GABA: a new imaging biomarker of neurodegeneration in multiple sclerosis?

This scientific commentary refers to 'Reduced gamma-aminobutyric acid concentration is associated with physical disability in progressive multiple sclerosis', by Cawley *et al.* (doi:10.1093/brain/awv209).

Conventional MRI has improved the diagnostic work-up and monitoring of many chronic neurological disorders, thanks to its ability to detect brain abnormalities with great sensitivity. One important limitation of conventional MRI, however, is its lack of specificity with regard to different pathological substrates underlying disease. A number of recently developed MRI techniques have shown the ability to complement conventional MRI by enhancing specificity to pathological changes. However, the ultimate goal of obtaining imaging biomarkers that closely reflect specific pathological features (such as progressive neuroaxonal damage/injury leading to neurodegeneration) and mechanisms (e.g. mitochondrial dysfunction, microglial activation, iron deposition) has yet to be achieved.

Among the various advanced MRI techniques, proton magnetic resonance spectroscopy (^{1}H-MRS) is unique in its ability to characterize the chemical pathology of brain tissue (Barker *et al.*, 2010). By applying this technique both to regions that appear altered and regions that do not show overt abnormalities on conventional MRI, it is possible to assess clinically meaningful metabolites and relate changes in them to different pathophysiological conditions. Thus, ^{1}H-MRS can provide *in vivo* quantification of brain levels of (i) N-acetylaspartate, a putative marker of neuroaxonal loss and dysfunction; (ii) choline-containing compounds, which provide an index of cellular membrane turnover; and (iii) lactate, the end-product of the anaerobic glycolysis that occurs in many pathological conditions. More recently, the use of higher field magnetic resonance scanners and editing sequences able to resolve overlapping resonances has allowed detection of other metabolites with good reliability (Barker *et al.*, 2010). Specifically, evaluation of GABA, the major inhibitory neurotransmitter in the human brain, has revealed a role in the modulation of many physiological processes, while dysfunction of the GABAergic system has been implicated in several neurodegenerative disorders (Rae, 2014). In this issue of *Brain*, Cawley *et al.* (2015) highlight the clinical relevance of assessment of GABA in a complex disease such as multiple sclerosis by revealing an association between reduced GABA concentration and physical disability.

In multiple sclerosis, recent *ex vivo* and *in vivo* studies have shown the relevance of neuroaxonal damage and loss to patient neurological status and worsening, highlighting the need for markers that can provide early and accurate information on neuronal activity and function. Unfortunately, however, many aspects of the neurodegeneration occurring in multiple sclerosis remain unclear. Mechanisms linking inflammation with neuroaxonal loss, such as metabolic energy failure, may be prevalent in the early, acute phase of multiple sclerosis, whereas other mechanisms seem to dominate in the later stages of the disease (Lassmann, 2014). In this context, the study by Cawley and co-workers is particularly illuminating. By using a spectral editing ^{1}H-MRS method, which is able to reliably separate GABA from other more abundant metabolites, the authors provide the first *in vivo* evidence for topographic variation of GABA levels in patients with progressive multiple sclerosis, with decreases in two key brain regions, sensorimotor cortex and hippocampus. In addition, they report that lower GABA levels in the sensorimotor cortex of patients are associated with impaired motor performance. Overall these findings suggest that altered GABA neurotransmission might be implicated in the mechanisms underlying neurodegeneration in progressive multiple sclerosis.

There is an urgent need to understand the precise mechanisms leading to neurodegeneration in progressive multiple sclerosis, in particular owing to the lack of an effective therapeutic approach in this phase of the disease. Previous reports of decreased presynaptic and postsynaptic components of GABAergic neurotransmission in multiple sclerosis (Dutta *et al.*, 2006), possibly as a result of inflammatory episodes that might influence neuronal excitability and survival (Rossi *et al.*, 2012), lend further support to the hypothesis that altered GABA neurotransmission might have a role in the mechanisms of neurodegeneration, as does evidence of a role for GABA in neuroprotection (Burnstock, 2015) and functional reorganization (Bhattacharyya *et al.*, 2013).

Given the complexity of multiple sclerosis pathogenesis, it is not possible to state categorically that reduced GABA levels contribute to the neurodegenerative process. However, if we add the work of Cawley and co-workers (2015) to previous ^{1}H-MRS studies on multiple sclerosis and other neurological conditions (Bai *et al.*, 2015; Riese *et al.*, 2015), it seems likely that the *in vivo* assessment of GABA levels through ^{1}H-MRS might represent a novel and specific biomarker of neurodegeneration and, consequently, a target for testing potential neuroprotective agents. To achieve this goal, efforts should be made to address some of the limitations of ^{1}H-MRS

(e.g. low spatial resolution) as well as the accuracy of the editing procedure for the detection of GABA resonance. Moreover, further studies are needed to investigate GABA reductions in larger multiple sclerosis cohorts and to assess longitudinally the sensitivity to change of this potentially unique biomarker of neurodegeneration.

Nicola De Stefano and Antonio Giorgio
Department of Medicine, Surgery and Neuroscience, University of Siena, Italy

Correspondence to: Nicola De Stefano, MD PhD
E-mail: destefano@unisi.it

doi:10.1093/brain/awv213

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What is the function of auditory cortex without auditory input?

This scientific commentary refers to 'Cross-modal activation of auditory regions during visuo-spatial working memory in early deafness', by Ding *et al.* (doi:10.1093/brain/awv165).

When a sensory input is absent during development, regions of the brain usually dedicated to processing input from that modality can be engaged to process input from a replacement sense. This is referred to as cross-modal plasticity, and studying it can provide rich and unique insights into the biological versus environmental constraints that act on brain development and brain function (Merabet and Pascal-Leone, 2010). For example, numerous studies report greater activation of typically 'auditory association cortices' in the superior temporal gyrus (STG), sulcus and planum temporale, in those born profoundly deaf than in their hearing peers when processing visual or somatosensory input (e.g. Karns *et al.*, 2012). There is also a wealth of research reporting enhanced behavioural performance on visuo-spatial tasks in deaf versus hearing participants (Bavelier *et al.*, 2006). Although it is tempting to make the intuitive assumption that these two findings must be linked, no studies with humans have yet demonstrated a clear link between the extent of cross-modal plasticity in auditory cortices in those born deaf and enhanced performance on visuo-spatial tasks. This is the question addressed by Ding and co-workers in this issue of *Brain* (2015).

In their study, Ding *et al.* asked hearing and congenitally deaf participants to perform a visuo-spatial working memory task while functional MRI data were collected. Deaf participants showed faster responses than hearing participants, although there was no group difference in task accuracy. In support of previous studies, Ding *et al.* report evidence of cross-modal plasticity (greater activation in deaf than hearing participants) in auditory association areas. The novel finding in their work is that deaf participants showed greater activation than hearing participants in auditory association regions, not only when complex visual stimuli were displayed, but also during the maintenance phase, during which only a static crosshair was visible on the screen. They also report correlations between amplitude of response in STG and task performance in deaf but not hearing participants, and argue therefore that auditory association cortices play an important role in visuo-spatial working memory in those born deaf.

This is an interesting finding and one that highlights the critical question for future research in this