BRAIN
SCIENTIFIC COMMENTARY

An unexpected iron in the fire of speech production

This scientific commentary refers to 'Elevated iron concentration in putamen and cortical speech motor network in developmental stuttering', by Cler *et al.* (doi:10.1093/brain/awab283).

Childhood-onset speech fluency disorder, also called stuttering, continues to be a source of wonder. Alterations in speech and language-based circuits have long been recognized in individuals who stutter (Fig. 1). However, with new methodologies, novel pieces of information continue to emerge regarding this ancient speech fluency disorder. In this issue of *Brain*, Cler and colleagues[1] apply a recently validated R_2^* (effective transverse relaxation rate) MRI protocol that can measure iron content in the brain. Using this technique, the authors show for the first time that iron content is increased in the speech network of individuals who stutter, compared to a fluent-speaking control group.[1] This finding supports and expands on recent work that used transcranial ultrasound to reveal increased mesencephalic iron deposits in individuals who stutter.[2] Remarkably, neither paper had a directional hypothesis, i.e. it was unclear what to expect. Nevertheless, these observations of increased iron content move stuttering even further into the field of neurodevelopmental movement disorders.

Iron content homeostasis is important during brain development and throughout adulthood and contributes to many cellular functions. Iron is present in neurons, oligodendrocytes, astroglia and microglia in the CNS.[3] Iron content is low at birth and increases thereafter, particularly in the basal ganglia, less so in the cortex. The speed of iron deposition varies, with deposition continuing into the fifth decade of life in the putamen and the globus pallidus.[4]

Cler and colleagues[1] observed a similar rate of increase of iron content with age in both individuals who stutter and a fluent-speaking control group, starting at a higher level in the stutter group. It is tempting to speculate that individuals who stutter diverge from controls early in development, with a group difference maintained into adulthood. Interestingly, however, Cler *et al.*[1] did not find a correlation between severity of speech disfluencies and iron deposits. This suggests that iron content is a trait rather than a state marker.

Iron deposits play a key role in neurodevelopmental disorders such as pantothenate kinase-associated neurodegeneration (PKAN), a basal ganglia disorder characterized by a progressive generalized dystonia. Of note, randomized controlled trials of oral iron chelators in patients with PKAN showed that the drugs were successful in lowering brain iron content, even though the study just missed a clinical end point.[5] The current findings on iron content in individuals who stutter may thus open up a potential new pathway for pharmacological intervention in stuttering.

Iron deposits have also been implicated in neurodegenerative disorders. Regional increases in iron distribution during ageing, especially in the basal ganglia, have been observed in neurodegenerative diseases such as Parkinson's and Alzheimer's.[3]

The relationship between iron and movement disorders is complex. Iron is an essential cofactor in dopaminergic metabolism.[6] By helping tyrosine hydroxylase to function correctly, iron enables the conversion of tyrosine into levodopa in the synaptic boutons of the striatum. Increased iron deposits have been observed in dopamine-deficit disorders,[7] and iron accumulation is thought to trigger oxidative stress and thereby promote neurodegeneration.[3] This cellular stress may disrupt cortico-basal ganglia-thalamocortical motor circuits and give rise to the phenotype of stuttering.

In stuttering, however, a hyperdopaminergic state has been postulated. This is somewhat difficult to reconcile with the speech and non-speech motor slowing seen in individuals who stutter. As we have previously speculated,[2] worsening of motor performance as a result of excess movement may constitute an explanation for the increased dopamine in stuttering.

Cler *et al.*[1] found increased iron content in the putamen and cortical areas relevant for speech, namely the left frontal opercular cortex, the inferior frontal gyrus, and the ventral precentral gyrus, all restricted to the left hemisphere at a conservative threshold. Increased cortical iron has been associated with cortical dysfunction.[8]

At least two key questions arise from this study. First, given that iron deposition increases early in childhood and continues in adulthood, do individuals with altered iron homeostasis fail to recover from stuttering? This would be of clinical relevance because a reliable biomarker for clinically diagnosing onset or progression to stuttering is lacking.

Second, do individuals who stutter present with general motor deficits? Motor behaviour has yet to be thoroughly studied alongside speech modification in individuals who stutter, even though abnormal finger tapping and other abnormal movements have been observed in affected individuals.[9] Going forward, we recommend assessing additional motor behaviours such as walking or manual dexterity,[2] to gain a clear understanding of the functional relevance of altered iron metabolism to stuttering. Future prospective studies assessing regional iron deposits, subtle motor changes and stuttering onset should shed light on this issue. In the meantime, examining post-mortem brain tissue for the presence of iron and related proteins could yield significant insights into the pathogenesis of stuttering.

To conclude, there are four take-home messages from this work. First, the findings should encourage researchers to use iron-sensitive markers in future studies on stuttering. Second, we recommend investigating motor behaviour beyond speech in studies of individuals who stutter, to gain a better understanding of the

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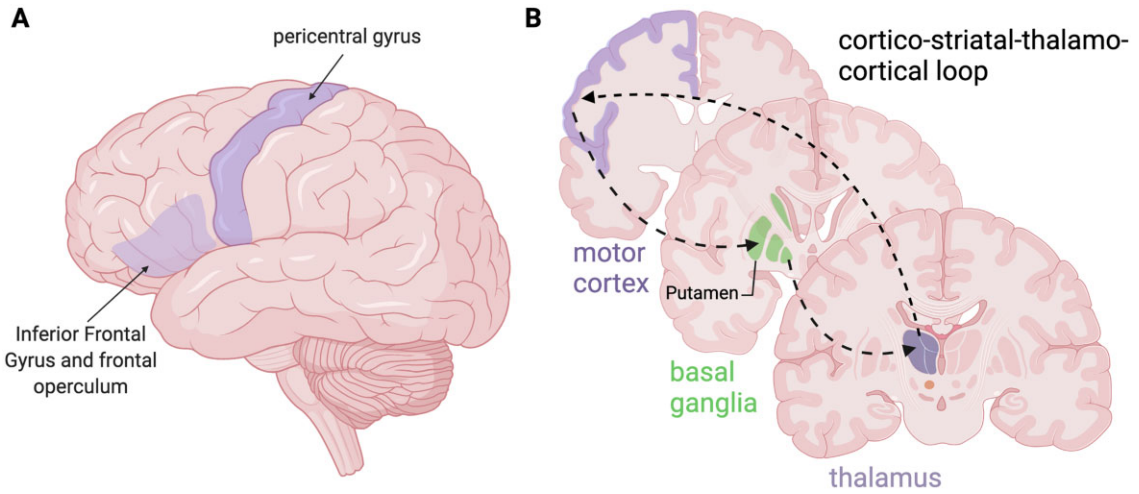

Figure 1 Basal ganglia and speech production circuits. (**A**) An illustration of cortical regions involve in speech production. (**B**) The cortico-striatal-thalamo-cortical loop connects cortical regions to the motor circuits of the basal ganglia (from the putamen) to a relay station in the thalamus. This loop is important for speech production and a deficit in this circuit is proposed to cause stuttering. **B** is modified from Turk *et al.*[10] Figure prepared using BioRender (https://biorender.com/).

functional relevance of basal ganglia involvement. Third, the long-held dogma that stuttering is a behavioural or psychological condition needs to be put to rest. Stuttering should no longer be classified as a 'communication disorder' but rather as a developmental movement disorder, and the next generation of ICD (International Classification of Diseases) should classify stuttering accordingly. And fourth, we should now feel compelled to forge ahead with developing effective biological treatments for this common condition.

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Competing interests

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