After three decades at a relative standstill, there are currently encouraging signs of innovation in the field of DBS technology. New pacemakers and electrode designs have been developed that enable less constrained programming of stimulation parameters and widen therapeutic windows. Translation of these advancements into clinical practice is of the utmost importance and will set the bar high for the development of closed-loop DBS technology. However, we believe that adaptive DBS has great potential to extend the therapeutic arsenal of DBS neurologists even further. Given the increasing complexity of devices, it will be essential to keep DBS optimization simple and sustainable. Autonomous DBS adjustment based on patient pathophysiology could provide a solution. Studies such as the one by Cagnan et al. are important first steps towards this vision, and will undoubtedly yield further important insights into motor system physiology and the pathophysiology of movement disorders.

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**References**


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This scientific commentary refers to ‘Molecular magnetic resonance imaging discloses endothelial activation after transient ischaemic attack’, by Quenault et al. (doi:10.1093/brain/aww260).

Many stroke patients experience preceding transient ischaemic attacks (TIAs). Despite significant advances in stroke management, TIA remains a diagnostic challenge. Defined as a transient neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction on neuroimaging (Easton et al., 2009), TIA is an exclusively clinical diagnosis with no biomarker as of yet to distinguish it from clinical mimics such as seizures, migraine aura, multiple sclerosis and psychosomatic disorders. The lack of timely diagnosis of TIA presents as a missed opportunity to treat and potentially prevent recurrent stroke. A sensitive and specific ancillary diagnostic tool would enhance clinical management by identifying true TIAs for stroke prophylaxis in a timely fashion, and reduce unnecessary testing to rule out TIA mimics. TIAs may be brief and transient but do these complex ephe-mera leave behind metabolic or vascular footprints that could perhaps be detectable via sensitive new imaging approaches? In this issue of *Brain*, Quenault and co-workers identify endothelial P-selectin as one such potential biomarker for TIA (Quenault et al., 2017).

Quenault et al. first sought to establish a reproducible mouse TIA model that has transient neurological deficits without MRI-evidenced brain lesions. Key characteristics of the model should include reversible hypoperfusion, transient cortical dysfunction, and most importantly, the absence of significant infarction, both in the
short and long term as evidenced by MRI. Previous reports have shown that under certain experimental conditions, ischaemia as brief as 30 min can induce delayed infarction days later (Du et al., 1996). Quenault et al. investigated the effects of middle cerebral artery compression for durations ranging from 5 s to 90 min, and concluded that 15-min occlusions may be suitable for mimicking TIA in mice. Having established this potential TIA model, they showed that although expression of both P-selectin and VCAM-1 were increased, only P-selectin was detectable at the endothelial surface. The authors therefore developed antibody-based microparticles of iron oxide targeting P-selectin in an attempt to reveal this vascular footprint of TIA.

P-selectin promotes platelet, endothelium and leucocyte interactions following cardiovascular events, and represents an important molecular target in vascular disease. P-selectin-targeted contrast agents have previously been used for *in vivo* detection of endothelial activation and dysfunction associated with transient ischaemic injury and acute brain inflammation (Rouzet et al., 2011). In the present study, Quenault et al. showed that in their mouse model of TIA, MRI signal voids associated with P-selectin upregulation were detectable by molecular MRI 6 h after ischaemic onset, peaked around 24 h, and were significantly diminished after 48 h. These temporal patterns would aid the timely diagnosis and management of a TIA, but might also allow repeated imaging to investigate recurrent clinical events. The latter possibility is boosted by rapid antibody dissociation and washout within a couple of hours after contrast injection.

To increase confidence in the specificity of the target biomarker, Quenault et al. assessed a positive control in which direct intracerebral lipopolysaccharide injection induced cerebral inflammation and P-selectin upregulation, and linked the MRI signal voids to vascular P-selectin immunofluorescence. Perhaps more importantly, the authors also tested whether the upregulation of vascular P-selectin as a putative MRI biomarker can distinguish TIA from epilepsy and migraine, two common TIA mimics. They showed that generalized seizures induced by intraperitoneal injection of kainic acid did not induce MRI-detectable signal voids within the hippocampus, where seizures predominate in this model.

In a separate set of animals, the authors used systemic administration of nitroglycerine as a pharmacological trigger of migraine. Here, pathology and interpretation may be more complex. While nitroglycerine indeed precipitates migraine-like attacks in susceptible individuals, and behavioural and tissue changes suggestive of cephalgia in experimental animals (Reuter et al., 2001; Ashina et al., 2013; Oshinsky et al., 2014; Sufka et al., 2016), it does not precipitate migraine aura, i.e. spreading depression, which is the TIA mimic during a migraine attack rather than headache *per se*. Spreading depression is an intense pan-depolarization wave that slowly propagates within the brain tissue silencing and otherwise disrupting neuronal activity for anywhere between minutes to hours (Ayata and Lauritzen, 2015). It is the electrophysiological substrate of migraine aura, and indistinguishable electrophysiologically or by routine MRI from the anoxic depolarization that occurs during a TIA. While the authors clearly show in this study that nitroglycerine-induced trigemino-vascular activation underlying migraine headache does not cause P-selectin upregulation, it remains to be determined whether spreading depression underlying migraine aura can induce P-selectin expression that can be detected by molecular MRI. This will have to be tested in a pure spreading depression model (Ayata, 2013). Additionally, it remains possible that other conditions associated with vascular inflammatory changes and transient neurological deficits could also be linked to vascular P-selectin upregulation, such as vasculitis and multiple sclerosis. These potential caveats should be further explored as well.

T2 and diffusion-weighted MRI are the most commonly used sequences for stroke neuroimaging, but these standard approaches provide limited diagnostic value for detecting TIA. Indeed, the authors confirmed that no ischaemic lesions were detected after 15-min transient occlusions in their mouse model, despite the reproducible hypoperfusion and vascular dysfunction. It is known that following cerebral ischaemia, multiple thresholds of response occur, depending on the parameter being measured. Protein synthesis may be the most sensitive parameter, with changes occurring when cerebral blood flow drops below 50% of baseline. Other responses follow sequentially graded thresholds, with disturbance of glucose and energy metabolism next to follow, followed by acidosis and then phosphocreatine and adenosine triphosphate decline, and eventually anoxic depolarization (Hossmann, 1994). In the context of presumably very mild perturbations induced by TIA, outright infarction or major derangements in metabolism would not be expected, so routine T2 and diffusion-weighted MRI may not be useful. Worth noting, however, is that pH imaging has recently been proposed as a way to map moderate-to-severe gradients in metabolic injury, complementing conventional stroke MRI for the stratification of heterogeneous tissue response following cerebral ischaemia (Zhou et al., 2003; Guo et al., 2016). Whether these emerging pH-based imaging techniques may also be relevant to TIA warrants further investigation.

Clearly, more experimental work needs to be done before clinical translation. For example, it would be interesting to know whether the upregulation of P-selectin is spatially specific (i.e. only elevated in ischaemic tissue) or whether expression also increases in adjacent regions or even in the entire ipsilateral hemisphere. Spatial specificity for an imaging biomarker would constitute a clear
Increased heart rate and energy expenditure in frontotemporal dementia

This scientific commentary refers to ‘Energy expenditure in frontotemporal dementia: a behavioural and imaging study’ by Ahmed et al. (doi:10.1093/aww263).

The obesity paradox, whereby being overweight or obese during mid-life is associated with higher rates of dementia in later life, while low body mass index (BMI) in older populations is associated with a higher risk of dementia, has been demonstrated in multiple studies of patients with Alzheimer’s disease (Fitzpatrick et al., 2009). In another neurodegenerative disorder, frontotemporal dementia (FTD), classic descriptions suggest a different pattern, specifically weight gain with disease onset due to hyperphagia and increased sweet intake. However, BMI has not been found to correlate with food intake in FTD, raising the possibility of altered metabolism in patients with FTD (Ahmed et al., 2016). In this issue of Brain, Ahmed et al. test this hypothesis by measuring activity levels and heart rate to characterize energy expenditure in patients with FTD (Ahmed et al., 2016). They conclude that resting and total energy expenditure are increased in FTD, suggesting that the basal metabolic rate in patients with FTD may be altered as a part of the disease.

A relationship between BMI, metabolism and several neurodegenerative disorders including Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis is now generally established, though the complex pathways mediating these associations across and within different