Extended testing for cognition: has awake brain mapping moved to the next level?

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Evolution of mapping concepts

Penfield, as depicted masterfully in the 1936 Boldrey's thesis, produced a detailed, direct electrical stimulation (DES)-generated, motor, somatotopic map, including specific stimulation sites of individual fingers [17, 21]. Harvey Cushing, Penfield's remote mentor, had stimulated non-human primates while working in England with renowned neurophysiologist, and later, Nobel laureate, Charles Sherrington, and produced in 1902 and 1903 rather coarse human maps with joint movements only [21]. Some 50 years earlier, in 1884, Victor Horsley had performed the first successfully organized intraoperative stimulation of a human cerebral cortex in a case of occipital encephalocele resulting in rapid conjugate eye deviation, attributed by Horsley to the stimulation of the quadrigeminal plate [36].

Penfield is also credited for mapping language, modifying Foerster's technique, and applied DES with bipolar electrodes producing a square waves with a frequency of 60 Hz and a duration of 0.2 to 0.5 ms, not remote to current settings [17, 30]. Applying similar principles, Ojemann, in a landmark 1983 paper, produced a probabilistic model of language organization derived from stimulation mapping of language-related functions including naming, reading, short-term verbal memory, mimicry of orofacial movements, and phoneme identification, thereby setting the foundations of modern intraoperative language mapping [26].

During the 4 subsequent decades, awake brain mapping (ABM) evolved exponentially, as accumulated literature suggested that, at least in glioma surgery, ABM maximised safe resections, representing a standard of care [9, 40]. Indeed, in the largest meta-analysis totalling 8,091 adult patients who underwent tumour surgery with and without ABM,

gross total resections were documented in 75% and 58% of patients, respectively, while late, severe neurological deficits were observed in 3.4% and 8.2% of patients, respectively [9]. However, as accrued data were analysed, a number of cognitive impairments appeared to emerge either as a result of neoplastic invasion or post-surgery sequelae, prompting the development of intraoperative tasks to test, detect, and protect, higher cognitive functions beyond language and movement, during ABM [4, 25, 33]. In a thoughtful meta-analysis, Ruis confirmed, quite convincingly, this gap in intraoperative testing, showing that among 232 qualifying studies, testing of memory, emotions, calculations, or other cognitive functions beyond language was performed or reported extremely rarely [31].

Current systematic review

In this issue of Acta, Landers et al. focused their efforts in systematically reviewing published evidence on the use of DES in white matter tracts subserving visuospatial attention and a group of three executive functions including inhibitory control, working memory, and cognitive flexibility [20]. Conclusions drawn from eleven qualifying studies indicated that the right SLF-II is involved in visuospatial awareness, as previously and rather extensively has already shown, while the left SLF-III and possibly the right SLF-I are involved in working memory; the cingulum appeared to be implicated in cognitive flexibility [20]. The authors insightfully recognised that their conclusions, based on the heterogeneity of study types and employed methods, could not unequivocally support their emerging hypotheses.

Beyond the unusual grouping of visuospatial attention with three core executive functions, with the former dominating the study populations with seven out of eleven studies, Landers et al. should be commended for investigating and drawing attention to intraoperative mapping of top-tier cognitive domains. As neurosurgeons interrelate

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increasingly with cognitive neuroscience, a working knowledge of what constitutes cognitive domains, and in this particular paper, what represents executive functions, may be useful, as definitions in the literature are far from consistent. Cognitive domains are numerous, distinct, hierarchical, and interrelated with executive functioning and cognitive control occupying the top hierarchy tier [15]. The cognitive subdomains of executive functions, in particular, involve reasoning and problem solving, in other words, “real-world adaptive success” [15, 32].

In addition, memory mapping has received limited attention in the literature although neurology studies have shown to be severely impaired in diverse anatomical substrates including cortical dementias and frontostriatal disorders and a variety of neuropsychiatric disorders affecting subdomains such as procedural, affective, prospective, and manipulation working memory [14, 15]. With regard to working memory as a core executive function, beyond operational definitions, it should be noted that the current systematic review could not power any conclusions. For example, the involvement of right SLF-I in working memory was based in one study of two patients. Therefore, in this specific white matter tract, caution is advised when extrapolating a single report of two cases as results of a systematic review.

A second challenge when interpreting DES outcome reports is the reliance on the operators’ interpretation during surgery. For example, since Makris introduced in 2004 the anatomical definition of SLF I, its anatomical existence has been disputed in a number of studies as was found in minority of subjects and attributed to be part of the cingulum in all cases of one study, as confirmed on both DSI and HCP templates [23, 37]. Although our group has consistently identified in white matter dissections the wavy, SLF I, in the upper bank of the cingulate sulcus, connecting the precuneus with the medial superior frontal gyrus, this controversy demonstrates how challenging it does remain to dissect, among other tracts, SLF I, even in an ideal, laboratory environment [37, 38]. Therefore reports on its reliable intraoperative identification and stimulation, particularly in a novel relation to working memory, should be considered carefully.

It remains always contingent on the surgeons/team, experience, and expertise to know what exactly the surgeon is stimulating, what is the proposed function of the stimulated region, what is the appropriate test for the proposed function, and how any results can be thresholded and interpreted, in the complex surgical environment. For example, although working memory impairment was attributed to SLF I in the cited paper, a more sustained attention compromise, subserved by medial frontal regions, may have contaminated working memory assessment [35].

Brain mapping challenges

These methodological challenges lead to a number of observations, often overlooked, in ABM studies, which are closely linked to wider neuroscience issues. First, successful ABM outcomes are predicated on clear understanding of the anatomical definitions, presumed function, and appropriate, intraoperative testing paradigms. However, a strictly defined, consensual map of cortical parcels and subcortical white matter segments is not currently available. Since Brodmann’s 43 cytoarchitectonic areas, Vogt’s and Vogt’s 185 myeloarchitectonic areas, and von Economo and Koskinas’ 107 regions, multiple parcellation maps have been generated, mostly clinically unvalidated [1, 2, 13, 24].

Notwithstanding the undisputed presence of neural networks and metanetworks, neurosurgeons need accurate anatomical definitions of areas such as the dorsolateral prefrontal cortex or ventral or dorsal premotor cortices, among others, so region-specific DES can be applied. Whether these specialised cortical parcels represent hyperconnected network hubs, regions of high nodal connectedness, or cortical epicentres, should not distract from the need of their accurate topological definition [8]. Many excellent probabilistic maps have been recently proposed, but these cannot be applied anatomically, without significant interobserver variability [28, 32]. Similarly, regardless if the brain function frameworks are topological or, most likely, hodotopical, as initially supported more than a century and a half ago, and regardless of the re-organisational plasticity of the neural tissue, certain network disruptions can and will inflict neurological deficits, in motor, language, and other cognitive domains [5–8, 19].

Second, the precise function of most cortical parcels and subcortical white matter tracts remains incomplete. For example, the arcuate fasciculus, perhaps the most widely studied language pathway, has been represented with conflicting anatomo-functional models as proposed sequentially by Dejerine in 1895, Geschwind in 1970, Catani in 2005, and Glasser and Rilling in 2008 and numerous other tractographic, track-tracing, and fibre dissection models [6, 10, 12, 13, 38].

Third, there is currently significant interobserver variability in selection and interpretation of intraoperative testing for language and other cognitive domains regardless of specialism or years of experience [34]. Our group documented lack of consensus among experienced specialists in interpreting common terminology (for example, definitions such as anomia or apraxia of speech) or selection of intraoperative tests (such as selecting tasks for the dominant dorsolateral prefrontal cortex or dominant parts triangularis) [34].

Mapping cognition

These methodological limitations, lack of standardization, and often lack of agreement on what is tested and how, even when testing structures we have been electrically stimulating for many decades, should be considered when wider cognitive functions beyond language are interrogated. Fortunately, a wealth of initial DES data is emerging from high-quality cognitive studies [22, 27, 32]. Recent reports accrue data on specific testing of wider cognitive domains including cognitive aspects of movement, such as awareness of voluntary actions using the hand manipulation task; interference control or achieving a goal through conflicting incoming information using the Stroop test; and face-based mentalising or mental state recognition using the “reading the mind in the eyes” test [3, 11, 29, 39]. It should be noted however that highly distributed rather than modular, context-sensitive cognitive metanetworks involving emotion, spatial cognition, and memory, among others, would be significantly more challenging to map [16].

ABM remains a cornerstone not only of maximum safe resection of gliomas, prolonging survival and protecting patients’ quality of life, but also validating emerging cognitive theories and generating novel, invaluable data in the functional organisation of movement, language, and other cognitive domains. It should be emphasized, however, that certain high order, flexible cognitive functions are subserved by widespread, large-scale, interacting, synchronised networks and a brief, temporary DES disconnection may not access specific cognitive subdomains or indeed may disconnect interacting networks; therefore, excessive claims should be tempered [16]. It is hoped that by reducing methodological and interobserver variabilities, producing precise and validated anatomo-functional maps, standardising mapping paradigms with inclusion of personalised data, and possibly creating inter-institutional registries of DES outputs, ABM will protect further patients’ quality of life and strengthen its unique contributions to cognitive and wider neuroscience [18, 32, 34].

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