LETTER TO THE EDITOR

Does dominant pedunculopontine nucleus exist? Probably not

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Sir,

We have followed with interest the recent discussion in *Brain* regarding the possibility of a ‘dominant’ right-hemispheric pedunculopontine nucleus pathology in freezing of gait in Parkinson’s disease (Fling et al., 2013, 2014; Lam et al., 2014). In the original study, Fling et al. (2013) used diffusion weighted imaging to demonstrate the presence of abnormal connectivity between the frontal cortex and the pedunculopontine nucleus in the right hemisphere of 14 patients with Parkinson’s disease and freezing of gait. The authors concluded that freezing of gait may be due to predominantly right-hemispheric pathology (Fling et al., 2013), an interpretation that is aligned with clinical (Nantel et al., 2012) and neuroimaging (Peterson et al., 2014) findings that indicate visuospatial impairment in the pathophysiological mechanism of freezing of gait. In a subsequent issue, Lam et al. (2014) provided evidence in support of this hypothesis. By comparing clinical outcomes of six patients with Parkinson’s disease and freezing of gait that either underwent left-sided ($n = 3$) or right-sided ($n = 3$) pedunculopontine nucleus deep brain stimulation surgery, the authors were able to demonstrate that the individuals with left pedunculopontine nucleus deep brain stimulation showed greater clinical improvement across many parameters, though most notably in their axial motor symptoms and gait-related items of the motor sub-scale of the Unified Parkinson’s Disease Rating Scale Part III (UPRDS-III) while OFF dopaminergic medication. The authors interpreted their findings as suggestive of a compensatory mechanism in the brainstem of patients with freezing of gait, such that those with left pedunculopontine nucleus deep brain stimulation were more fully able to recruit neuroplastic mechanisms to overcome the pathological disturbances associated with freezing of gait. Together with evidence of the right hemisphere’s preferential involvement in gait (Fling et al., 2014), these studies were taken as providing evidence to suggest that freezing of gait in Parkinson’s disease is related to right-hemispheric pathology.

Despite these interesting results, the relatively low sample sizes presented in each study raise concerns regarding reproducibility. Indeed, if these insights are to retain clinical benefit, they must be confirmed in larger samples. To test whether freezing of gait symptoms were associated with right-hemispheric pathology, we explored this issue in a cohort of 84 non-demented, right-handed individuals with idiopathic Parkinson’s disease and self-reported freezing of gait (screened via a positive score on Question 3 of the Freezing of Gait Questionnaire) (Giladi et al., 2000). In these 84 subjects, we assessed for the presence of ‘dominant’ disease by comparing the motor severity (as measured by the motor subscale of the UPDRS) (Goetz et al., 2007) between the two sides of the body. Specifically, we calculated the ratio of the sum of UPRDS-III items for the right side (items 30, 32, 34, 36, 38, 40, 42, 50, 52, 54 and 56) and left side of the body (items 31, 33, 35, 37, 39, 41, 43, 51, 53, 55 and 57). Patients who scored $> 1$ on this ratio showed greater left-sided symptoms at disease onset (as determined by semi-structured interview) were classified as Parkinson’s disease with predominantly left hemispheric pathology (and vice versa). Patients whose reports were ambiguous or demonstrated bilateral motor involvement at the time of diagnosis were excluded ($n = 14$, 17% of whole sample). In contrast to the results of the two aforementioned studies, we did not observe a substantial difference in the proportion of subjects with self-reported freezing of gait and right-hemispheric pathology: [right hemisphere: 40/70 (57%); left hemisphere: 30/70 (43%); $\chi^2 = 1.43$, $P = 0.232$]. Our results thus suggest that despite a possible increase in the prevalence of right-hemisphere pathology in patients with freezing of gait, there are
substantial numbers of individuals with left-hemispheric pathology, demonstrating that freezing is not in fact caused by pathology of the right hemisphere alone.

These results raise an interesting question—namely, if freezing of gait is not due to right-hemispheric impairment of the cortico-pontine system, then which pathophysiological process might be responsible for the onset of the paroxysmal phenomenon? In previous neuroimaging studies, we used virtual reality technology to elicit freezing behaviour during bilateral lower limb tapping and shown impairments in activity within cortical regions responsible for cognitive control and the caudate nucleus of the striatum (Shine et al., 2013a), as well as impaired connectivity between these structures (Shine et al., 2013b). Importantly, in both cases, the patterns we observed occurred equally across both hemispheres (Shine et al., 2013a, b), indicating more broad impairments across frontostriatal circuitry across multiple levels of the nervous system, independent of the hemisphere involved (Shine et al., 2013c). This interpretation is supported by another recent study (Hall et al., 2014), in which we showed that freezing of gait in early-stage Parkinson’s disease (Hoehn and Yahr stage <3) was not associated with other parkinsonian symptoms classically attributed to localized pathology within the brainstem, such as autonomic dysfunction (Braak et al., 2003), REM sleep behaviour disorder (Scaglione et al., 2005) and mood disturbance (Reny et al., 2005).

In conclusion, we believe that the best practice at present is to assume that freezing of gait in Parkinson’s disease is not distinctly due to a right-lateralized pathological process, although, future prospective studies may help to further clarify these issues, particularly in light of recent advances in the neuroimaging analysis of the brainstem and related structures (Karachi et al., 2012; Beissner et al., 2014).

References


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