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Title:
The neurobiology of non-organic disorders – fMRI/PET/SPECT

Learning Objectives:
1. Understanding commonly employed imaging modalities in non-organic disorders
2. Understand limitations of current literature concerning non-organic disorders
3. Understand limitations of current functional imaging techniques in understanding non-organic disorders.

CME Questions:
1. fMRI may employ paradigms with activation epochs interspersed with inactivity to elicit BOLD responses indicative of brain activation. True/false
2. Functional imaging is a consistent and reliable method to diagnose functional disorders. True/false
3. fMRI has the potential to teach us about neural networks involved in specific tasks and compensation for disease. True/false

Keywords (Max 5):
1. Functional MRI
2. Functional disorders
3. Positron emission tomography
4.
5.

Introduction/Abstract (Please see instructions for formatting details):
Many of neuro-ophthalmology’s most challenging conditions are rooted in sub-structural pathology. Functional imaging has the potential to unravel many of these brain mysteries by illustrating regional metabolic (inferred activity) differences within the brain at rest and during specific tasks. Within this context, functional imaging (PET, SPECT or fMRI) may teach us about functional disorders – either conversion or malingering. Group data in these disorders has provided interesting, but varied and at time disparate results. Despite the promise and potential (and at times hype), functional imaging at present does not have the ability to assist in the diagnosis of individual patients.
**Question:** Can imaging reliably & objectively diagnose functional disorders?

**Background**

Functional disorders are common in clinical practice; indeed, it has been estimated that 20% of outpatient neurologic encounters harbor unexplained medical symptoms (Mace 1991). Such disorders are also common in ophthalmology clinics, where 1-5% of patients manifest medically unexplained visual loss (Kathol 1983, Sletteberg 1989), and such impairments run a chronic course in up to 50% of patients (Barris 1992). Accordingly, neuro-ophthalmology is often the crossroads for functional disorders within these specialties. *Despite their frequency, these disorders are poorly understood.*

When exploring the neurobiology of a particular disease, investigators establish disease-specific requirements and employ certain tools. Such methodology is best exemplified by conditions such as progressive supranuclear palsy (PSP). PSP has an established case definition, and a described course. A case of PSP in Europe would share these features with a case documented in North America, and patients visiting several clinics would receive the same diagnosis at each, assuming similar criteria were applied. MRI features such as midbrain atrophy have been well described and do not vary among imaging centers. The applicable genetics have been elucidated in familial forms. The pathology inclusive of tau protein accumulation is well documented. Within this framework, we can begin to understand the neurobiology of this tauopathy: why the protein accumulates, what dysfunction does it cause in the favored locations, and potential interventions to reverse the disease.

This well established model couldn’t be applied to current day understanding of functional conditions. These disorders do not have established, agreed-upon diagnostic criteria, and the same functional patient may receive several different diagnoses from different physicians based on a similar symptom set. The final word on many functional disorders belongs to the psychiatrists, who use the DSM as a codified bible (ironically, most of the functional disorders are seen outside of psychiatry clinics). Even within this context, the diagnostic rules have changed. While DSM-IV included diagnoses of somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder, these have been removed from DSM-V. The latter dispenses with the DSM-IV arbitrary symptom count for somatization disorder, instead renaming this ‘somatic symptoms disorder’ with an emphasis on maladaptive thoughts and behaviors. DSM-V’s somatic symptoms disorder can also accompany organic medical disorders. The criteria for conversion disorder have been modified to emphasize the importance of the neurological exam and the exclusion criteria of psychological factors at the time of diagnosis. These criteria will continue to morph with time and increasing medical knowledge. It is worth remembering the long list of medical diagnoses that have been considered factitious or functional in the past but which now are accepted as clearly organic and have well-explained pathophysiologic basis. Gowers’ 1893 textbook classified Parkinson's disease, chorea, torticollis, epilepsy and narcolepsy as functional because at the time there was no autopsy-visible lesion to stamp them “organic”. Commonplace disorders such as blepharospasm were also thought to be functional in the recent past. There are no current traditional imaging, genetic or other biomarkers at present that help in diagnosis or prognosis. Tissue samples are normal, and autopsy fails to establish the histological features indicative of functional disorders. *New knowledge regularly creates old fools.*

**The Evidence/Science:**

Functional imaging is very difficult to do in the target population for several reasons. First, we cannot agree on clear diagnostic criteria for the diagnosis – this would make it virtually impossible to design a workable multi-center trial. Second, this population is very difficult to recruit – attesting to this fact is that the largest published series of functional visual patients studied with functional imaging to date is 8. Additional difficulties confounding the literature include the heterogeneity of the functional groups – visual, motor, sensory, movement disorder symptoms, with further variable within these groups (e.g., one or both eyes, degree of claimed visual loss, duration of symptoms, etc.). Adding to these problems is the variability of imaging equipment and protocols, a problem that could be
overcome with elements of standardization, but a situation that renders the current literature difficult to assess. Since the 1990s, protocols continue to undergo refinement and improvements (Tiihonen 1995).

**fMRI**

Functional MRI (fMRI) has many advantages pertaining to functional imaging and has become the imaging tool of choice. The technology when used during an activation task involves the use of BOLD (blood oxygenation level dependent). Although there are numerous small series or single cases concerning motor or sensory functional deficits, there are very few such cases with visual symptoms.

Becker et al reported an interesting single case of a 25-year old male with functional “complete" visual loss OU (Becker 2013); these authors were able to study the subject during and after episodes of visual loss. An unaltered visual cortical response to checkerboard stimulation was observed during functional blindness; however, more complex visual stimuli such as faces or objects produced hypofunction in the occipital lobes with hyperfunction in the postcentral gyrus bilaterally and right superior temporal lobe. Extraction of the emotion-specific activity revealed increased activity in the left medial frontal gyrus and anterior cingulate cortex plus bilateral angular gyrus (hypothesized to be involved in moral reasoning and emotional regulation).

The largest study involving visual stimuli with medically unexplained visual loss was reported by Werring et al in 2004 (Werring 2004). These investigators recruited 5 patients with unexplained visual loss fulfilling DSM-IV criteria for conversion disorder. Among this cohort, 4/5 had bilateral visual field defects, and the duration of symptoms ranged from 2-10 years. Monocular whole field 8hz red photic stimulus was used to elicit fMRI responses with 20-second epochs alternating with darkness. The control group consisted of 7 healthy volunteers. Patients demonstrated reduced visual cortex activation, with increased activation of the left inferior frontal cortex, left insula-claustrum, bilateral striatum and thalami, left limbic regions and left posterior cingulate cortex. This visually-based example fits the general functional imaging model as described below.

Stone et al studied the fMRI findings in a group of 4 conversion weakness patients compared to healthy controls simulating weakness. During attempted ankle plantar flexion, both the conversion patients and the controls showed less activation of the responsible motor cortex compared to plantar flexion on the normal side; conversion patients showed activation in the basal ganglia, insula, lingual gyri and inferior frontal cortex; however this was not present in controls feigning weakness. Controls (but not conversion patients) activated contralateral supplementary motor areas when moving the “weak” side (Stone 2007). Employing a different paradigm, Voon et al studied 8 patients with conversion tremor compared to volunteers feigning tremor; conversion tremor demonstrated hypoactivation of the right temporoparietal junction, and less connectivity between right temporoparietal junction, sensorimotor regions (sensorimotor cortex and cerebellar vermis) and limbic regions such as the cingulate and ventral striatum (Voon 2010).

“Common” Pattern: hypofunction of primary cerebral area with hyperfunction of other areas; the hyperfunctioning regions may have inter-individual variability and have been reported to involve a large variation of regions. In addition, while group differences may be present (conversion vs feigned symptoms vs asymptomatic with history of conversion), the ability of the technology to distinguish an individual patient’s conversion vs. organic diagnosis is limited and suspect because of the variability of findings, very small magnitude of signal changes elicited by fMRI, and unknown meaning of these areas of activation (causal, consequence or compensation).

**SPECT**

Single photon emission computerized tomography lacks sufficient resolution to address detailed issues of functional localization and has been largely supplanted by PET or more commonly, fMRI. Nonetheless, this imaging modality ushered in future functional imaging studies in non-organic disorders (Tiihonen 1995).
PET
Positron emission tomography is a useful method for functional imaging but has several drawbacks. It is labor intense and expensive, requiring a cyclotron near or on-site to generate radioactive metabolites; perhaps most importantly, PET involves ionizing radiation which limits the enthusiasm of healthy volunteers. (Vuilleumier 2005; Spence 2000). Functional imaging studies of functional disorders utilizing PET have focused on non-visual symptoms. Vuilleumire et al studied 7 patients with functional sensorimotor syndrome using PET; decreased contralateral basal ganglia activation was evidenced during the symptoms, which resolved upon recovery. Spence et al studies 3 patients with unilateral weakness compared to 4 volunteers simulating unilateral weakness with PET; patients displayed left dorsolateral prefrontal hypoaivation when attempting to move the limb, while feigned weakness was associated with right dorsolateral prefrontal cortex (regardless of side).

Commonalities
Although patients and protocols vary widely, there are some common themes buried within the functional imaging literature concerning non-organic disorders. Hypoactivation is commonly seen in the expected cortical regions for a given task (e.g., motor strip with functional paralysis) with hyperactivation in other areas; the specifics of these “other” areas varies widely but has included RIGHT anterior cingulate and orbitofrontal cortex, parietal operculum, supplementary motor areas, ventral premotor cortex; LEFT inferior frontal cortex, insula-claustrum, thalamus, cerebellum, supplementary motor areas, limbic structures, posterior cingulate cortex, inferior parietal cortex; and BILATERAL striatum, thalami, putamen, cerebellum. (Burgmer 2006; Stone 2007; Voon 2010; Voon 2010a)

Lie Detection: an illustrative example
There are now two private corporations that sell fMRI assessment as a method for lie detection, No Lie MRI (http://www.noliemri.com/) and the Cephos Corporation (http://cephosdna.com/); however, fMRI (similar to traditional lie detector tests) are not admissible in US courts.

Answer: Can imaging reliably & objectively diagnose functional disorders? Not yet, but stay tuned…

CME Answers:
1. True
2. False
3. True

References: Author(s) Last Name separated by a Comma, Title/Article, Source (i.e. Journal Name), Volume #, Page #, Year
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