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Commentary

NEUROIMAGING AND THE FUTURE OF PERSONALIZED TREATMENT IN PSYCHIATRY

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Over the past decade, two parallel narratives have dominated the fields of clinical neuroscience and treatment outcome research in psychiatry. On one side, developments in neuroimaging methods have allowed an increasingly more sophisticated neurobiological understanding of the cognitive and affective processes perturbed in psychiatric disorders. It has also led to a questioning of the degree to which clinical diagnoses reflect distinct neurobiological mechanisms, especially within the domain of mood and anxiety disorders,[1,2] and whether alternative brain-based formulations should be used.[3] Small neuroimaging-coupled clinical studies have begun identifying signatures of treatment response,[4] which often look similar across disorders, but these studies typically lack important treatment control conditions.

On the other side, multiple large government-funded clinical treatment studies have been carried out, independent of potential commercial interests. However, these clinical trials have generally failed to reveal any clear difference in outcome between most types of treatment despite large sample sizes and modern experimental designs, with most of the patients experiencing only partial or no relief of their symptoms. Thus, despite theoretical differences between interventions (i.e. different medications or psychotherapies), there are few overall differences between their outcomes, with large differences between individuals.

We have thus now reached the point at which we can with more clarity only state the central question under-riding the field, rather than provide its answers, namely: How does understanding more about the brain through neuroimaging advance treatment outcomes for psychiatric disorders that have otherwise advanced little in decades?

BARRIERS TO THE APPLICATION OF NEUROIMAGING TOOLS FOR GUIDING TREATMENT SELECTION IN CLINICAL PRACTICE

The importance of individual differences in treatment outcome have opened the door to a personalized medicine approach wherein biological measures are used to predict who will respond to which treatment. As a consequence, there are now several large government- and industry-sponsored efforts underway aimed at using neuroimaging to predict individual differences in treatment outcome in depression.[5] Unlike the prior small-scale neuroimaging-coupled treatment studies, which generally included only a single open-label treatment arm, these new studies together will be well-enough powered and designed to begin drawing generalizable conclusions. The utility of neuroimaging in clinical practice, however, is presently limited by three obstacles: (1) the need for specialized training and equipment for its administration and analysis, which translates also into greater expense, (2) that subtle differences in data

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acquisition and analysis methods can result in dramatically different results, and (3) the fact that most antidepressant medication treatment is conducted by nonpsychiatrists with little or no training in neuroscience, and that carefully regimented psychotherapeutic interventions are hard to achieve in routine clinical practice.

Advances are already being made to develop MRI methods that are more quantitative and independent of MRI manufacturer and field strength.[6] This may allow similar acquisition of at least some types of neuroimaging data on any hospital or outpatient scanner. Developments in data analysis pipelines and convergence in the field on a relatively small number of experimental paradigms is likewise going to improve standardization and validation of predictive neural signals. Recent national roll-out efforts within the Veterans Affairs system in the US has demonstrated that high-quality and relatively standardized psychotherapeutic treatment is possible at scale within a high-volume health system.[7]Nonetheless, optimal solutions to these obstacles will take time to develop, and thus are not likely to yield tools that can directly guide clinical practice for at least 5–10 years. Moreover, the fact that most antidepressants are prescribed by nonpsychiatrists with little background in neuroscience represents a high bar for neuroimaging to overcome for its general acceptance and use in the treatment of mental illnesses. Arguably, little progress has been made in this domain. Moreover, whether an optimal neuroimaging predictor will prove cost-effective remains an open question that may not be answerable for sometime. Because the current studies are the first attempt at large-scale coupling of neuroimaging and treatment prediction, it is also not likely that they will even be able to generate definitive answers that will alone be sufficient to change clinical practice. In sum, as the literature develops to support potential routine clinical use of neuroimaging in guiding treatment selection, how might neuroimaging otherwise contribute to personalized medicine in psychiatry?

NEUROIMAGING AS A "COMMON LANGUAGE" FOR PSYCHIATRIC THERAPEUTICS

Arguably the biggest limitation in the development of therapeutics in psychiatry is that interventions have been developed in parallel, guided by varied theoretical bases. As such, interventions do not "speak the same language" in which their mechanisms of action (and personalized application) can be compared, leaving us only able to compare their average clinical effects. Absence of a common language also results in intervention being further refined without the context of how other interventions work, or even of the validity of the theories driving design of the intervention. Thus, long before neuroimaging will become a tool for routine clinical practice, it can provide answers to key questions around the mechanisms of therapeutics and a common language in which to compare them.

It has long been debated, but never convincingly answered, to what degree and in which ways are antidepressant psychotherapy and medication treatments similar or different. One idea holds that psychotherapy involves "top-down" prefrontal processes, while medication involves "bottom-up" limbic processes,[8] however evidence in support of this hypothesis is scant. It is unknown how different antidepressant medications, which all share common pharmacological processes (e.g. serotonin signaling) but diverge in others (e.g. norepinephrine signaling) compare at the level of effects on the brain. Similarly, effective psychotherapeutic interventions for the same disorder may be based on different theoretical foundations (e.g. exposure- vs. cognitive-based therapies for posttraumatic stress disorder), but whether their theoretical bases and mechanisms of action are dissociable remain unknown and untested. Finally, there is no consensus as to whether any particular treatment works by normalizing abnormal neurobiology or is effective by virtue of it recruiting intact neural pathways.

NEUROIMAGING TO DEFINE THE TARGETS OF TREATMENT

By establishing a common language for interventions, neuroimaging will yield neural circuit-level signatures that predict and change with successful treatment. As such, these signatures can themselves be targets of interventions, even if they were derived through the study of an entirely different intervention. For example, pretreatment activity in the anterior cingulate and medial prefrontal cortex appears to predict outcome with a range of antidepressant treatments,[4] suggesting that this neuroimaging signature may be a neural circuit target around which interventions can be developed. Indeed, conventional repetitive transcranial magnetic stimulation (rTMS) appears to also target this circuitry, wherein outcome is predicted by resting-state connectivity of this region, and rTMS in turn alters its connectivity.[9] Unlike for medications, however, the locations to which rTMS is applied, and ways in which neuromodulation occurs, can be readily adapted even from patient-to-patient. Thus, by establishing the cingulate and medial prefrontal cortex as a treatment target, next-generation neuromodulatory treatments can be designed and refined based entirely on their ability to optimally modulate this neural target. This perspective is consistent with the "experimental medicine" approach recently advocated as the best path for the development of new treatments.[10] Here, neuroimaging would be used to measure the neural circuit target of treatment, much like neuroreceptor binding in cell culture can define a cellular target for a medication treatment. Likewise, neuroimaging could serve as neurobiological validation for more easily acquired proxy measures, such

as behavioral performance on a relevant task. New interventions can then be tested for their ability to affect specific neural circuit targets, with further optimization supported by these neuroimaging readouts, even if the target was initially derived from studies of completely different interventions.

CONCLUSIONS

The use of neuroimaging as a tool for personalized treatment in psychiatry has often been treated with skepticism because of the obstacles identified above, though this view originated from the expectation that the primary outcome of neuroimaging-coupled clinical trials should be creation of a clinic-ready, sufficiently low-cost, assessment tool. Here I argue that while this is an exciting potential outcome, neuroimaging will have a major impact on personalized treatment even if it does not become a routine test in general clinical practice. Rather, neuroimaging will be fundamental to our ability to contrast the mechanisms of action of different interventions and begin to understand whether effective treatment occurs through normalization of information processing abnormalities, or engagement of unimpaired compensatory pathways. Moreover, neuroimaging will define the neural circuit-level targets of treatment and will serve as a marker of the efficacy with which those targets are impacted by new or adapted interventions. Thus, neuroimaging will no doubt form the basis of neural circuit-level experimental medicine approaches critical to the expansion of the psychiatric treatment armamentarium.

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