Infantile Nystagmus Syndrome: What Can fMRI Tell Us?

To the Editors:

In a recent novel functional magnetic resonance imaging (fMRI) study on adult patients with infantile nystagmus syndrome (INS), Leguire et al. claimed that the cerebellum, particularly the declive (vermis lobule 6), is involved in the INS “neural circuit.” We question this claim, and even whether such a circuit exists.

The role of the cerebellum in ocular motility is beyond doubt. fMRI studies have now reported several vermian sites from lobules 4 to 9 in the control of saccades, optokinetic nystagmus (OKN), and smooth pursuit. It would be surprising if vermian activity were not correlated with INS, but this does not mean such activity causes the nystagmus. There is a fundamental ambiguity in using fMRI to identify any putative INS circuit.

The authors compared the BOLD response between adults with nystagmus fixating a visual target in their null region (nystagmus least) and outside the null region (nystagmus more intense). The ON-OFF difference was therefore an increase in nystagmus intensity. This was confirmed by eye movement recording, but in the 3 presented cases, the ON condition was a jerk nystagmus involving the prolific production of saccades (fast–phases). It is not surprising, therefore, that cerebellar regions light up during this experiment, because lobules 6 and 7 are well known to be involved in saccade control (“oculomotor vermis”). Control subjects do not have nystagmus and their task of fixating a small target would not require many saccades, which is consistent with the absence of relative declive activity in the control group. Indeed, a similar pattern occurs when comparing OKN to fixation in normal subjects, presumably reflecting the effect of quick-phases.

One would also expect other differences. During the patient ON condition, the slow phases would be expected to generate much more retinal slip (retinal image motion) than in the OFF condition, but control subjects would experience minimal retinal slip. Retinal slip information is transmitted to the uvula, consistent with the reported analysis. Similarly, many neocortical regions would be expected to be activated by the retinal slip, as also seen in OKN.

It is important to recognize the limitations of this study. Due to the poor temporal resolution of the BOLD response, this study can never distinguish between the brain activity causing the nystagmus and the brain activity caused by the nystagmus (including fast-phases and retinal slip). Moreover, it cannot answer whether an INS neural circuit really exists.

INS is a developmental disorder where the nystagmus usually emerges postnatally, possibly due to anomalous timing of early sensory and oculomotor development, including idiopath. Although not inconceivable, it is unlikely that this would lead to a completely novel circuit. More likely, the postnatal development of gaze-holding and/or smooth pursuit are modified but probably beyond fMRI resolution. If this is the case, the authors’ results may provide a fascinating glimpse of the neural substrate of the visual costs of not maintaining good fixation and smooth pursuit (albeit in an adult). More subjects will improve statistical power, but not disambiguate this fundamental limitation. Future fMRI work needs to control for the consequences of slow phases, including retinal slip (perhaps by retinal stabilization or control yoking) and fast-phases (as in the OFF condition in this study).

REFERENCES

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