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Towards metabolic disconnection – symptom mapping

This scientific commentary refers to 'Metabolic lesion-deficit mapping of human cognition' by Jha *et al.* (doi:10.1093/brain/awaa032).

Structural and functional neuroimaging methods have contributed to our understanding of the anatomy of higher cognitive functions. MRI has often been the method of choice because it allows for the simultaneous and non-invasive study of brain structure and function in health and disease. In the presence of brain pathologies, structural MRI is traditionally used for lesion delineation and provides an estimate of the lesion location, its size, and how far it extends into cortical and subcortical regions (Bates *et al.*, 2003). Several studies have demonstrated, however, that the timing of neuroimaging relative to symptom onset, as well as the particular modalities used, can influence the results obtained (Shahid *et al.*, 2017; Forkel and Catani, 2018). For instance, the extent, contrast and shape of lesions can change over time and differ between imaging modalities. These anatomical observations can be complemented by functional MRI sequences that shed light on the deterioration of brain functional networks and their reorganization (Corbetta *et al.*, 2005).

Despite the success of neuroimaging, clinicians are accustomed to seeing patients with cognitive deficits indicative of brain lesions, and yet no visible evidence of such lesions on the MRI scan. There are a number of possible explanations for this incongruent presentation. In some patients, cognitive impairments may be caused by other underlying conditions (e.g. effects of toxins, infections); in others, our conventional imaging tools may be insufficient to detect damaged tissues. It is also possible for the brain to appear structurally intact, and yet for its function to be compromised because individual regions are no longer working together effectively. Hence, the absence of a structural lesion on conventional MRI does not preclude the presence of a functional disconnection. Reliable neuroimaging methods are therefore crucial to aid diagnostics, inform treatment pathways and improve quality of life for patients. But despite our best efforts to improve methods for studying structural and functional disconnections in patients, we still lack advanced imaging tools to identify 'hidden damage' (Thiebaut de Schotten and Foulon, 2018).

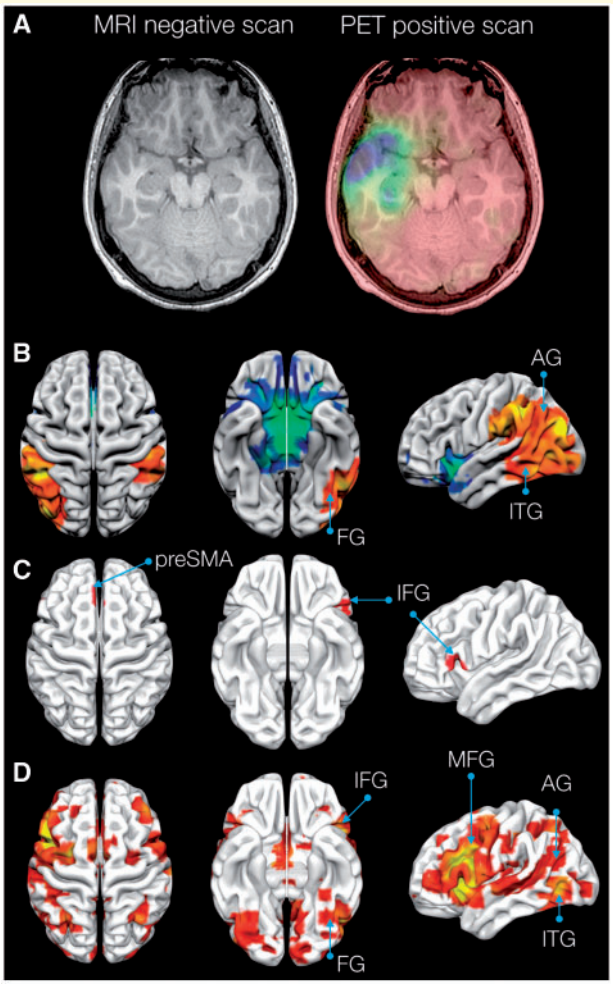

Figure 1 The 'hidden lesion'. (**A**) MRI-negative and PET-positive scans of the same patient (from Jha *et al.*). (**B**) Metabolic lesion-symptom map for phonemic verbal fluency as identified by Jha *et al.* (**C**) Example of a structural lesion-symptom map for phonemic verbal fluency as obtained from Kinkingnéhun *et al.* (2007). (**D**) Functional activation maps from healthy controls performing a verbal fluency task in an MRI scanner. Maps derived from Neurosynth (www.neurosynth.org, Yarkoni *et al.*, 2011). AG = angular gyrus; FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; preSMA = presupplementary motor area.

The absence of visible brain lesions can have far-reaching implications. For example, patients with traumatic brain injury often present with cognitive impairment but lose medico-legal cases because of a lack of evidence of lesions. Recent studies have shown, however, that differences in perfusion imaging and tractography measures can be evident in traumatic brain injury patients despite a clinically 'negative' structural MRI (Metting *et al.*, 2013). Another example is non-lesional focal epilepsy, which may be confirmed by EEG, but where cognitive impairments are not contingent on the presence of a visible lesion (Rayner *et al.*, 2019). In the absence of demonstrable lesions, neurosurgeons are primarily guided by the clinical symptoms exhibited by a patient and the EEG results. Thus, it is clear that new neuroimaging strategies are required to reveal hidden lesions to improve diagnosis, treatment and, subsequently, patients' quality of life.

In this issue of *Brain*, Jha and co-workers introduce a novel approach to lesion-deficit mapping based on metabolic imaging (Jha *et al.*, 2020). The authors provide proof-of-principle for their approach using retrospective PET neuroimaging data from 159 patients undergoing investigation for epilepsy but with negative structural MRI results. The advantage of metabolic disconnection mapping over classical lesion-symptom mapping is that cerebral glucose metabolism can be extracted as graded deviations, whereas lesion maps are extracted as binary masks. The metabolic gradient includes hypofunction and hyperfunction, which may reflect deterioration and reorganization of brain function and may thus improve clinical-anatomical correlations.

Jha *et al.* (2020) assessed cognition with a clinical neuropsychological battery that included 16 commonly used measures probing memory, verbal fluency, affect, and intelligence. The cerebral glucose metabolism scans were performed using ^{18}F-FDG PET/CT

Glossary

^{18}F-FDG PET/CT: A PET scan uses a small amount of a radioactive drug, or tracer, to show differences between healthy and pathological tissue. The most commonly used tracer is FDG (fluorodeoxyglucose). In the study by Jha *et al.*, 30 min after the injection of 250 MBq ^{18}F-FDG, a CT scan was acquired for attenuation correction, and this was followed by 15 min of PET acquisition.

Metabolic disconnection: Brain regions are structurally connected to each other to work together by means of integration, inhibition or disinhibition. If these processes are functionally impaired without a lesion being evident on conventional structural imaging, this is considered metabolic disconnection.

imaging. Evaluating these scans revealed metabolic lesions in patients with no visible lesions on standard MRI (Fig. 1A). Metabolic lesions were also more uniformly distributed across the brain as compared to lesions resulting from stroke. In stroke, lesions tend to adhere to the vasculature of the brain, resulting in clusters of lesioned voxels on MRI (Mah *et al.*, 2014). The results of Jha *et al.* thus suggest that ^{18}F-FDG PET/CT imaging may be helpful for comprehensively mapping symptoms to the brain.

Jha *et al.* generated their metabolic-symptom maps by means of voxel-wise mass-univariate inference between the metabolic lesions and the neuropsychological assessments. Most functions were associated with both positive and negative metabolic activity across the brain (see example in Fig. 1B). Unlike classical lesion-symptom mapping which points to the most critical area (Fig. 1C), metabolic approaches may reveal the underlying network affected by a lesion. These networks resemble results from functional imaging in healthy controls for the same cognitive domains (Fig. 1D).

In a final step, the authors tested their dataset for predictive fidelity by using verbal IQ and Hospital Anxiety and Depression Scale (HADS) depression measures in a Bayesian regression analysis, which yielded high predictive values for individual patient scores. These results indicate that Jha *et al.* have laid the foundations for some exciting future research applications. Given the broad clinical impact of a method that can reveal 'hidden lesions', the approach should be extended. Rather than relying on a radioactive tracer, it could be extended to a non-invasive sequence (e.g. diffusion-perfusion MRI; Hillis *et al.*, 2005). Combining metabolic lesion mapping with multimodal imaging, such as tractography and EEG, will greatly enhance our understanding of the relation between structural and functional lesions. For instance, extending this line of investigation from its current focus on grey matter to also include white matter tractography could allow one to partially decipher the structural mechanisms behind the metabolic changes identified. Overall, having a continuous measure of a lesion is a great advantage as it increases statistical power and could allow for grading of the lesion (e.g. core, penumbra, oedema). This study thus represents a significant step forward in the quest to map and understand brain function and pathology, while also having the potential to greatly improve clinical diagnosis and treatment.

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Competing interests

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Rethinking the nature of inhibitory control deficits in Tourette syndrome

This scientific commentary refers to 'Impaired automatic but intact volitional inhibition in primary tic disorders', by Rawji *et al.* (doi:10.1093/brain/awaa024).

Tourette syndrome is a neurological condition of childhood onset that is characterized by the frequent occurrence of unwanted movements and vocalizations—referred to as tics—that can vary in frequency, complexity and intensity. One of the defining characteristics of tics, and one that distinguishes them from other kinds of abnormal movement, is that they can often be effectively suppressed for a period of time. However, tic suppression is typically associated with increasing levels of discomfort, which are most often experienced as an increasingly strong urge-to-tic.

Many researchers have assumed (erroneously in our view) that the limited ability to suppress tics must therefore result from some underlying impairment in volitional control processes, and have sought evidence in support of this view by investigating performance on volitional (inhibitory) control tasks, with quite mixed results. While a recent meta-analysis concluded that there was a small volitional control deficit associated with Tourette syndrome (Morand-Beaulieu *et al.*, 2017), most studies have reported no differences in performance relative to matched control samples, and several studies have reported paradoxically enhanced volitional control over motor outputs in Tourette syndrome (Mueller *et al.*, 2006). Furthermore, where impairments in inhibitory control in Tourette syndrome have been reported, these studies have most often been confounded by the presence of co-occurring clinical conditions (Jung *et al.*, 2013).

When considering the brain processes that give rise to tics, it is as important in our view to consider mechanisms linked to the generation of tics as it is to consider those mechanisms associated with their volitional suppression; and it is in this context that the study by Rawji and co-workers in this issue of *Brain* makes a welcome and important addition to the literature (Rawji *et al.*, 2020). In their study, Rawji *et al.* investigate whether there is a dissociation between processes linked to the generation of tics, which may be linked to a failure of inhibition within cortical-striatal-thalamic-cortical brain networks (Albin and Mink, 2006), and those processes involved in the voluntary suppression of tics. They argue that volitional control tasks (e.g. Go/NoGo or Stop-Signal tasks) largely measure mechanisms involved in tic suppression but not tic generation, and explore whether a masked-prime task—thought to measure automatic inhibition—might be more appropriate for assessing the mechanisms by which tics are generated (assuming a failure of automatic inhibition in Tourette syndrome).

Specifically, Rawji *et al.* investigated how a group of adults with Tourette syndrome performed on a version of the Conditional Stop Signal Task and on the Masked-Prime Task, relative to groups of healthy control subjects. The Stop Signal Task assesses the individual's ability to cancel a planned manual response, given sufficient time. If the stop signal occurs too late during the response planning process, then the response will be executed as planned. This form of inhibition is known as reactive inhibition. Importantly, individual performance on this task was carefully assessed by adjusting the presentation of the stop signal depending upon the participant's performance on previous trials. Additionally, a conditional response version of the Stop Signal Task was run to allow the research team to assess proactive rather than reactive inhibition (see Rawji *et al.* for details).

In the Masked-Prime Task, participants produce a manual response according to a visual cue that is preceded by an unseen (masked) compatible or incompatible pre-cue. Previous work has demonstrated that the presence of the pre-cue can speed or slow a participant's average response times to the cue, depending upon the time interval between the pre-cue and cue (Eimer and Schlaghecken, 2003). When the pre-cue leads to a consistent slowing of response time this is termed a negative-compatibility effect, and is thought to be the result of an automatic inhibitory process that is triggered by the pre-cue.

Consistent with previous reports, Rawji *et al.* found that volitional inhibition of motor output (both proactive and reactive inhibition), as assessed by the Conditional Stop Signal Task, was not impaired in their sample of adults with Tourette