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EDITORIAL

What role can function magnetic resonance imaging (fMRI) have in guiding therapy for depression?

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1. Introduction

The treatment of severe depression remains a major challenge in the field of psychiatry. Treatment resistance is defined as limited or no clinical response after two consequent attempts for antidepressant therapy over the course of two months [1]. There is still a missing consensual definition adopted globally in the professional community.

At the same time, resistance to psychological therapy and/or combined pharmacological and psychological treatment should also be considered, which, however, has not been properly investigated and defined. The functional MRI (fMRI) markers of treatment resistance have been addressed in most recent review by Katoula [2].

Typically, the assessment of pharmacological treatment in medicine is guided by triangulation of data that emerge from three (and sometimes four) sources of inquiry: clinical assessment, molecular laboratory tests in blood samples, imaging diagnostics, and sometimes electrophysiological tests (like ECG and EEG) [3]. For example, the normalization of ECG and EEG is adopted as critical parameters to direct the pharmacological treatment in cardiology and neurology.

Unlike other medical specialties, psychiatry does not triangulate (or quadriangulate) its clinical assessments over biomarkers, which reflect the causal structure and pathogenetic mechanisms of disease [4]. Instead, it focuses on the dynamics of the score exclusively from clinical scales that actually construct diagnostic criteria and serve as theranostic targets.

Various methods have been proposed to select and monitor treatment response in psychiatry. The mainstream approach has been the administration of observer-based rating scales, or interviews. Those typically comprise 8–12 items formulated as questions or statements, with the responses usually estimated on a 5-point Likert scale. The most common instruments in clinical psychopharmacology of depression are Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale. There exists controversial assumption that the assessment based on the observer's interpretation is 'objective.' However, it remains by all means 'subjective,' simply formulated in third-person perspective [5].

By contrast, nominally 'subjective' self-evaluation scales have been developed, which practically repeat the same psychological content, however, from first-person perspective, i.e. from the point of view of the patient [6]. Among the widely adopted self-assessment scales, one may consider the Beck Depression Inventory (BDI), Zung Depression Inventory, and Von Zerssen Depression Scale (DS). While BDI has been developed exclusively to monitor the psychological treatment by means of cognitive behavioral therapy (CBT) in terms of the dynamics in the so-called 'dysfunctional' thoughts, transformed into items from the scale, the Von Zerssen DS was delivered to monitor the antidepressant treatment response in medical settings [6].

All those tests capture eight major symptoms (in first-person narratives) or signs (in third-person assessment of the observer) of depression: dysthymia; pessimistic thoughts; cognitive dysfunctions; apathy and lack of motivation; anhedonia; decreased appetite; sleep disturbances; suicide ideation. The reduction of the score on those scales with 25–30% is considered as usual therapeutic target [7].

However, most of the treatment strategies in psychiatry as a medical discipline imply biological methods, such as pharmacotherapy, transcranial magnetic stimulation, transcranial direct current stimulation, electroconvulsive therapy, among others. The mechanisms of action of those methods are directed at the causal and pathogenic factors of disease, which lay in the domain of natural sciences, whereas the clinical assessment rests in the domain of the subjective narratives. This discrepancy is known also as 'explanatory gap' [8].

2. Conclusion

The studies of underpinning biological mechanisms of disease and their respective signatures in terms of biomarkers have been separated from clinical diagnostic assessment, which as a rule is the primary step performed in order to select a patient for the given intervention. This is another major confound in psychiatry as medical discipline, because clinical classifications are based exclusively on interviews and have failed to incorporate biomarkers so far [4,5].

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While fMRI may be a useful diagnostic marker for future classification of affective disorders, including depression, there is still limited convincing evidence that it can be used to track response to treatment at this current time.

Nonetheless, some advances have been made for inclusion of fMRI as a potential tool to select and monitor treatment response in depression. Those are presented in the expert opinion to follow.

3. Expert opinion

The key findings in the field concern introduction of pharmaco-magnetic resonance imaging (pMRI) [8].

pMRI is a complex approach for selective application of neuroimaging to inform drug choice and monitoring of treatment effect of medications targeting processes in the central nervous system. In psychiatry, and more specifically in affective disorders, it is used to determine brain networks that construct the hypothetical neural mechanisms of depression and their dynamics in the course of anti-depressive treatment [9].

Those networks may be identified on structural or functional level, the latter being investigated at rest or during active conditions processing, a.k.a. task-related fMRI.

Resting-state fMRI is a method that captures the spontaneous fluctuation of the blood oxygenation level-dependent (BOLD) signal from the brain distributed networks.

Two types of connectivity across neural networks have been identified: effective and functional. Effective connectivity [10] is studied in terms of dynamic causal modeling, which penetrates into the direction and causal influence of the connections: inhibitory, excitatory, and self-inhibitory. Our studies revealed that aberrant connectivity of insula and orbitofrontal cortex accounts for the diagnosis of severe mental disorders, including depression. Functional connectivity [11], on the other hand, represents different order relations within and across networks without causal inference about the nature of the connection. Most recently, we have demonstrated that node centrality and node strength of the full functional connectivity matrix accounts for 92% prediction of the clinical diagnosis [11]. In the near future, it may provide further insights and guidelines in the selection of antidepressant therapy [12].

It may well be applied to monitor the treatment response, besides other laboratory techniques, such as quantitative EEG, to inform the treatment of depression [13], which is one key potential in the field.

Task-related fMRI has been applied to assess the dynamics of the therapeutic response in mental disorders [14], especially for CBT of obsessive-compulsive disorder.

One key weakness in the field is the interpretability of the results from task-related fMRI due to their limited generalizability. That is entailed from the large-scale intra- and inter-individual variability of the BOLD signal under very heterogeneous stimuli, which are usually designed specifically for laboratory settings. Those comprise either cognitive tasks, emotional images (pictures), or behavioral tasks. The latter most often include money incentive delay (MID) or similar tasks. Sometimes, cognitive and affective stimuli are combined as well. Another key weakness is that the field research is often driven by theoretical assumptions. However, the non-linear complexity of both mental and nervous processes undermines many of those theoretical assumptions [15].

The critical issue, however, is that all those stimuli, with few exceptions, are not adopted from clinical diagnostic practice and therefore the results from fMRI studies cannot be translated back to clinical reasoning and decision-making [3,7].

This challenge has been recently addressed by a novel approach that can combine clinical self-evaluation scales and fMRI is one experiment. In that approach, the stimuli represent items (statements or questions) from diagnostic self-assessment test, such as the aforementioned Depression Scale. The latter conditions are contrasted in block design with resting state, on the one hand, and with diagnostically neutral items, on the other hand (statements from general interests scale). The subjects can see all items projected on an LCD screen or via goggles and provide their responses with a four-button response pad, where every button is corresponding to certain level of agreement with the statement as expressed in the original Likert scale. We contrast the responses to diagnostic and to neutral items between patients with different diagnoses and healthy controls and thereby define the specific networks modulated by diagnostic conditions [15,16].

That concept is defined on theoretical level as trans-disciplinary validation. The rationale behind that definition is two-fold. In the first instance, the clinical scales, which belong to the disciplinary domain of the ideographic (subjective narrative) knowledge, are validated with a method from another, independent, nomothetic, or explanatory disciplinary system (in this case, fMRI). In the second instance, there is applied the assumption about translation across the two domains, which is prerequisite for bridging the explanatory gap in psychiatry [7,15].

The progress in our investigations over the past six years has demonstrated that there exist different patterns of activation in the brain during items responses to diagnostic and neutral items from the relevant scales. That was confirmed on direct comparison with statistical parametric mapping (SPM) analysis of the activations with two samples t-test when compared patients with major depressive episode to healthy controls in terms of establishing sensitivity [15]. Further, the paradigm was complemented with paranoid items, and contrasts between patients with MDD and schizophrenia was established in terms of specificity [17].

Moreover, the BOLD signal is modulated in different ways on the level of group independent components analysis dependent on the diagnostic scale and the diagnostic group [17].

Further convergence of clinical and neuroimaging methods was validated by means of multivariate linear method. In that methodological framework, three modalities of magnetic resonance tomography are mapped together to produce multivariate signal: structural, functional resting state, and functional task-related MRI. In the first place, this approach has been applied to enhance the diagnostic precision on psychiatry by means of semi-unsupervised machine learning, which account for both clinical loadings and MRI biological

signatures of disease [18,19]. However, the same may be implemented into transformative data-driven model to inform drug choice and therapeutic monitoring as far as it incorporates a state-dependent clinical measure of depression (that is, sub-scale from paranoid-depressive scale).

From practical perspective, that would imply that the D-S (respectively PD-S) may be applied as a proxy-measure of the brain circuitry, thereby bridging the clinical assessment with the underlying mechanisms of disease.

The views expressed above are not uniformly accepted in the field. They present just one possible perspective, which takes into account some limitations, such as the ongoing replication crisis in the field [20], which restrains the application of task-related fMRI for stable prediction of the treatment response and its use for robust comparisons of different treatment strategies in terms of monitoring and outcome in neuropsychiatry.

Another global limitation that affects all fMRI studies, both resting state and task related, is the critical lack of standardized universal normative whole brain atlas in neuroimaging, based on large-scale samples.

It is clear now that reproducible MRI requires thousands of involved subjects [20]. Such a target apparently is out of reach for the purpose of selection and monitoring of therapy that require complex longitudinal designs and extraordinary effort. Furthermore, it is not the case with most of the previous investigations [21] as well as with our studies. However, Arnone [21] has summarized 31 research publications with sample sizes, which are comparable to our imaging studies. Treatment response has been determined using common fMRI tasks, which represent affective images (like emotional pictures or sad faces), cognitive tasks (like Sternberg and Stroop tasks), or self-judgment conditions, with consistent findings concerning hyperactivation of the amygdala and ventral components of anterior cingulate cortex, which predict treatment response. In effect, those tasks may well be regarded as projective tests and translated into clinical practice as proxy-measures of the brain activity to inform biological treatment strategies. In these ways, the therapy will be informed and eventually guided by evidence, which reflects the pharmacodynamics nature of depression, and its clinical correlates at the same time, which is the ultimate goal of the field.

In order to get closer to such goal, the field has to adopt more clinically relevant tests as fMRI tasks and/or translate findings with newly designed specific fMRI paradigms back to clinical reality as indirect measures of brain activity.

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