Editorial

Functional Neuroimaging: some critical issues

Karishma Rupani[1], Avinash De Sousa[2]

[1]Assistant Professor, Department of Psychiatry, Seth G.S. Medical College and K.E.M. Hospital, Mumbai.
[2]Consultant Psychiatrist and Founder Trustee, Desousa Foundation, Mumbai.
Corresponding author – Avinash De Sousa
E-mail – avinashdes888@gmail.com

Functional neuroimaging is any means to determine the effects of brain injury or disease on brain systems and functioning related to cognition and behavior and determined how treatment changes brain systems [1]. Functional neuroimaging has improved our understanding of neurobiology and bran processes in play during various routine tasks in both normal subjects and patient populations and also has also helped elucidate the role of various brain circuits and areas in the pathogenesis and maintenance of psychiatric disorders. There have been thought of using functional neuroimaging in day to day clinical practice and making the imaging modality affordable and available to all.

We've come a long way from post-mortem studies to understand the brain to structural imaging methods such as computed axial tomography (CAT) scans and magnetic resonance imaging (MRI) have allowed us to begin to visually depict the shape and size of the living brain. Structural neuroimaging technologies are useful to identify focal brain lesions that is coarse brain damage in living patients. However, in Psychiatry in the early stages of Depressive Disorders, psychosis and minimal cognitive impairment, to name a few, no abnormalities are seen on structural neuroimaging such as CT scan or MRI brain.

With the advent of functional Neuroimaging, which includes Diffusion Tensor imaging (for white matter tracts integrity), functional MRI (fMRI), PET scan, SPECT measure regional blood flow and metabolism. MRS, represents a novel approach to directly assess in vivo brain levels of specific chemicals of interest, such as N-acetyl aspartate (NAA), phosphocreatine, creatine, Choline and others. These allowed for the non-invasive study of patients' brain function, measuring chemicals in bodily fluids, normal sensorimotor, cognitive, and affective processes expanded. Thus functional neuroimaging also gives us an insight into abnormalities in affective and cognitive processes, which are not seen on structural neuroimaging such as CT scan or MRI brain [2].

Psychiatry in the Modern Era

Early successes in group studies of patients with dementia, stroke, and temporal lobe epilepsy laid the foundation for what would be an explosion of studies using functional neuroimaging, with an emerging discipline termed psychoradiology. Psychoradiology is an emerging field that applies radiological imaging technologies to psychiatric conditions [3]. The term was selected to parallel that of the field of neuroradiology, and to reflect the evolution of the research field of psychiatric neuroimaging to a new medical practice discipline. The broad aim of this field is to keep up with the advances in the RDoC initiative from the NIMH in the USA which was structured with the objective of measuring the behavioural and neurophysiological features related to psychiatric illness. It is also an effort aiming towards precision medicine in psychiatry to guide more individualized treatment planning and precision medicine. However, with some exceptions, neuroimaging is still a research tool.

Brain regions and psychiatric manifestations

You would agree that symptom clusters in patients in the real world sometimes do not meet the criteria required to make a diagnosis as per the classificatory system that we have at present. On the other hand some clusters are common to more than one diagnoses in the classificatory system. Because functional neuroimaging depicts focal brain dysfunction in the absence of structural abnormalities, it's application extended beyond those in dementia.

Brain region abnormalities in depression

Taking an example of depressive disorders, functional brain scans, such as SPECT (single photon emission computed tomography) or PET (positron emission tomography) have shown that patients presenting with the same symptoms of depression can have very different functional connectivity in their brains [4], some of the anatomic circuits of depression and mood regulation have been revealed by converging evidence from SPECT, PET, and fMRI studies of depression, a network of brain regions have been revealed by convergent neuroimaging findings, which includes the dorsal prefrontal cortex, ventral prefrontal cortex, anterior cingulate gyrus, amygdala, hippocampus, striatum, and thalamus, and together contribute to the pathophysiology of depression [5]. In a large proportion of depression cases, decreased activity is found in the frontal lobes, the insular cortex, and the anterior cingulate gyrus [6].

However, some patients with depression have increased perfusion in the precuneus, which correlates with rumination and self-criticism [7]. In contrast, some patients with depression also have decreased temporal lobe function. Many patients with depression show increased thalamic activity (metabolism or perfusion). Portions of the thalamus have direct connections to the amygdala, the seat of fear, and anxiety [8]. This increases our understanding of the neurobiological origin of depression as a syndrome.

Functional neuroimaging, such as SPECT and PET, can also predict who will respond to certain antidepressants. For example, those who are likely to respond to SSRI antidepressants show increased perfusion in the ventral frontal cortex and anterior cingulate SSRI antidepressants often induce decreased activity and perfusion in these areas, as well as in the thalamus. In contrast, some patients with depression have markedly decreased dorsal frontal cortex and medial frontal cortex activity and perfusion. These patients are less likely to respond to SSRI medications, but may respond better to noradrenergic antidepressants. Treatment-resistant depression may show markedly increased activity and perfusion in the subgenual cingulate [9].

Autism and Schizophrenia

The idea that neurodevelopmental illnesses, such as autism and schizophrenia, result from abnormal connectivity among large scale networks has been reinforced by the development of resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) has profoundly affected our understanding of the functional connectivity of the brain. Together with DTI, we can attempt to understand the large-scale organization of the brain, the so-called connectome [10].

Newer trends

In cases of Parkinson's Dementia, Dementia with Parkinsonian features, Lewy Body Dementia, Parkinson plus syndrome with dementia, 99mTc-TRODAT-1 (TRODAT) SPECT scan, which acts as a marker for Dopamine transporters (BIOMARKER) is helpful in tailoring treatment/prognosis. It is as good as a biological fingerprint, like genetics [11]. A novel amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PIB), was used in a study done in 16 patients with diagnosed mild Alzheimer's Disease (AD) compared with controls, AD patients typically showed marked retention of PIB in areas of the association cortex. The results suggest that PET imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects [12].

Tailored diagnosis

The information derived from functional neuroimaging is then subjected to pattern recognition or machine learning techniques, which have shown promise for detecting biomarkers from neuroimaging data and making diagnostic predictions in clinically defined psychiatric disorders and to jumpstart neuroscience drug development that has been stalled for decades. In recent years, more advanced algorithms such as deep learning (DL) have been increasingly used to investigate the neuroimaging features of psychiatric and neurological disorders [13].

For example it was found that gyrification-based connectome analysis provided a promising means to improve individual prediction of a transition to psychosis in Clinical High Risk (CHR) individuals [14]. High-resolution measurements for tissue temperature, tissue stiffness, macro molecular changes, and

metabolism can be done with comprehensive image analysis to build a disease discrimination model, potentially leading to tailored diagnosis and treatment plan [15].

Predicting treatment response and treatment selection

Mayberg and others performed two RCTs to identify if neuroimaging patterns could differentially predict outcomes to treatment with an antidepressant medication or cognitive behaviour therapy (CBT). In their first study, they used the fluorodeoxyglucose-PET and found that resting metabolism of the right anterior insula could distinguish remitters from non-responders to treatment with the antidepressant escitalopram and CBT. In the second study they performed a resting state fMRI study that identified patterns in the subcallosal cingulate cortex and three other brain regions that distinguished responders and non-responders to antidepressant medication (Escitalopram or Duloxetine) and to CBT Thus application of functional neuroimaging can be used for preemptive decision making, wherein this cohort of patients could have benefited from the protocol of treatment resistant depression, such as electroconvulsive therapy, or ketamine or neuromodulatory treatment (rTMS) might be initiated earlier to avoid months of ineffective treatment [16].

Interventional Psycho-radiology

One potential future role of psychoradiology may be to guide minimally invasive or non-invasive procedures for psychiatric patients under radiological imaging guidance precisely localize the optimal brain regions for the targeted neurostimulation treatment under imaging guidance to improve therapeutic efficacy for psychiatric patients. Helen Mayberg and others have been pioneers in interventional psychoradiology, performing deep brain stimulation (DBS) which has been approved by the FDA in the USA for movement disorders and for humanitarian use in severe treatment-unresponsive OCD with different target areas in the brain. For example, the striatum, subthalamic nucleus or internal capsule have been selected as targets of DBS [17].

Challenges we face and future directions

First, because neuroimaging findings were often not replicated, hence only the result of a single study cannot be generalized. Using deep learning, optimal representation from raw data with analytical methods to extract clinically useful information for individual patient care planning needs to go a long way. Thus the future of psychiatry shall be determined by the rapid strides that we make in the field of functional neuroimaging.

REFERENCES

1. Hillary FG, DeLuca J, (Eds). Functional neuroimaging in clinical populations. Guilford Press: UK; 2007.
2. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. Am J Psychiatry 2008;165(3):313-20.
3. Wang T, Liu J, Zhang J, Zhan W, Li L, Wu M, Huang H, Zhu H, Kemp GJ, Gong Q. Altered resting-state functional activity in posttraumatic stress disorder: A quantitative meta-analysis. Scientific Reports 2016;6(1):1-4.
4. Henderson TA, van Lierop MJ, McLean M, Uszler JM, Thornton JF, Siow YH, Pavel DG, Cardaci J, Cohen P. Functional neuroimaging in psychiatry—aiding in diagnosis and guiding treatment. What the American Psychiatric Association does not know. Front Psychiatry 2020;11:276.
5. Nagafusa Y, Okamoto N, Sakamoto K, Yamashita F, Kawaguchi A, Higuchi T, Matsuda H. Assessment of cerebral blood flow findings using 99mTc-ECD single-photon emission computed tomography in patients diagnosed with major depressive disorder. J Affect Disord 2012;140(3):296-9.
6. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am J Psychiatry 2012;169(7):693-703.
7. Dumas JA. What is normal cognitive aging? Evidence from task-based functional neuroimaging. Curr Behav Neurosci Rep 2015;2(4):256-61.
8. Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, et al. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. J Neurosurg 2003;99(6):1010–7

9. Thornton JF, Schneider H, McLean MK, van Lierop MJ, Tarzwell R. Improved outcomes using brain SPECT-guided treatment versus treatment-as-usual in community psychiatric outpatients: a retrospective case-control study. J Neuropsychiatry Clin Neurosci 2014;26(1):51–6.
10. Georgiades S, Szatmari P, Boyle M, Hanna S, Duku E, Zwaigenbaum L, Bryson S, Fombonne E, Volden J, Mirenda P, Smith I. Investigating phenotypic heterogeneity in children with autism spectrum disorder: a factor mixture modeling approach. J Child Psychol Psychiatry 2013;54(2):206-15.
11. Chou KL, Hurtig HI, Stern MB, Colcher A, Ravina B, Newberg A, Mozley PD, Siderowf A. Diagnostic accuracy of [99mTc] TRODAT-1 SPECT imaging in early Parkinson's disease. Parkinson Rel Disord 2004;10(6):375-9.
12. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55(3):306-19.
13. Viera S, Pinaya WH, Mechelli A. Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders. Neurosci Biobehav Rev 2017;74:58-75.
14. Das T, Borgwardt S, Hauke DJ, Harrisberger F, Lang UE, Riecher-Rössler A, Palaniyappan L, Schmidt A. Disorganized gyrification network properties during the transition to psychosis. JAMA Psychiatry 2018;75(6):613-22.
15. Huang X, Gong Q, Sweeney JA, Biswal BB. Progress in psychoradiology, the clinical application of psychiatric neuroimaging. Br J Radiology 2019;92(1101):20181000.
16. Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, et al. Functional connectivity of the Subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am J Psychiatry 2017;174:533–45.
17. Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, McIntyre CC, Gross RE, Mayberg HS. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry 2018;23(4):843-9.

****

Acknowledgements – Nil
Source of Funding – Nil
Conflict of Interest – Nil