LETTER TO THE EDITOR

Reply: The cerebellum in Parkinson’s disease and parkinsonism in cerebellar disorders

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Sir,

We thank Pedroso et al. (2013) for their interest in our paper (Wu and Hallett, 2013), in which we discussed the role of the cerebellum in Parkinson’s disease; other types of parkinsonism were not included. Such parkinsonian disorders often contain overt pathological changes in both basal ganglia and cerebellar systems. The origin of these changes is generally thought to be primary in both locations, but it is conceivable that the primary pathology is in one location and secondary in the other. It is important to recognize that genetic mutations can cause different phenotypes and that the nomenclature should not be taken literally. The spinocerebellar ataxias (SCAs) can present as a parkinsonism, as Pedroso et al. (2013) have described for SCA3. Therefore because it is an ‘ataxia’ does not mean that the cerebellum is the only site of primary pathology.

In another SCA example, our group investigated patients with SCA2. In both patients with familial Parkinson’s disease and asymptomatic carriers with SCA2 mutations, a striatal dopaminergic deficit has been demonstrated (Kim et al., 2007; Wang et al., 2009). In patients with SCA2 without parkinsonism symptoms, Varrone et al. (2004) found striatal dopamine transporter loss, and the striatal dopamine transporter density correlated with the severity of cerebellar ataxia; in addition, a transcranial brain parenchyma sonography study found hyperechogenicity in the substantia nigra (Mijajović et al., 2008). In a recent functional MRI study in a family with SCA2 mutation, including asymptomatic carriers and mutation carriers with parkinsonian symptoms (Wu et al., 2013), we found that whereas both the asymptomatic carriers and patients had decreased connectivity within the basal ganglia-thalamus-cortical motor loop compared with the control subjects, the asymptomatic carriers had increased connectivity of other large-scale brain networks, including the cortico-cerebellar circuits, presumably to compensate for the dysfunction of the basal ganglia to maintain brain function in the early stage of dopaminergic deficits. The simultaneous effects of progressive disruption of basal ganglia motor circuits and failure of compensatory cerebellar mechanisms as dopaminergic dysfunction progresses may contribute to the onset of clinical symptoms. This could indicate that the basal ganglia damage was primary and increased stress on the cerebellum for compensation led to the cerebellar damage. If so, this would be in a direction similar to what we described in Parkinson’s disease.

Now that it is clear that there are strong reciprocal connections between basal ganglia and cerebellum, it allows for pathological influences to go both ways, and Predroso et al.’s (2013) speculation that ‘parkinsonism in primary cerebellar disorders [is] related to cerebello-thalamo-cortical circuit involvement and [consequent] basal ganglia impairment’ is possible. However, our knowledge regarding neurodegeneration remains limited and whether any entity is due to a multifocal process or spread from one primary locus (Luk et al., 2012) is one of the exciting topics in neuroscience at present.

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References


