected brain activation sites and DPN status

		Crude model		Adjusted model†	
Paradigm	Cluster size (voxel)	β (95% CI)	*P*	β (95% CI)	*P*
MT					
Left foot					
R. precuneus	842	−1.5 (−2.22, −0.77)	<0.001	−1.53 (−2.36, −0.7)	0.001
L. precuneus		−1.44 (−2.47, −0.41)	0.008	−1.76 (−2.91, −0.61)	0.005
R. cerebellar tonsil	359	−1.26 (−1.98, −0.55)	0.001	−1.58 (−2.37, −0.79)	<0.001
R. lingual gyrus (BA17)		−2.09 (−3.48, −0.69)	0.005	−2.43 (−3.97, −0.89)	0.004
R. superior parietal lobule	43	−1.08 (−1.94, −0.22)	0.016	−1.06 (−1.97, −0.15)	0.025
Right foot					
L. middle frontal gyrus (BA11)	671	−1.11 (−1.92, −0.31)	0.009	−1.25 (−2.2, −0.31)	0.012
L. cerebellar tonsil (site 1)	396	−1.67 (−2.53, −0.81)	<0.001	−1.84 (−2.86, −0.82)	0.001
R. lingual gyrus (BA17)	383	−1.8 (−3.13, −0.46)	0.01	−2.28 (−3.75, −0.81)	0.004
L. lingual gyrus (BA17)		−1.71 (−2.78, −0.65)	0.003	−2.12 (−3.33, −0.91)	0.002
R. inferior semilunar lobule	42	−0.76 (−1.56, 0.05)	0.063	−0.96 (−1.88, −0.03)	0.043
L. inferior frontal gyrus (BA47)	35	−0.96 (−1.68, −0.24)	0.011	−0.99 (−1.83, −0.14)	0.024
L. cerebellar tonsil (site 2)	33	−1.44 (−2.53, −0.34)	0.013	−1.63 (−2.92, −0.35)	0.015
L. declive	30	−0.97 (−2.12, 0.17)	0.092	−1.42 (−2.65, −0.19)	0.026
Imagery task					
SMIT					
R. lingual gyrus (BA18)	2,649	−3.66 (−5.07, −2.26)	<0.001	−3.64 (−5.33, −1.94)	<0.001
L. lingual gyrus (BA18)		−2.07 (−3.41, −0.73)	0.004	−2.07 (−3.7, −0.45)	0.015
R. cerebellar tonsil	865	−1.14 (−1.86, −0.41)	0.004	−1.32 (−2.18, −0.45)	0.005
L. posterior cingulate	618	−1.68 (−2.56, −0.79)	0.001	−1.8 (−2.86, −0.74)	0.002
L. cuneus		−2.35 (−3.86, −0.83)	0.004	−2.34 (−3.92, −0.76)	0.006
R. lingual gyrus (BA19)	482	−1.56 (−2.69, −0.44)	0.009	−1.44 (−2.74, −0.14)	0.031
R. inferior semilunar lobule (site 1)	422	−1.64 (−2.43, −0.86)	<0.001	−1.72 (−2.65, −0.79)	0.001
L. superior frontal gyrus (BA6)	274	−1.67 (−2.55, −0.8)	0.001	−1.62 (−2.57, −0.66)	0.002
L. middle temporal gyrus	199	−1.52 (−2.5, −0.55)	0.004	−1.66 (−2.75, −0.56)	0.005
L. cerebellar tonsil	189	−1.23 (−2.1, −0.35)	0.008	−1.31 (−2.32, −0.3)	0.013
R. posterior cingulate	79	−1.03 (−2.05, −0.01)	0.049	−0.85 (−2.06, 0.35)	0.156
R. inferior semilunar lobule (site 2)	57	−1.27 (−2.15, −0.38)	0.007	−1.17 (−2.21, −0.14)	0.029
R. Cuneus	40	−2.15 (−3.35, −0.95)	0.001	−2.08 (−3.33, −0.83)	0.002
RMIT					
L. lingual gyrus	749	−1.56 (−2.93, −0.18)	0.028	−1.52 (−2.97, −0.08)	0.04
R. lingual gyrus		−4.17 (−6.52, −1.82)	0.001	−4.41 (−6.98, −1.85)	0.002
L. lingual gyrus	125	−1.49 (−2.95, −0.04)	0.045	−1.56 (−2.82, −0.31)	0.017

Reference group is patients without DPN. †Multivariable model adjusted for age, BMI, and duration of diabetes.

perceptual cognitive imagery fMRI paradigms in patients with diabetes with and without DPN. All tasks activated the corresponding motor and sensory regions in the brain. These tasks also activated brain regions involved in visual processing (lingual gyrus, cuneus), cognition (posterior cingulate gyrus, middle temporal gyrus), decision making (superior, middle, and inferior frontal gyri; middle cingulate gyrus), and motor preparation (premotor cortex, supplementary motor area, cerebellar tonsil, inferior semilunar lobule, superior parietal lobule). These are part of the extended action observation network (10,13) and the mirror neuron network (14), allowing the processing of movements performed by others for replication.

During the motor task, patients with DPN had decreased activation of the motor coordination and visual processing regions, potentially because of reduced afferent input from the foot. We also found evidence of CNS compensation, with greater activation of motor coordination and sensory facilitation regions in patients with DPN having lower muscle strength and range of motion.

During both imagery tasks, sensorimotor cortex activation in patients with DPN extended beyond the foot to regions mapping to the hands and face, while activation in patients without DPN was limited to the foot. Expansion of the foot somatosensory cortex area has been previously reported in the context of painful DPN (4). We now demonstrate similar dynamic plasticity in both somatosensory and motor cortices during perception-cognition and preparation for complex walking movements.

Patients with DPN had lower activation across the motor preparation, visual, and cognition networks during SMIT. Activation in the motor preparation regions was inversely associated with functional performance, again suggesting CNS compensation for poor functional performance.

Brain activation intensity differed between SMIT and RMIT. Patients without DPN had greater activation in the visual processing network during RMIT, suggesting greater dependence on processing of visual cues when navigating a rough surface. In contrast, patients with DPN had greater activation of most regions during RMIT. In fact, there was no difference in activation levels between patients with and without DPN during RMIT, except in the lingual gyrus, suggesting that patients with DPN cope with more-demanding walking tasks with greater CNS activation.

Study limitations include the relatively small sample size; however, all participants had type 2 diabetes with no significant differences between those with and without DPN. Our findings may be confounded by disturbed neurovascular coupling reported previously in patients with type 2 diabetes (15), although participants with known cerebrovascular disease were excluded. The imagery tasks captured perceptual cognitive responses during motor preparation rather than actual task performance, which is another limitation. However, the differences in activation patterns were significant after correction for multiple comparisons and adjustment for confounders. Importantly, we correlated activation patterns within the scanner with functional parameters tested outside the scanner.

Our findings suggest that CNS responses in patients with DPN are muted compared with patients without DPN. However, these patients retain the ability to compensate for peripheral neurological deficits by enhancing CNS activation when faced with more challenging tasks or when functional deficits are substantial.

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