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Lesions causing freezing of gait localize to a cerebellar functional network

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Abstract

Objective—Freezing of gait is a disabling symptom in Parkinson's disease and related disorders, but the brain regions involved in symptom generation remain unclear. Here we analyze brain lesions causing acute onset freezing of gait to identify regions causally involved in symptom generation.

Methods—Fourteen cases of lesion-induced freezing of gait were identified from the literature and lesions were mapped to a common brain atlas. Because lesion-induced symptoms can come from sites connected to the lesion location, not just the lesion location itself, we also identified brain regions functionally connected to each lesion location. This technique, termed lesion network mapping, has been recently shown to identify regions involved in symptom generation across a variety of lesion-induced disorders.

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Potential Conflicts of Interest

None.

Author Contributions

Study concept and design (AF, MDF); data acquisition and analysis (SEL, SL); drafting the text or figures (AF, SEL, MDF).

Results—Lesion location was heterogeneous and no single region could be considered necessary for symptom generation. However, over 90% (13/14) of lesions were functionally connected to a focal area in the dorsal medial cerebellum. This cerebellar area overlapped previously recognized regions that are activated by locomotor tasks, termed the cerebellar locomotor region. Connectivity to this region was specific to lesions causing freezing of gait compared to lesions causing other movement disorders (hemichorea or asterixis).

Interpretation—Lesions causing freezing of gait are located within a common functional network characterized by connectivity to the cerebellar locomotor region. These results based on causal brain lesions complement prior neuroimaging studies in Parkinson's disease patients, advancing our understanding of the brain regions involved in freezing of gait.

Keywords

Cerebellum; freezing of gait; neuroimaging

Introduction

Freezing of gait (FOG) is an episodic disorder of human locomotion, characterized by sudden and brief episodes of the inability to produce effective forward stepping.[1] The most common cause of FOG is Parkinson's disease (PD), where its prevalence ranges from ~10% in the Hoehn and Yahr stage 1 to more than 90% in stage 4.[2] Although FOG is a common cause of falls and a major determinant of quality of life, the brain regions involved in generating this mysterious motor phenomenon remain unclear.[3]

Neuroimaging studies in PD patients suffering from FOG have identified many structural and functional abnormalities across a variety of brain regions.[4] Implicated regions include components of the motor and premotor networks, executive-attention network, right-sided visuospatial network, caudate nucleus, and locomotor centers in the brainstem.[4] Although highly valuable, it is difficult to determine whether these observed abnormalities are co-incidental, causes, consequences, or compensations for FOG symptoms, an important distinction when seeking to identify therapeutic targets.

In the current study, we take an alternative approach towards identifying the neuroanatomical substrate of FOG. Specifically, we focus on cases of acute-onset FOG following focal brain lesions. Lesion-induced FOG symptoms are not identical to all the forms of FOG seen in PD, which is quite heterogeneous.[1, 3] However, the main reason to study lesion-induced FOG is that it allows for causal conclusions regarding FOG symptoms and focal neuroanatomical locations. Further, lesion-induced symptoms can potentially lend insight into the neuroanatomical substrate underlying similar symptoms in different diseases.[5, 6] The difficulty in studying lesion-induced FOG lies in the fact that these lesions cases are rare and many lesion-induced symptoms fail to localize to a single anatomical location.

To circumvent these problems, we used a recently validated technique termed lesion network mapping to investigate lesion locations causing FOG.[6] This approach involves three steps: 1) transferring the three-dimensional volume of a brain lesion onto a reference brain; 2)

identifying the network of brain regions functionally connected to this lesion volume using a normative connectome dataset; and 3) overlapping lesion-associated networks to identify regions common to a clinical syndrome.[6] The technique is based on the concept of diaschisis and the fact that symptoms can emerge from regions connected to the lesion location, not just the lesion itself.[7] Although this technique is relatively new, it has been used by different research groups to investigate a variety of lesion induced symptoms including visual hallucinations,[6] auditory hallucinations,[6] pain,[6] aphasia,[6] hemichorea,[5] Capgras syndrome,[8] coma,[9] and impaired decision making.[10] In each case, the technique has linked heterogeneous lesions to specific brain regions involved in symptom expression.[6] This technique has also been used to identify the common substrate underlying lesion-induced symptoms when that substrate has no known a priori localization.[5]

Methods

Case selection

Case reports of lesion-induced FOG from the existing literature were identified through a systematic search at http://www.ncbi.nlm.nih.gov/pubmed/ including items published from 1993 up to 2013 with the terms “freezing of gait”, “gait disturbance”, “stroke”, “MRI” and/or “lesion”. Citations from each selected article were cross-referenced. Inclusion criteria were: (1) documented examination describing symptoms of FOG, defined as either marked hesitation with or inability to initiate gait, episodes of abrupt involuntary cessation of locomotion, especially during turns or at transition points, in the absence of significant weakness (2) clearly delineated and circumscribed brain lesions displayed in the article and (3) close temporal relationship between symptom onset and image acquisition. Exclusion criteria included (1) extrinsic compression injuries, (2) significant mass effects, (3) report of whole brain anoxia (4) the presence of competing etiologies for FOG (e.g., idiopathic PD, normal pressure hydrocephalus or neurodegenerative disease), (5) insufficient clinical or radiological detail and (6) poor image quality. Fourteen cases were identified using these criteria (Table 1, Supplemental Table Online).

Lesion mapping

The lesion location as displayed in the published figure was manually traced onto a reference brain (MNI152 brain, 2 mm × 2 mm, http://fsl.fmrib.ox.ac.uk/fsldownloads). Neuroanatomical landmarks were used to ensure the accurate transfer of the lesion location onto the template brain. In cases where more than one lesion was displayed, lesions were mapped together and treated as a single lesion for subsequent analyses. All lesions were mapped true to their laterality. The cohort of 14 lesions is displayed in Figure 1A.

Lesion network mapping

To investigate the networks associated with FOG lesions, we applied the recently validated technique termed lesion network mapping.[6] This technique involved three steps: 1) the volume of each lesion is transferred to a reference brain 2) the network of brain regions functionally connected to each lesion volume is computed using resting state functional connectivity MRI data from a large cohort of normal participants, and 3) the resulting lesion-network maps are thresholded and overlaid to identify common network sites across

the lesions. Importantly, this technique does not require full 3D lesion volumes and has been shown to work equally well using 2D information from published lesion images.[6]

Our normative resting state functional connectivity MRI dataset consisted of 98 healthy participants (48 male participants, ages 22 ± 3.2 years), part of a larger publicly available dataset.[11] Full methodological and processing details for the normative resting state functional connectivity MRI (rs-fcMRI) dataset are available.[12] Briefly, participants completed one or more rs-fcMRI scans during which they were asked to rest in the scanner with their eyes open. Rs-fcMRI data were processed in accordance with the strategy of Fox et al.[13] as implemented in Van Dijk et al.[14] Functional data were preprocessed to decrease image artifacts and between-slice timing differences. Data were then spatially smoothed using a Gaussian kernel of 6 mm full-width at half-maximum and temporally filtered (0.009 Hz < f < 0.08 Hz). Next, several spurious or nonspecific sources of variance were removed by regression of the following variables: 1) six movement parameters computed by rigid body translation and rotation during preprocessing, 2) mean whole brain signal, 3) mean brain signal within the lateral ventricles, and 4) the mean signal within a deep white matter ROI. Inclusion of the first temporal derivatives of these regressors within the linear model accounted for the time-shifted versions of spurious variance.

Resting state functional connectivity maps were created for each lesion volume using a standard “seed-based” approach. Specifically, the time-course of the blood oxygen level dependent (BOLD) signal within the lesion volume was extracted for each participant in the normative cohort. Correlations between this extracted signal and all other brain voxels were identified and results were combined across participants using a T-test.

Lesion network overlap

Each of the 14 individual lesion-seeded rs-fcMRI network maps was thresholded at a *t* value of positive or negative 2 ($p<0.05$, uncorrected) to identify voxels significantly connected to each lesion location. To ensure that results were not dependent on our choice of threshold we repeated the analysis with t value thresholds of 3 and 4.25. After applying this statistical threshold, the resulting network maps were binarized and overlapped to identify regions of shared positive or negative correlation (Figure 1B). Regions in this overlap map showing connectivity to 90% (13/14) lesions were identified and center of gravity coordinates for each region were computed.

To ensure that results were not dependent on cases in which the lesion location may be inaccurate (such as tumors, progressive symptoms, or multiple lesions), we repeated our analysis using a subset of 7 cases involving acute-onset, non-progressive FOG following single lesions due to cerebrovascular injury (Case numbers 1,5,7,8,12,13,14).

Specificity analyses

To evaluate specificity and to control for the possibility that our findings might have been obtained with any set of lesions resulting in abnormal motor control, we compared our FOG lesions to lesions causing two other movement disorders: asterixis and hemichorea-hemiballismus. We chose these two disorders as they are common lesion-induced movement disorders, are readily available in the literature, and were used in a recent publication by our

lab.[5] Hemichorea-hemiballismus cases included 29 patients with lesions located in cortex, STN, putamen, caudate, midbrain, and subcortical white matter. Asterixis cases included 30 patients with lesions located in the thalamus, cortex, brainstem and cerebellum.[15] Full details regarding both of these lesion cohorts have been published previously.[5, 15]

Two statistical approaches were used to compare lesion network mapping results between FOG lesions and control lesions, a Liebermeister test and a two-tailed T-test. Both statistical analyses identify voxels significantly more connected to FOG lesion locations than control lesion locations. The difference between these statistical tests is that the Liebermeister test classifies voxels in a binary fashion (connected or not) and is more commonly used in lesion analysis,[16] while the t-test takes into account the strength of the connection and is more commonly used in functional neuroimaging. The inclusion of both tests avoids limitations associated with either alone. FOG lesions were compared to the two control cohorts combined (i.e. FOG versus hemichorea-hemibalismus plus asterixis) and each control cohort individually (i.e. FOG vs. hemichorea-hemibalismus and FOG vs. asterixis). Multiple different statistical approaches and comparisons were done to ensure that results were robust to different analytic approaches.

Because the goal of these analyses was to assess the specificity of FOG lesion network mapping results, statistical maps were masked to anatomical regions containing sites of peak FOG network overlap (cerebellum, thalamus, and subcallosal cingulate), using the Harvard-Oxford structural atlas within FSL.

Overlap with cerebellar locomotor regions

We compared our lesion network mapping results to two separate fMRI studies of human locomotion. The first study compared active vs. passive stepping.[17] The largest peak across the entire brain was located in the left cerebellar vermis (MNI x=−8,y=−42,z=−26) with a secondary peak in the right cerebellar vermis (x=8,y=−44,z=−26). The second study contrasted mental imagery of locomotion (walking and running) vs. mental imagery of lying.[18] The largest peak across the entire brain was located in a large cluster centered in the bilateral cerebellar vermis with a left-sided peak at (MNI x=−6, y=−48, z=−14). Given that secondary peaks in this cluster were not specifically reported, we used MNI x=6, y=−48, z=−14 as the location of the right sided coordinate. Regions of interest were generated by creating 6mm spheres centered at these coordinates. Functionally connectivity between these regions of interest and each lesion location was computed using our normative functional connectivity dataset and Pearson's correlation. Resulting r values were converted to a normal distribution using Fisher's r to z transform and statistics were computed using a students t-test. Average Fisher z values were converted back into r values for display.

Functional connectivity of the cerebellar overlap site

To identify brain areas functionally connected to our cerebellar overlap site, we used our cerebellar site (thresholded at 13/14) as a seed region to generate a rs-fcMRI map. Peak coordinates in this map were identified using a cluster analysis with a threshold of t=6 (positive correlation only) and two local maxima per cluster (Table 2). This network map is displayed on the cortical surface using CARET[19] and in volume space using FSL.

Results

Our literature search identified 14 cases of lesion-induced FOG (Figure 1A, Table 1, Supplemental Table Online). There were 3 females, mean age was 63.6±15.6 years (range: 35–83) with a mean follow-up period, when recorded, of 7 months (range: 24hrs-2 years). Lesion etiology was heterogeneous, with ischemic stroke being the most common. Five cases reported response to L-dopa, none of which improved. Lesions were anatomically heterogeneous with seven primarily in the brainstem, three in the basal ganglia, three in the cortex and one in the subcortical white matter. Five lesions were mostly right sided, four were mostly left sided and five were bilateral.

Next, the network associated with each lesion location was computed and areas of network overlap identified (Figure 1B). Despite marked heterogeneity in lesion location, greater than 90% overlap of positively correlated lesion-derived networks occurred in two areas: the bilateral cerebellum (MNI x=16 y=−44 z=−26, x=−20 y=−44 z=−26, Figure 2A) and bilateral thalamus (MNI x=12 y=−20 z=4, x=−10 y=−18 z=2, Figure 2B). Greater than 90% overlap of negatively correlated networks occurred in the bilateral subcallosal cingulate (MNI x=10 y=20 z=−12, x=−14 y=22 z=−12) (Figure 2C). The cerebellar and thalamic overlap sites were more robust to different thresholds (>50% lesion network overlap even at the highest threshold), than the subcallosal cingulate site (36% network overlap at the highest threshold).

To determine whether this connectivity was specific to lesions causing FOG, we compared networks derived from FOG lesions to networks derived from lesions causing other movement disorders (hemichorea-hemiballismus and asterixis). Voxels in the bilateral dorsal medial cerebellum were significantly more connected to lesions causing FOG than lesions causing other movement disorders using two different statistical approaches (Figure 2D and G, $P < 0.05$). In contrast, voxels in the thalamus and the subcallosal cingulate were non-specific, with no significant difference in connectivity between lesion cohorts (Figure 2E, F, H and I). To ensure that our cerebellar results were robust to choice of control cohort, we also compared FOG lesions to just asterixis lesions (Figure 3A, B) and just hemichorea-hemiballismus lesions (Figure 3C, D). To ensure that our cerebellar results were not driven by FOG lesions with uncertain localization (e.g. tumors, multifocal lesions) we repeated our analysis with a subset of seven single-focus lesions due to acute cerebrovascular events (Figure 3E, F). Results were unchanged across all variations in our statistical or analytic approach.

Because our nodes in the cerebellum seemed close to regions previously identified in neuroimaging studies of locomotion, we created regions of interest based on the coordinates in these prior studies. We found that our lesion locations causing FOG showed significant connectivity to both these cerebellar locomotor regions ($p < 0.05$). Further, this connectivity was significantly greater than that seen with lesions causing either hemichorea-hemiballismus ($p<0.001$, Figure 4A) or asterixis ($p<0.05$, Figure 4A). These results were significant regardless of whether we used a single left sided cerebellar ROI or bilateral ROI generated using the coordinates from Jahn et al.[18] Finally, the spatial distribution of our

lesion network mapping results matched the location of these cerebellar locomotor regions (Figure 4B, C).

Given the emphasis our results placed on this particular location within the cerebellum, we evaluated the connectivity of this site to the rest of the brain (Figure 5A). There was one dominant cortical connection, namely the bilateral leg area of the primary motor cortex, as well as several subcortical sites implicated in motor control (Table 2). As expected, the network of voxels functionally connected to this cerebellar site incorporated the heterogeneous lesion locations resulting in FOG (Figure 5B).

Discussion

In this study we find that lesions to multiple different brain areas can cause FOG, but these areas are part of a common functional network. Specifically, lesion locations resulting in FOG are functionally connected to a focal area in the dorsal medial cerebellum. This cerebellar area overlaps sites activated in prior studies of human locomotion. These findings complement prior work in other types of FOG, provide insight into the neuroanatomical substrate underlying this disabling symptom, and may have implications for identifying treatment targets.

Lesion Network Mapping in FOG

Because lesions causing FOG are relatively rare and occur across different brain areas, traditional approaches to lesion mapping have been limited. Our recently validated technique, lesion network mapping, expands lesion analysis by integrating brain connectivity.[5, 6] This technique allows us to determine whether lesion locations share a specific pattern of connectivity, and if so to what region. Regions functionally connected to lesion locations tend to be involved in symptom generation, as previously shown for visual hallucinations, auditory hallucinations, pain, aphasia, hemichorea, and impaired decision making.[5, 6, 10] When applied to lesions causing FOG, this same technique implicates focal areas in the dorsal midline cerebellum that are specific to lesions causing FOG. Because heterogeneous lesion locations causing FOG share connectivity to the dorsal medial cerebellum, and lesions are known to cause dysfunction in connected brain regions,[7] we suggest that this cerebellar region and its associated network may play a role in generating FOG symptoms.

The role of the cerebellum in locomotion

Bipedal locomotion is a complex process thought to involve a network of cortical and subcortical regions.[20–22] One of these regions, termed the cerebellar locomotor region (CLR), lies at the midline of the cerebellar white matter. Stimulation of this region can induce locomotion in experimental animals.[21,23,24] Neuroimaging studies suggest that a similar CLR may exist in humans. Prior studies have used mental imagery of gait[25] or special foot pedals that allow for active stepping in the MRI scanner.[17] Both approaches identified focal increases in the cerebellum postulated to represent the location of the human CLR.

In the current study, these cerebellar regions previously implicated in locomotion were functionally connected to lesion locations causing FOG. This connectivity was specific to lesions causing FOG versus lesions causing hemichorea or asterixis. Further, the spatial distribution of our lesion network mapping results matched the location of these cerebellar locomotor regions. Collectively, these results suggest that the CLR may play a role in the pathophysiology of FOG in addition to its known role in locomotion.

An interesting question is why, if this cerebellar region is involved in FOG, do patients with cerebellar lesions present with other balance and gait abnormalities but only rarely with FOG. One possibility is that most cerebellar lesions impact a larger area than the focal site identified here, perhaps causing other symptoms that mask or preclude FOG itself. In other words, FOG may require dysfunction of a focal region of the dorsal medial cerebellum, but also require that other regions of the cerebellum remain intact. This type of focal dysfunction may be more likely to occur when lesions occur outside the cerebellum, to sites connected to just one part of the cerebellum. Along these lines, it is worth noting that the only cerebellar lesion in our FOG case series (case #3) is a focal lesion in the vicinity of the cerebellar locomotor area that spares surrounding cerebellar structures.

Another possibility is that preservation (rather than dysfunction) of this CLR node along with lesions to other parts of the locomotor network (defined based on connectivity to the CLR) is responsible for lesion-induced FOG.

Will these findings be relevant for PD-related FOG?

An important question is whether the present results, based on lesion-induced FOG, are relevant for FOG in PD, a much more prevalent and pressing clinical problem. Answering this question requires future work, however there are reasons to think the present results will be relevant.

First, both lesion-induced FOG and PD-related FOG share many clinical features. Both cause an episodic disorder of human locomotion, characterized by sudden and brief episodes of the inability to produce effective forward stepping.[1] However PD-related FOG is heterogeneous and composed of various subtypes.[1, 3] Of these PD subtypes, the one most similar to lesion-induced FOG is likely the “resistant” or “unresponsive” subtype.[3] In this subtype, FOG fails to respond to levodopa, similar to patients with lesion-induced FOG included in the present study (Table 1). As such, while lesion-induced FOG may not match the clinical phenotype of all PD-related FOG subtypes, it is similar to the subtype in greatest need of a treatment.[26]

Second, regions identified in prior lesion network mapping studies have been implicated in generating similar symptoms in different disorders. For example, lesions that cause visual hallucinations are connected to extrastriate visual cortex, a region known to be hyperactive when visual hallucinations are caused by diseases such as macular degeneration.[6] Similarly, lesions causing hemichorea are functionally connected to the posterolateral putamen, a region that becomes hyperintense on MRI in hyperglycemia-induced hemichorea and a region in which atrophy correlates with chorea severity in Huntington’s disease.[5] As such, it

is possible that the dorsal medial cerebellum, implicated here in lesion-induced FOG, will play a role in FOG in other disorders such as PD.

Finally, while the CLR is not featured prominently in most neuroimaging studies of PD-related FOG,[4] several studies have found abnormalities. Specifically, both anatomical connectivity[27–29] and functional connectivity[30] with the CLR have been reported to be abnormal in PD patients with FOG.

The pathophysiology of PD-related FOG is still unclear and 4 main hypotheses have been formulated: the threshold, decoupling, interference and cognitive model.[1] Our findings best support the first two models, which see FOG as a mainly motor problem.[31] However our results also support the interference and cognitive models. Specifically, the cerebellar region identified by our lesion network analysis falls within 5 mm of the peak activation seen with dual-tasking,[32] a manipulation known to exacerbate FOG.[1]

Treatment targets?

Although some FOG subtypes in PD respond to dopaminergic treatments, FOG is often medication-resistant.[3] This has prompted investigation into brain stimulation treatments. However, the optimal brain stimulation target for FOG remains unknown. Deep brain stimulation of the pedunculopontine nucleus (PPN) has shown some promise, but results have been variable and the role of the PPN in locomotion has been questioned.[20, 22] Interestingly, and in keeping with our findings, in PD patients PPN stimulation increases rCBF in the bilateral cerebellum.[33]

Another stimulation target with some evidence of efficacy in FOG is primary motor cortex, especially the leg area, which has been targeted with both invasive[34] and non-invasive stimulation.[35, 36] Our cerebellar site, identified based on lesions that cause FOG, is also closely connected to the leg area of M1 (Figure 5A). This finding is consistent with the notion that targets of brain stimulation may be brain networks rather than single regions.[37] Whether our cerebellar site and its associated connectivity network will prove valuable for improved targeting of therapeutic brain stimulation for FOG is a testable hypothesis for future work.

Limitations

Several potential confounds of our lesion network mapping technique have been previously addressed including using a 2D figure to approximate a 3D lesion, using a connectome from a younger cohort to approximate an older cohort, and the impact of different functional connectivity processing techniques. All these variables were found to have little effect on lesion network mapping results.[6] However, there are still important limitations to the current study.

First, due to their rarity lesion cases were retrospectively identified and not directly examined by us. This introduces potential bias based on our search criteria, limits the available clinical and neuroimaging information, and results in a heterogeneous group of lesion cases. However, this heterogeneity should bias us against the current findings of a common functional network. For example, the only FOG lesion that failed to show

connectivity to our midline cerebellar region was a case of lymphoma in which the published image likely failed to capture the full extent of the lesion (case 11). To help mitigate this concern regarding heterogeneity, a sub-analysis with a more homogenous group of FOG lesions was conducted and produced similar results (see Figure 3E, F).

Second, our analysis comes very close to identifying a factor necessary for a lesion to produce FOG, however this should not be interpreted as sufficient. A degree of specificity is present given that two other lesion-induced movement disorders – hemichorea and asterixis – do not share this connectivity, but this is certainly not an exhaustive list of potential comparison conditions. Ideally, we would contrast our FOG lesions with lesions causing a different gait phenotype such as gait ataxia or higher-level gait disorder (HLGD). Unfortunately, there is significant phenotypic overlap between FOG and these conditions. For example, four of our 14 cases of lesion-induced FOG also had some degree of gait ataxia and HLGD patients may have FOG.[38] Even with phenotypic separation, connectivity to our cerebellar site may not be specific for FOG. For example, large lesions causing lower extremity hemiparesis could potentially be connected to our cerebellar site but produce such severe weakness as to preclude FOG. An intact corticospinal tract, relatively intact cerebellum, and perhaps other yet to be identified factors may be required for lesion-induced FOG.

Finally, as discussed in detail above, our analysis was restricted to lesion-induced FOG, which may or may not share the same neuroanatomical substrate with all forms of PD-induced FOG.[3] The applicability of our results to PD-induced FOG require future work.

Conclusions

Lesions to multiple different brain areas can cause FOG, but these areas are part of a common functional network connected to a focal area in the dorsal medial cerebellum. Our findings based on causative brain lesions complement previous neuroimaging studies focused on FOG correlates in symptomatic patients. These results may guide the development of new therapies for treatment-resistant FOG such as identification of targets for brain stimulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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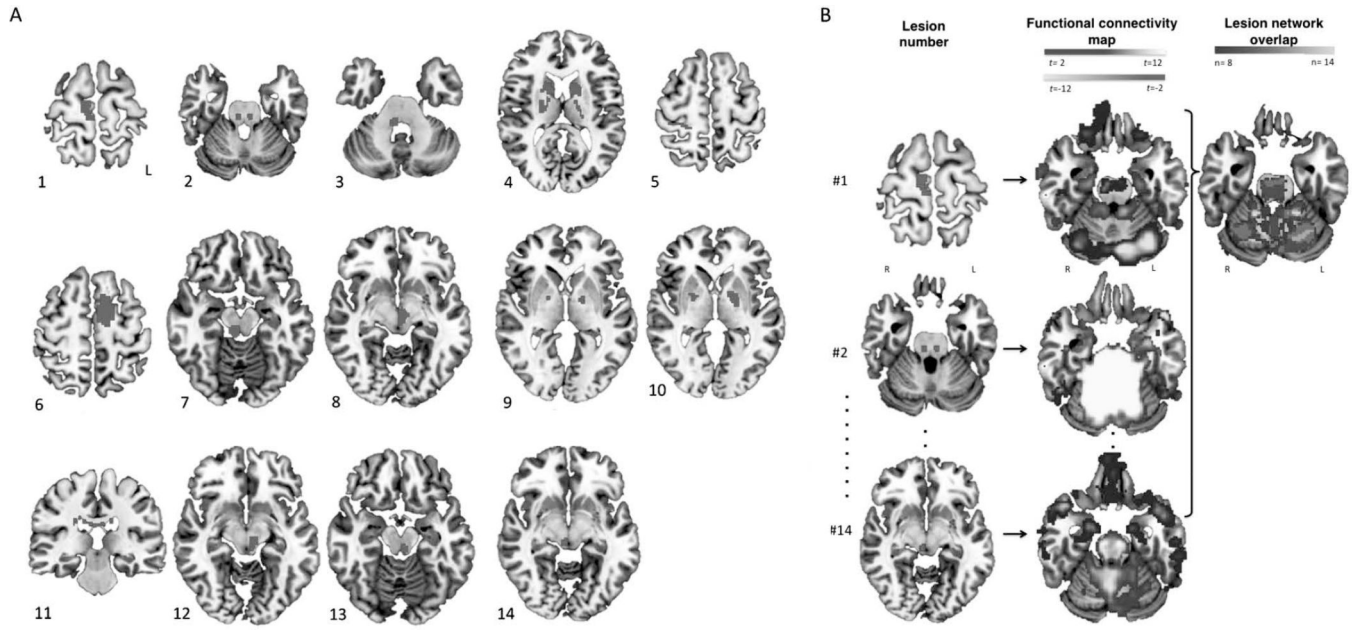

Figure 1.

A) Lesion location for 14 cases of lesion-induced FOG, manually traced onto a reference brain (MNI152 template). All lesions were traced true to their laterality, right/left orientation for each lesion as shown on the upper left cross-section. B) Lesion network mapping technique. Each lesion location (left) was used as a seed region to generate a functional connectivity map based on resting state fMRI data from healthy controls (middle). The 14 functional connectivity maps were then overlapped to identify brain regions functionally connected to the greatest number of lesion locations (right).

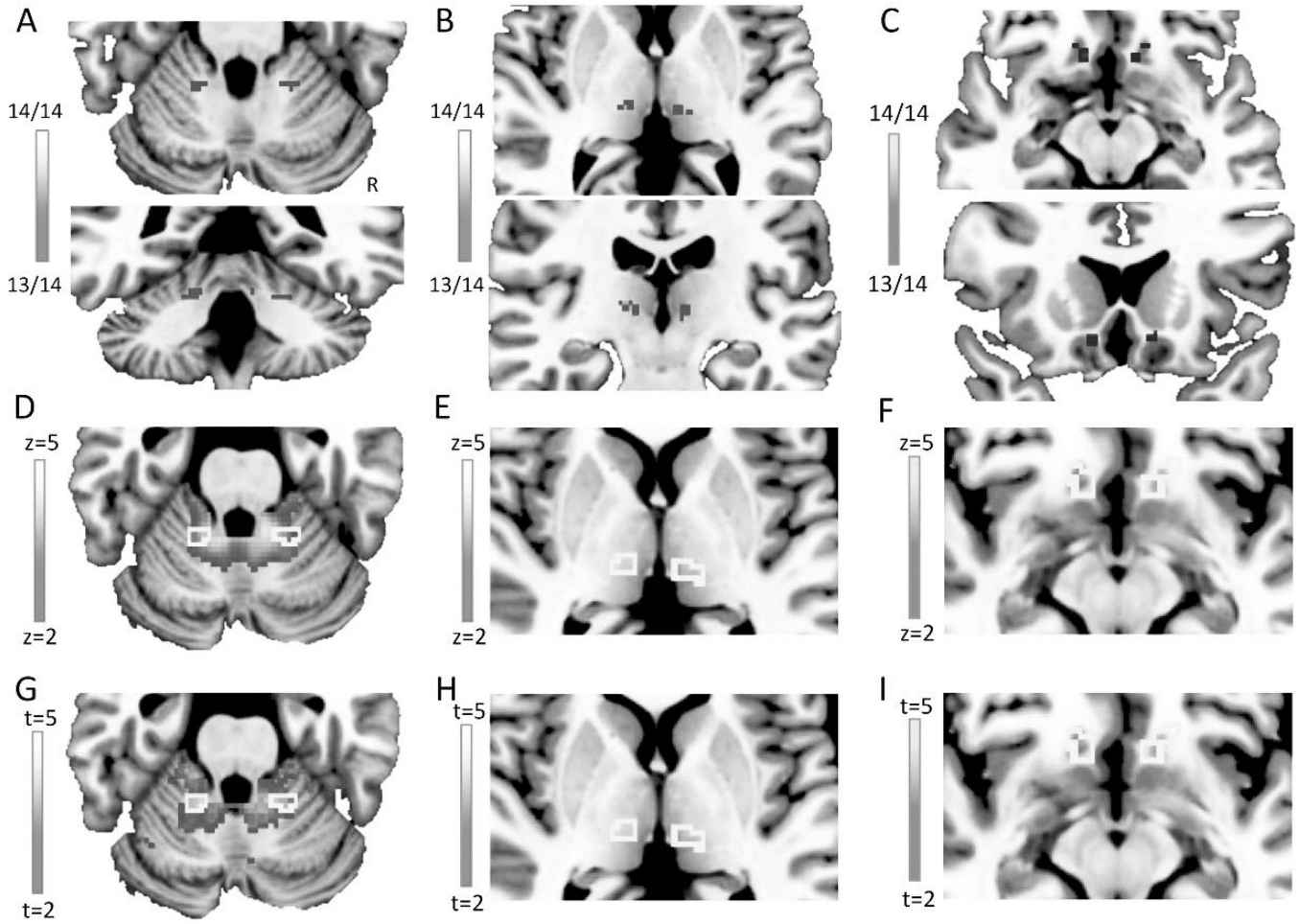

Figure 2.

Lesion network mapping results. The vast majority (> 90%) of lesion locations resulting in FOG were positively correlated to sites in the cerebellum (A), thalamus (B) and anti-correlated to sites in the subcallosal cingulate (C). Functional connectivity maps from lesions causing FOG were compared with those causing other movement disorders (asterixis and hemichorea-hemiballismus) using two statistical tests: voxel-wise Leibermeister test (D–F) and unpaired t test (G–I). FOG lesion network overlap sites in the cerebellum, thalamus and subcallosal cingulate (see panels A-C) are outlined in light grey (green in the online version of the figure) for reference. Statistical comparison maps were masked to the cerebellum (D, G), thalamus (E, H) and subcallosal cingulate (F, I), using Harvard-Oxford structural atlases. Connectivity to the dorsal medial cerebellum, but not the thalamus or subcallosal cingulate, is specific to lesions causing FOG.

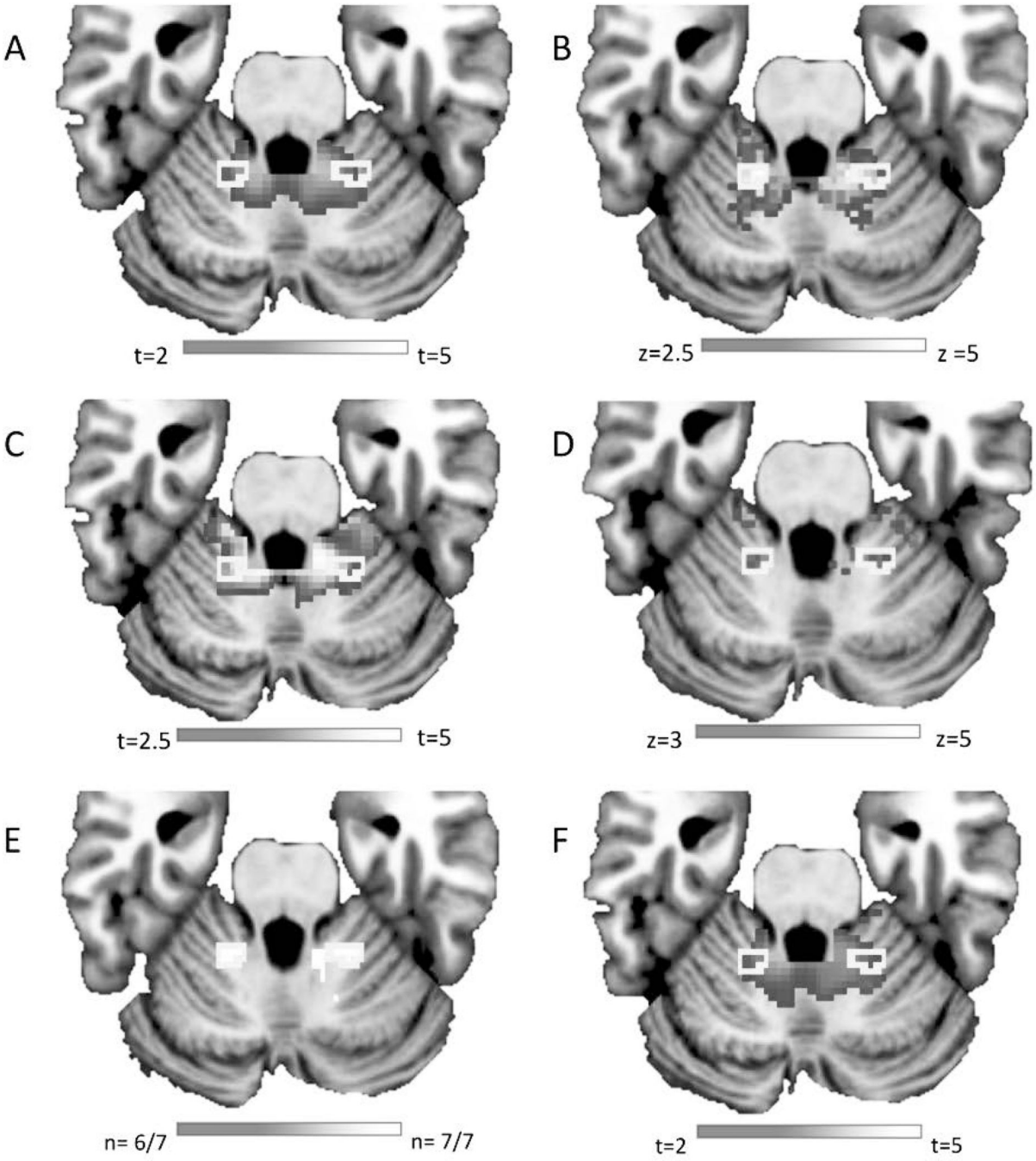

Figure 3.

Lesion network mapping results in the cerebellum are robust to several different analysis approaches. Lesion networks derived from FOG lesions are compared to those from asterixis lesions using two statistical tests: unpaired t test (A) or Leibermeister test (B) and to hemichorea-hemiballismus lesions using an unpaired t test (C) or Leibermeister test (D). Lesion network overlap persists in the same location when the inclusion criteria are restricted to cases of acute stroke (E) and remains specific when compared to other movement disorders (asterixis and hemichorea) (F). All images are masked to the

cerebellum. The original FOG network overlap site in the cerebellum (see Figure 2A) is outlined in light grey (green in the online version of the figure) for reference.

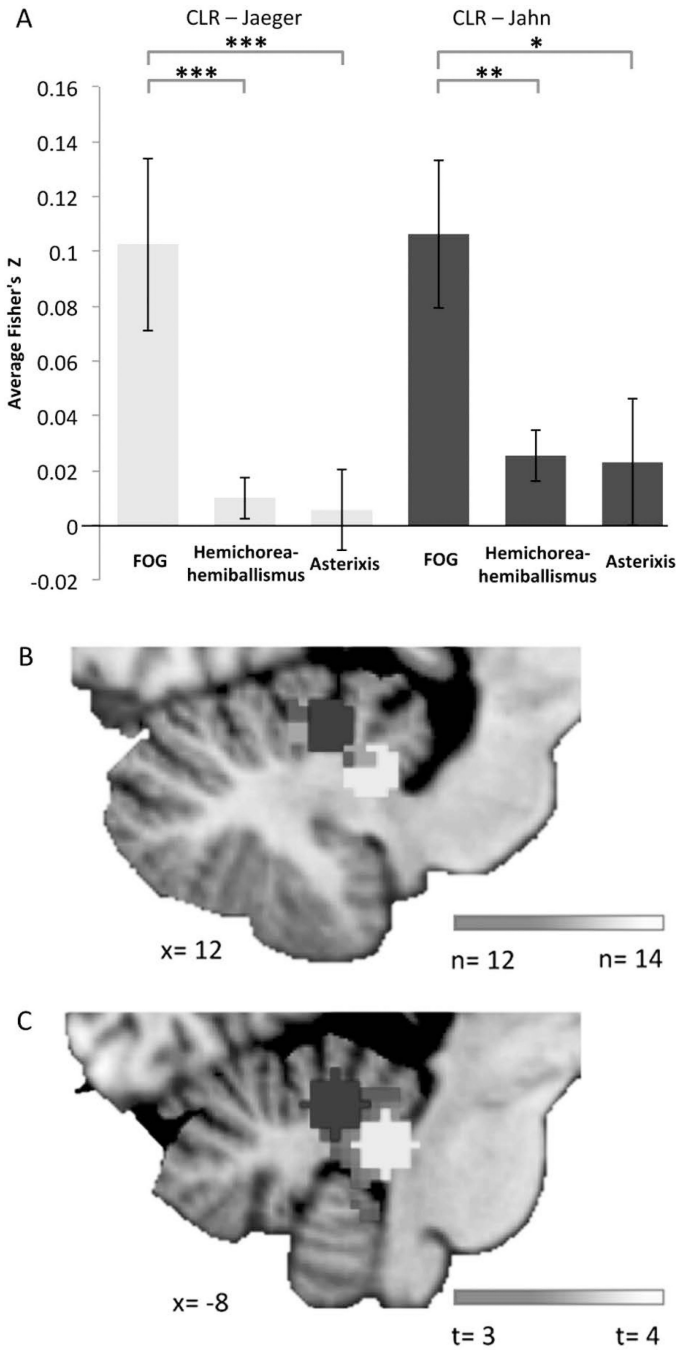

Figure 4.

Lesions causing FOG are more connected to cerebellar locomotion regions (CLR) than lesions causing other movement disorders. (A) Mean correlation between lesions causing different movement disorders and one of two putative CLR sites. Topographical display of the FOG lesion network overlap map (B) and voxel-wise t test map comparing FOG to hemichorea-hemiballismus and asterixis (C) are overlaid on two 6mm ROIs centered at the CLR site as outlined by Jahn et al (dark grey, blue in the online version of the figure) and Jaeger et al. (light grey, green in the online version of the figure). T- test map was placed in

front (B) or behind (C) the CLR ROIs for display purposes. ***P<0.001, **P<0.005, *P<0.05.

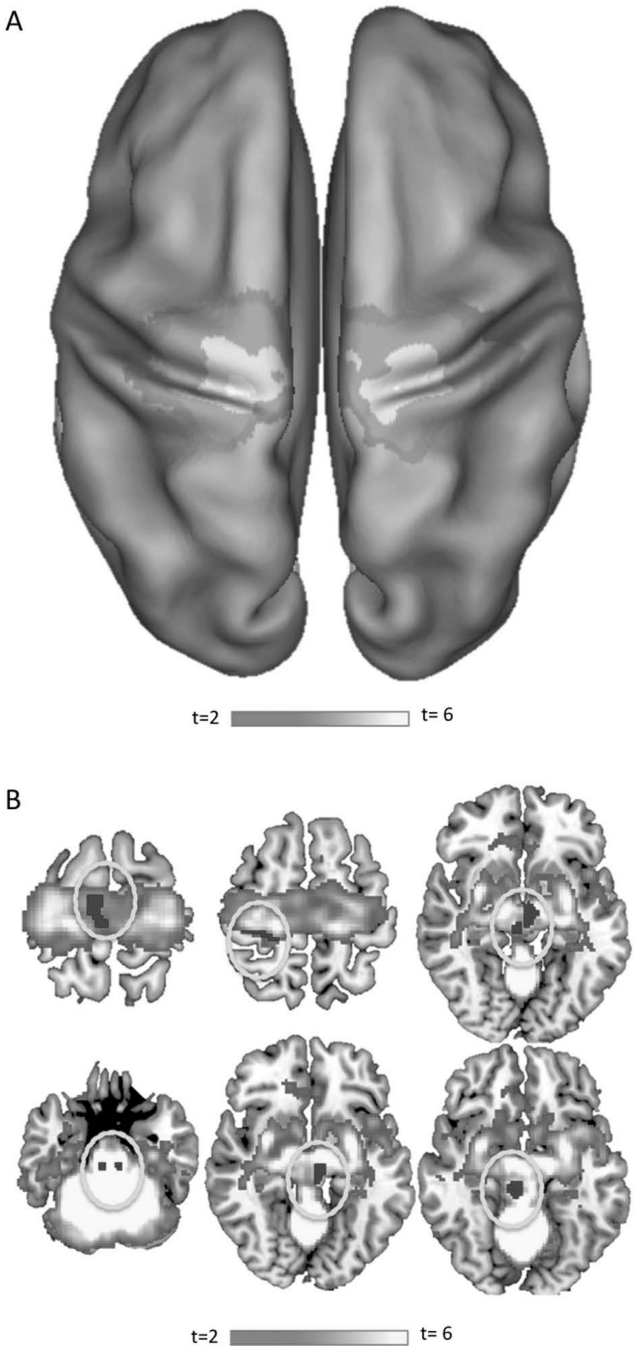

Figure 5.

Resting-state functional connectivity with the FOG network overlap site in the cerebellum. The map is displayed on the cortical surface using CARET (A) highlighting the bilateral leg area of the primary motor cortex. The same map is displayed on an MNI template brain (B) highlighting subcortical network nodes. Superimposed on the network map in (B) are lesions causing FOG (in dark grey and circled in light grey, blue and circled in green in the online version of the figure).

Table 1

Lesional FOG cases included in the analysis.

Case[ref]	Age/Sex	Underlying Diseases	Cause of Lesion	Clinical Description	Follow-up duration	Evolution of Symptoms and treatment effect	Neuroimaging Findings*
1[39]	35/F	Gestational DM	Small cortical vein thrombosis	FOG (especially at doorways and initiating gait), speech impairment, axial bradykinesia, balance disturbance, distal postural tremor	3 months	Improvement after 72h, able to initiate steps/turns unprompted.	FLAIR MRI: right parasagittal frontal hyperintensity.
2[40]	70/M	HL, depression	Ischemic stroke	FOG during initiation or turning, intermittent resting leg tremor, distal bradykinesia and rigidity (worse in lower extremities)	Unknown	Progressive worsening of gait. No effect of L-dopa, entacapone, ropinirole and amantadine.	FLAIR MRI: bilateral brainstem hyperintensities
3[41]	68/M	Natural killer cell / T-cell lymphoma	Metastatic disease	FOG episodes, start hesitation, short step, forward flexion posture, festination, postural instability	2 months	Ambulation normalized with chemo.	T2w MRI: hyperintense lesions in the dorsal brainstem/cerebellum
4[42]	43/M	Chronic renal failure	Hemodialysis-induced PRES	Parkinsonian signs including FOG, bradykinesia, and postural instability	4 weeks	Gradual spontaneous improvement. No effect of L-dopa and amantadine.	DWI MRI: bilateral basal ganglia hyperintensities (also ADC dark)
5[43]	70/F	Still's disease, HT	Traumatic subarachnoid haemorrhage	Difficulty initiating gait, hyperreflexia, widened stance, slow gait and short stride.	1 month	Improvement and normalization over 1 month with physical therapy	FLAIR MRI: linear hyperintensity (arrow) within the right post-central sulcus
6[44]	37/M	None	Ischemic Stroke / possible seizure	Gait initiation disturbances with paucity of movement, severe bilateral generalized lower extremity bradykinesia with normal motor power and tone.	20 days	Sudden onset gait symptoms 18 months after lesion, 90% improvement over 20 days. No effect of L-dopa	FLAIR MRI: hyperintensities in the left medial frontal lobe (also ADC dark / DWI bright)
7[45]	83/F	HT	Brainstem haemorrhage	Difficulty initiating gait with significant balance disturbance	4 months	Stable	T1w MRI: hyperintensity in right brainstem
8[46]	66/M	DM, HT	Ischemic stroke	Marked start hesitation, short irregular unsteady steps, unable to perform tandem gait, ataxia, blurred vision	3 days	Significant gait improvement, ocular findings unchanged	T2w MRI: hyperintensity in left midbrain tegmentum (also DWI bright)
9[47]	71/M	HT	Unknown	Impaired gait initiation, postural instability with frequent falls, hypomimia, hypokinetic dysarthria, severe palilalia, moderate segmental akinesia, cognitive impairment	6 years	Progressive gait disorders for 4 years, followed by stable condition for next 2. No effect of L-dopa; slight improvement on amantadine.	T2w MRI: bilateral "lesions" affecting GPe and GPi
10[47]	74/M	HT	Unknown	Impaired gait initiation,, postural instability, falls, hypomimia and slight hypokinetic dysarthria, cognitive impairment	5 years	Progressive gait disorders for 3 years, followed by stable condition for next 2 years. No effect of L-dopa; slight improvement on amantadine	T2w MRI: bilateral focal hyperintensities of GPe and the GPi
11[48]	76/M	Primary CNS lymphoma (B-cell type)	lymphoma	Gait ignition difficulty, bilateral paratonia, retropulsion in sitting position, wide gait, shortened steps at turns	Unknown	Unkown	Post-contrast T1 MRI: Enhancement of corpus callous, extending up midline and into parasagittal white

Case[ref]	Age/Sex	Underlying Diseases	Cause of Lesion	Clinical Description	Follow-up duration	Evolution of Symptoms and treatment effect	Neuroimaging Findings*
							matter bilaterally
12[46]	52/M	DM, HT	Ischemic stroke	Gait initiation difficulty, unable to tandem gait, ataxia, blurred vision, short irregular steps with variable amplitude	6 weeks	Improvement in gait	DWI MRI: Hyperintensity in left dorsal midbrain tegmentum
13[49]	66/M	DM, HT	Ischemic stroke	FOG, truncal and leg ataxia, impaired convergence, upward gaze, skew deviation of eyes, unable to tandem gait	3 days	Gait improved significantly after 3 days (eye problems persisted)	FLAIR MRI: hyperintensity in the left posterior midbrain tegmentum (also DWI bright)
14[46]	80/M	HT	Ischemic stroke	Locomotion initiation difficulty, blurred vision, gait ataxia, broad gait, short steps	24 hrs	Ataxia improved slightly	T2w MRI: Hyperintensity in right dorsal midbrain tegmentum (also DWI bright)

*Abbreviations:: images are shown in Supplemental Table Online; ACA: anterior cerebral artery, BPH: benign prostatic hypertrophy, DM: diabetes mellitus, DWI: diffusion weighted images, FLAIR: fluid-attenuated inversion recovery, FOG: freezing of gait, GPe: globus pallidus pars externa, GPi: globus pallidus pars interna, HL: hyperlipidemia, HT: hypertension, MRI: magnetic resonance imaging, MTX: methotrexate, PRES: posterior reversible encephalopathy syndrome, T1w: T1 weighted, T2w: T2 weighted.

Table 2

Brain regions functionally connected to the FOG network overlap site in the cerebellum. Local maxima in MNI space were identified using a cluster analysis on the voxelwise map shown in Figure 5.

luster #	Local maxima #	t value	x (mm)	y (mm)	z (mm)	Location
1	1	53.1	16	−46	−26	Dorsal medial Cerebellum (right)
	2	50.9	−18	−44	−26	Dorsal medial Cerebellum (left)
2	1	7.97	18	−28	64	Primary motor cortex, medial (right)
	2	6.83	28	−22	54	Primary motor cortex, medial (right)
3	1	7.55	−44	−70	−46	Ventral lateral cerebellum (left)
	2	6.3	−46	−56	−46	Ventral lateral cerebellum (left)
4	1	6.9	−14	−28	64	Primary motor cortex, medial (left)
	2	6.79	−18	−28	58	Primary motor cortex, medial (left)
5	1	7.97	30	0	−10	Putamen (right)