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LETTER TO THE EDITOR

Voodoo surgery? The distinct challenges of functional neuroimaging in clinical neurology

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Sir,

I read with interest the article by Lyon (2017), which provided an excellent cautionary note regarding the analysis and interpretation of functional MRI data. I concur with her overall conclusion that, in spite of recent scepticism, functional MRI remains a very useful technique, provided one is vigilant in maintaining best practice in terms of 'good (experimental) design, analysis and reporting'. However, many of the issues that Lyon (2017) raises relate to functional MRI data from groups of (often healthy) participants to answer (often theoretical) questions on cognitive function. It is important to recognize that functional MRI is commonly applied in the clinical setting as well, which gives rise to a unique and fundamentally different set of challenges. Such applications are associated with more immediate and life-altering sequelae, and it behoves both clinicians and scientists to be aware of the distinct methodological limitations of such clinically-based applications.

Consider, for example, patients with pathological brain lesions (e.g. a tumour or epileptogenic focus), who commonly undergo functional MRI to localize areas of 'eloquent cortex' that should be spared during lesion resection (Matthews *et al.*, 2006; Chong and Cook, 2013). Even at the most fundamental level, the neurophysiological cornerstone of functional MRI—the blood oxygen level-dependent (BOLD) response—may not necessarily provide an accurate measure of neural activity in such patients. Brain tumours, which are often highly vascularized, can affect the localization and intensity of the BOLD signal through changes in vascular autoregulation, as well as through direct structural compression, resulting in a disruption of the tight neurovascular coupling that is seen in healthy physiology (Logothetis, 2002; D'Esposito *et al.*, 2003; Lauritzen, 2005). In addition, concurrent disease processes (e.g. cerebrovascular disease), as well as certain commonly prescribed medications (e.g. dopaminergic drugs, certain anti-depressants) may alter either vascular flow or neurovascular coupling (D'Esposito *et al.*, 2003). The consequence may be a BOLD signal that is attenuated, absent, or even inverted, and/or falsely localized (Peeters and Sunaert, 2007).

With regards to task design, a challenge in preoperative functional MRI is determining, not necessarily what is 'good', but rather what is appropriate. The cognitive neuroscience literature is replete with well designed paradigms that probe many different aspects of cognition. However, in clinical practice, cognition has traditionally been modularized into monolithic constructs (e.g. 'attention', 'memory', 'language', 'executive function'). Although this is clinically convenient, it becomes problematic when interpreting the nature of activations in an individual patient. For example, in the case of language, the distribution of activity will vary based on the nature of the task (e.g. word generation versus sentence completion; noun versus verb generation; comprehension versus word generation), as well as the baseline against which the conditions of interest are compared (active versus passive) (e.g. Zacà *et al.*, 2013). Precisely which paradigms predict an improved postoperative outcome are yet to be

determined, and are likely to vary significantly depending on the nature and location of the individual lesion.

More broadly, there are fundamental differences in the statistical inferences that underlie theoretically-driven experiments, which seek to uncover generalizable truths, versus those that underlie clinical questions, which aim to guide patient management. As Lyon (2017) correctly notes, a key priority in research is to avoid false positive (type I) errors—an especially topical concern given recent claims of a reproducibility crisis in science (Open Science Collaboration, 2015). Consequently, most studies apply corrections for family-wise error that result in more conservative statistical thresholds. In contrast, the emphasis of preoperative functional MRI is often to decide on a safe resection margin while preserving areas of eloquent cortex. The preference here is therefore to identify a greater number of functionally relevant voxels, which would require more statistically liberal thresholds to avoid false negative (type II) errors.

After navigating the aforementioned issues, a clinical team might then be faced with the substantial challenge of translating statistical parametric maps of BOLD activity into the choice of a resection margin that preserves a particular cognitive function, while ensuring complete resection of the lesion itself. Of course, BOLD activity does not necessarily indicate a causal relationship between the underlying brain tissue and a given cognitive process. It is therefore not possible to predict the functional consequences of resecting those areas on the basis of functional MRI alone, and it is unsurprising that there are no guidelines on the postoperative consequences of sparing one subset of functionally activated areas over another. In the absence of such evidence, most clinicians today would advocate interpreting clinical functional MRI data on an individualized basis, in the context of data from other available techniques (e.g. EEG, ECoG, MEG, PET, SPECT) (Chong and Cook, 2013). This combined approach leads to greater sensitivity and specificity to the localization of brain function, compared to any one technique alone (Gaillard *et al.*, 2011).

This list of pitfalls is far from exhaustive, but was selected to highlight the contrasting challenges in interpreting functional activity in a medical setting, when data from a single patient with brain pathology are used to guide a treatment plan (see Desmond and Chen, 2002; Lehéricy *et al.*, 2007; Warren *et al.*, 2017 for other issues). In seeking to overcome these challenges, the very flexibility that Lyon (2017) writes has been the curse of functional MRI may, in the clinical setting, be a blessing. Many groups have developed excellent methodologies to address the aforementioned issues in practice (e.g. dynamic statistical thresholding) (Stippich *et al.*, 2007). These flexible approaches allow one to navigate and control for many of the above issues, with the goal of tailoring preprocessing and analysis pipelines to individual patients. This is particularly important given that the extent of activation in some patients may be considerably less than others due to differences in physiology (e.g. baseline vascular autoregulation and neurovascular coupling); the variable nature, location and size of their lesion; and the presence of any concurrent neuropathology (e.g. cerebrovascular disease) or medications.

Functional MRI remains a very useful tool to guide clinical decisions and, as in research-based applications, requires a high level of scientific rigour. Increasingly, it is finding many more applications in the clinical domain (e.g. to identify biological markers of disease, or to monitor disease progression) (Matthews *et al.*, 2006). It is critical therefore to be thoroughly aware of the distinct priorities, methodologies and limitations of a clinical versus research-based approach, with the medical consequences of a statistical decision likely to be more than just a 'dead salmon'. The question of whether functional MRI in combination with other techniques can have a positive effect on surgery-related morbidity and disease-related mortality remains to be determined in cleverly designed, prospective studies that maintain methodological rigour, while incorporating imaging algorithms that account for the vast range of individual differences. As one of the fathers of modern medicine noted, 'Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease' (Osler, 1903). Such is the challenge that has faced clinical medicine since its inception, and will continue to face the modern neurologist, not least in the field of functional neuroimaging.

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