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Commentary

Embarking on antidepressant response prediction using brain perfusion estimation

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Major depressive disorder (MDD) is one of the most severe and disabling psychiatric disorders. Although considered a single entity, this disorder is highly heterogeneous. From the clinical standpoint, the polythetic definition of MDD allows hundreds of possible symptoms combinations to meet the MDD criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. Furthermore, biological evidence supports the idea of different neurophysiological subtypes of this disorder [2]. Antidepressant drugs, although with different mechanisms of action, have been shown to be more efficacious than placebo in treating MDD [3]. However, the current prescription of an antidepressant treatment follows a trial and error approach, which takes into account tolerability, safety, costs, and a history of positive response to a specific treatment [4] rather than evidence-based criteria. Not surprisingly, remission rates following antidepressant monotherapy are low, and each 8–12 weeks duration period of each subsequent antidepressant trial poses a high risk for developing chronicity [5]. The identification of pre-treatment biomarkers predicting treatment response to antidepressant drugs can reduce the number of unsuccessful trials and improve the quality of life of patients with MDD. Although recent advances in neuroimaging held promise for delivering such biomarkers, no consensus has been reached so far. Reproducibility, small sample size, methodological standards have hampered this research.

In this issue of *EClinicalMedicine*, Cooper and colleagues [6] report the results of an imaging study within the randomized placebo-controlled clinical trial Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) that was under-taken to identify imaging biomarkers of treatment response to 8-week administration of a selective serotonin reuptake inhibitor, sertraline, in chronic early-onset MDD. Baseline cerebral blood perfusion levels of large-scale networks, that have been found to be altered in MDD, resulted as moderators (i.e., pre-treatment variables predicting differential treatment outcome) of the brain response to treatment. In particular, limbic system perfusion (relevant for emotional and reward function) was associated with responses to both types of treatment; sertraline effects on depressive symptoms were associated with perfusion changes in distinct neural systems that are highly relevant for the cognitive and emotional aspects of MDD pathophysiology, such as the default mode [7] and associative networks. In contrast, placebo response moderators were located in frontal regions, which have been previously associated with psychotherapy response [8].

Cooper and colleagues sought to determine the clinical significance of their findings by estimating remission rates that would follow using a composite perfusion moderator computed across all the moderator regions in their sample and found a faster improvement and almost twice higher remission rates (defined as HAM17 score ≤ 7 at the last visit) in those subjects treated with the favorable perfusion-predicted treatment relative to those receiving the unfavorable perfusion-predicted treatment (53% vs 24% for sertraline and 49% vs 18%, respectively), with a medium-large effect size of the prediction for the composite moderator (0.557).

Key strengths of this research when compared to current literature are: the use of a non-invasive functional magnetic resonance imaging technique (i.e. arterial spin labeling) that provides a highly-reliable quantitative measurement of brain perfusion, the large sample size, and the availability of a placebo control group, which takes into account the inevitable and relevant unspecific effects of treatments in MDD.

Nevertheless, some critical points need to be considered: First, the absence of alternative active treatments (another antidepressant drug with a different mechanism, psychotherapy [8], neuromodulation [2]) limits the ability to perform a treatment selection yet. Second, although perfusion measures have high reliability, comorbidity and previous drug treatments warrant a further external replication of these findings to prove their generalizability [9], particularly in light of the lack of the efficacy of sertraline that shows a similar remission rate to placebo (33% vs 37%).

Still, the findings reported by Cooper and colleagues are important as they clearly point out that the outcome of the same treatment may be different in two individuals even with the same diagnosis. The future

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possibility that using a short and safe scan, available in most last generation MRI scanners, we can obtain a number of vital information for treatment selection that will save time and reduce disability and morbidity, that is paved in this study, is an important translational step from the neuroscience insights into the brain mechanism of a drug response and its clinical use to come up.

Future studies incorporating multiple biological variables (genetic, multimodal imaging, neuropsychology) [10] and treatments in moderators for guiding treatment selection, validated prospectively using randomized controlled trials, are warranted to meet the goal of precision medicine in Psychiatry.

Author contributions

F.S. and R.C.W. contributed equally to the design and writing of this commentary.

Conflict of interest statement

Neither of the authors has a conflict of interest with regard to this publication.

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