LETTER TO THE EDITOR

Reply: Does dominant pedunculopontine nucleus exist? Probably not

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Sir,

We are pleased to continue the discussion with regards to our recent manuscript detailing altered structural connectivity of the locomotor network within the right hemisphere of individuals with Parkinson’s disease who experience freezing of gait (Fling et al., 2013). Our previous work has asserted the possibility of right hemisphere pathology as a principal neural component underlying freezing of gait, with an emphasis placed on disrupted communication between locomotor centres in the brainstem and cerebellum with medial areas of the frontal and prefrontal cortices (Fling et al., 2013, 2014a). In their letter to the editor, Hall and colleagues (2014) provide data demonstrating that freezing of gait is evident in Parkinson’s disease regardless of which side of the body is more affected. The authors report no difference in the proportion of subjects (n = 70) with self-reported freezing of gait and left-side motor symptom dominance in 40/70 participants compared to right-side dominance in 30/70. It is suggested that because there are substantial numbers of individuals with greater right-side motor involvement (and by proxy, left-hemispheric striatal pathology), freezing of gait is not caused by pathology of the right-hemisphere alone.

Idiopathic Parkinson’s disease is characterized by asymmetry of symptoms at disease onset, which is generally maintained, although symptoms tend to become more bilateral with disease progression (Hornykiewicz, 1966). The characteristic asymmetric manifestation of motor symptoms is related to greater impairment of dopaminergic function in the contralateral striatum as indicated by reduced dopamine storage and dopamine transporter uptake (Leenders et al., 1986; Brooks et al., 1990a, b). The ‘choice’ of side predominance in patients with Parkinson’s disease could be pure chance (Djaldetti et al., 2006). These authors suggest that ‘similar to other complex diseases such as cancer, the ignition of detrimental cellular pathways might be randomly determined by a combination of factors too numerous to fully characterize’ (Djaldetti et al., 2006).

The dominant side of hemispheric neurodegeneration can differentially affect particular functions for people with Parkinson’s disease. For example, recent work demonstrates that individuals with greater right-hemisphere pathology have larger kinaesthetic deficits than those with principally left-hemisphere involvement (Wright et al., 2010). This is in agreement with literature reporting similar results for visual and visuospatial tasks (Starkstein et al., 1987; Ebersbach et al., 1996; Harris et al., 2003; Davidsdottir et al., 2005). The fact that both visual and kinaesthetic asymmetries seem to predominantly affect left-side dominant Parkinson’s disease may mean that both originate from early asymmetrical nigrostriatal neuron loss (Wright et al., 2010). Whereas these functions seem to be defined by asymmetric striatal dysfunction,
freezing of gait is not associated with the cardinal motor features of Parkinson’s disease (tremor, bradykinesia or rigidity) (Giladi, 2001; Bartels et al., 2003). However, freezing of gait is correlated with postural instability (Giladi et al., 2001), spatial contrast sensitivity deficits (Davidsdottir et al., 2005), and an inability to appropriately engage and release inhibition (Cohen et al., 2014), rather than with general motor and/or executive deficits. These functions (body schema, spatial orientation, proprioceptive processing and cognitive inhibitory control) are all principally lateralized to the brain’s right hemisphere (Wolpert et al., 1998; Aron, 2007; Goble et al., 2012).

We suggest that while the results of Hall and colleagues are interesting, they are not necessarily inconsistent with the results of Lam et al. (2014) and Fling et al. (2013, 2014b), nor do they negate the interpretations reached in those studies. In our original paper (Fling et al., 2013), as well as the majority of manuscripts examining the clinical phenomenon of freezing, there is a relatively equal number of patients with motor symptomology on the right or left side of the body. We therefore suggest that freezing of gait is not necessarily reflective of asymmetric striatal involvement, which defines motor-symptom dominant side in Parkinson’s disease, but is more likely the result of impaired neural circuitry within the locomotor and cognitive/higher-order motor networks of the brain’s right hemisphere, regardless of motor-symptom dominant side.

References


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