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Beyond Depression Commentary: Wherefore Art Thou, Depression Clinic of Tomorrow?

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Abstract

An exciting review in this issue (Forgeard et al., 2011) highlights a number of emerging themes in contemporary translational research in this area. A primary challenge for the next generation of researchers reading this work will be how to carry out the grand charges levied by Forgeard et al., on the ground, i.e., to lay the foundations for moving the emerging basic science of depression into the Depression Clinic of Tomorrow. Addressing these challenges could suggest changes in the nature of the basic science, and questions that are being asked, and employed approaches in contemporary depression research. Preconditions for clinical adoption discussed in the review include 1) beginning to hold neuroscience-based measures of features of depression to the same standards held for other depression measures in the clinic, 2) attending to how the proposed methods might actually end up being feasibly imported into the clinic, and 3) what interventions targeted at mechanisms of depression might look like in the next decade.

Keywords

Cognitive Therapy; Neurobehavioral Treatments; Mood Disorders – Unipolar; Brain Imaging Techniques; Cognitive Neuroscience; Emotion

An exciting review in this issue by many of the luminaries in depression research (Forgeard, et al., 2011), highlights a number of emerging themes in contemporary translational research in this area. These themes span mechanistic explanations of psychological constructs such as learned helplessness to the need for transdiagnostic process-related thinking at a biological level, ending with a call to bring these themes into actual depression clinics, e.g., using novel neuroscience-inspired behavioral interventions to target specific mechanisms. This vision of integrating basic science with clinical care is the way that other medical disciplines have increasingly successfully gone, and takes steps towards realizing the ultimate dream of the National Institute for Mental Health's current Strategic Plan. Forgeard et al. have noted that the basic research is there – we increasingly know what mechanisms to target, and, in many cases, how to target them.

A primary challenge for the next generation of researchers reading this work will be how to carry out the grand charges levied by Forgeard et al., on the ground, i.e., to lay the foundations for moving the emerging basic science of depression into actual clinics. In some sense, this should be easy. Survey research suggests that both patients and providers are crying out for neuroscience, particularly, brain scans, to be adopted into the psychiatry clinic

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(Illes, Lomber, Rosenberg, & Arnow, 2008). In that study, respondents professed that with strong inputs from neuroscience, patients believe they would follow clinical recommendations, attend therapy more regularly, do their therapy homework, take their medications, etc. Yet, following decades of mechanistic research including much predictive work, no biomarker has been adopted clinically for depression treatment. Rather, treatments are designed conceptually or follow outlines written decades before the current prevailing neuroscience, prescribed almost at random (usually based on provider expertise or experience), and evaluated almost entirely by patient self-report.

So, there remains a “hopefully temporary gap that now separates the clinician from the research worker” (Zubin, 1955). Here, I consider recommendations in Forgeard et al.’s review with a strong eye towards eventual clinical adoption. The basic conclusion will be that under such a perspective, even our basic work might have a different flavor. I will specifically address ways we might prepare for the Depression Clinic of Tomorrow by concentrating on preconditions for clinical adoption of the work discussed in the review including: 1) beginning to hold neuroscience-based measures of depression features to the same standards applied to other measures in the depression clinic, 2) attending to how the proposed methods might actually end up being imported into the depression clinic at the level of implementation, and 3) considering what interventions targeted at mechanisms of depression might look like in the next decade

Selecting Instruments for the Depression Clinic of Tomorrow: Holding Translational Neuroscience to the Standards of Other Clinical Instruments

There are well-developed standards and methods for instruments used in evaluating clinical states and outcome (e.g., Fredrikson & Furmark, 2003). Inclusion of measures such as questionnaires or rating scales in endeavors such as clinical trials is based on adherence to these standards. As we have developed the basic technologies for measuring aspects of brain function we have attended largely to the exciting possibilities of the science. If we are to begin incorporating measures such as neuroimaging into clinical trials, cognitive neuroscientists too will have to attend to these basic standards. First looks at the literature suggest that indeed, neuroimaging has not been held to the same standards as more common self-report and rating-scale measures (Frewen, Dozois, & Lanius, 2008), including considerations of basic psychometric properties such as attention to rigorous scale construction, test-retest reliability, and internal consistency. There are many reasons why these criteria may not have been imposed in the past, particularly due to expense, the very small numbers of participants typical of neuroimaging studies, lack of availability of standard measures, lack of statistical programs for calculating relevant measures, and frankly the fact that psychometrics are among the least exciting parts of clinical research; neuroimagers are accustomed to living in the most exciting of the field’s moments. I suggest that by attending to these features, the neuroscience of depression will become even more exciting because someday, someone other than a neuroscientist might even avail themselves of what it has to offer. Attending to these features will also improve our basic science.

For example, consider scale construction. Forgeard et al. discuss many candidate psychological and neural mechanisms that could be included in a patient-based assessment of aspects of depression, from self-report assessments of constructs like learned-helplessness (e.g., attributional style measures) to process-based measures of psychological constructs (e.g., behavioral assessments of attentional and memory biases for negative information) to neuroimaging assessments of relevant constructs like amygdala reactivity and prefrontal control. How these measures will or should fit together in the forthcoming clinical world is unclear. The state of the art in neuroimaging papers is to correlate imaging data with self-report. This speaks broadly to relatedness among measures but does not describe their

complementarity. Rather, clinicians regularly suggest that self-report and interview-based measures provide insights that we might not think to look for with brain imaging. Thus, a challenge for upcoming research will be to consider how to integrate self-report, behavioral, physiological, and imaging data at the level of the clinic, and specifically, to understand the complementary potential *clinical* roles of each type of measure. Taking this type of approach would likely mean a change in basic analytic approaches from t-tests and correlations to more interesting aspects of variance parcellation. Considerations such as the following could emerge: 1) What complementary data do self-report, behavioral, physiological, and neuroimaging data provide? 2) At what point do we “need” neuroimaging data to help guide treatment? 3) Are there behavioral or physiological proxies for concepts such as learned helplessness that would provide as much information as neuroimaging in some circumstances? 4) Once a clinician has done excellent assessment with self-report, what piece of an essential clinical picture of depression does a neuroimaging assessment fill in?

Consider also reliability. Discussions in Forgeard et al. centered around the potential for going to, e.g., a “prefrontal cortex” specialist. This marvelous notion is predicated on the idea that we can: 1) measure deficits in prefrontal function, 2) perform an intervention, and then 3) re-measure the deficit to see whether it changed, in single patients. Without that ability the utility of the prefrontal technician cannot be assessed. But the ability to measure change is entirely predicted on the stability of the measurement technology. That is, first we must be able to show that an individual not undergoing the intervention is likely to display the same indices of prefrontal on different days. Neuropsychological measures are held to this standard, but their specificity to the mechanisms discussed by Forgeard et al. are unclear. In contrast, imaging studies to date rarely report reliability of their primary measures, and certainly this is not a requirement, even for pre-post imaging studies. To increase adoption it will thus be useful to incorporate multiple baselines and multi-time-point assessment, particularly, of controls in assessments to be used in the Depression Clinic of Tomorrow to document reliability. In particular, showing reliability of individual differences for quantities of interest to Forgeard et al. that are most questionable in fMRI assessment will be key. For example, Forgeard et al. discuss activity in the lateral habenula, an area of dorsal thalamus associated with reward processing, which, until recently, was believed to be impossible to image; as imaging technologies improve showing that assessments of such key structures are both reliable and valid will be key to their clinical adoption.

Finally, consider validity. The primary focus of Forgeard et al.’s discussion regards construct validity – the notion that measured constructs represent something important in the world. It begins with a discussion of validation for the idea of learned helplessness, a psychological construct which has been around for decades, and progresses through discussion of various depression subtypes. What these different features have to do with one another (e.g., are they orthogonal?) is a matter for integrative science to pursue. For example, Dr. Mayberg describes phenomena of increased limbic reactivity and decreased prefrontal control in depression. These are two well-researched processes and compelling data support each in depression. But there is little data suggesting they occur in different people. Rather, connectivity data suggests that the same people with increased amygdala reactivity also have decreased prefrontal control (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), possibly as a function of a single latent feature, abnormal connectivity between these systems. This distinction is important for eventual clinical translation because it will suggest whether a single processes will be of interest, in which case we would develop treatments for it, or two processes exist, in which case we might want to treat each, separately.

A suggestion, then is to consider what dimensions might appear on a clinically-relevant neuroimaging-derived clinically-relevant depression profile. Research working toward profiles of a “whole depressed person” rather than a single construct may have more clinical utility than research geared towards traditional research questions. For example, would we want to report on a given patient’s amygdala activity in response to negative information, in concert with their prefrontal regulatory control, in addition to their nucleus accumbens activity to reward, insula response to interoceptive cues, etc.? Subtyping patients across these dimensions could suddenly become more interesting than the usual single-task or resting-state based assessments common in today’s neuroimaging endeavors.

Making Assessments Feasible for the Depression Clinic of Tomorrow

Thus far, we have considered how basic research on processes discussed by Forgeard et al. might change to become more clinically relevant. But we have not considered the idea of whether clinicians would actually adopt that work even if it were relevant. Last year I asked Dr. Beck when he thought pre-treatment scans would make it to the depression clinic. His response was that “pre-treatment scans would be great. But I’d just like to get clinicians to use the BDI!” Frankly, despite decades of research on the importance of assessment of individual differences in concepts as basic as severity, their assessment has not routinely become part of the clinic.

So, what, in addition to reasonably reliable and valid instruments will it take? I suggest a number of goals are in order, many of which are rarely considered in neuroscience-based studies of depression.

1. Standardized databases. The only way that clinical instruments find utility in other areas is because we know what “normal” and “abnormal” mean with respect to a given patient of a given age, gender, education, SES, etc. Building such databases for translational, e.g., neuroimaging assessments, (i.e., requesting enough money in our grants to allow these corpi to be built for indices we believe in) will be key to making the instruments into something clinicians might want to use. Importantly, this will entail reporting our data differently. fMRI data are reported in difficult-to-understand units such as “percent change” from an arbitrary baseline. PET data are reported even more idiosyncratically. Reporting our data in an interpretable way, e.g., in Z-scores reflecting standard deviations away from the mean of healthy individuals would make our new technologies accessible to clinicians and patients, so ideally, they could interpret “amygdala activity” without getting a new Ph.D. Of course, this will involve solving rarely discussed but ever-present technical problems like how to equate neuroimaging data across scanners, unless we want patients to fly to a single location that acquired the normed corpus for each assessment.
2. Creating clinician-understandable reports on neuroscience-based features. If learning that it is important to go to the prefrontal technician takes a radiologist’s skilled interpretation of a blob-filled brain image, this model is unlikely to catch on. Rather, pairing imaging or other neuroscience-based tests with easy-to-interpret guidelines for how to use them will be key. Automated reporting of fMRI data, particularly in the domain of depression where the field has barely agreed on relevant assessments, is a nascent science with much room for growth.
3. Making the technologies affordable. I’ve been asking clinicians what it will take them to put the kinds of assessments described by Forgeard et al. in their clinics. They say it has to be “less than 30 minutes, under \$300, and easy for the non-scientist to order.” So we have our work cut out for us. There are a few ways to go here. Lobbying, as clinicians, for insurance to reimburse for pre-treatment

neuroimaging will be a first step following gold-standard studies (hint, the CPT codes already exist!). And figuring out where assessments like fMRI fit into the broader array of technologies-of-the-future in understanding whether to send someone to a prefrontal or limbic specialist will be key. Accounting for little features like patient preferences will surely be huge in this regard.

Mechanistically Targeted Treatments in the Depression Clinic of Tomorrow

So what will the treatments be like in the Clinic of Tomorrow? Clearly, a goal will be to target identified mechanisms. Ideally, these targeted treatments will be based on a pre-treatment assessment rather than according to the random prescriptions and treatment deliveries of convenience that pervade today's clinics.

Initial forays into such targeted treatments are beginning to emerge. Treatments targeted at cognitive mechanisms have begun to innervate the research world, including exercises addressing attention biases (MacLeod, Soong, Rutherford, & Campbell, 2007; Schmidt, Richey, Buckner, & Timpano, 2009), memory biases (Joormann, Hertel, LeMoult, & Gotlib, 2009) and prediction of negative outcomes (Holmes, Lang, & Shah, 2009). They are not yet used routinely in clinics. Similarly, as Dr. Davidson noted, neurally inspired treatments, alternately called “neurobehavioral therapies” or, inheriting from our colleagues in neurology, “neuropsychological exercises” have gained intense interest in the past decade (Siegle, Ghinassi, & Thase, 2007). These treatments target specific brain mechanisms. For example, we have explored the potential for increasing prefrontal emotion regulation simply by completing cognitive non-emotional tasks known to activate relevant prefrontal regions (Siegle, Ghinassi, et al., 2007). To date, there are few demonstrations that these interventions actually improve function in the mechanisms toward which they are targeted, and particularly little evidence that they work best for the people with the mechanisms who need these specific interventions. Thus, we have our work cut out for us before we can send our patients to the prefrontal or habenula specialist. But we are working on it.

A final literature which is beginning to emerge regards the potential for neurofeedback associated with specific brain structures or circuits. The new technology of real-time fMRI has allowed us to begin training depressed participants to decrease activity in the subgenual cingulate (Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011), and amygdala (Johnston, Boehm, Healy, Goebel, & Linden, 2010) and other areas that recurred throughout Forgeard et al.'s conversations. Yes, there are no studies of these features in clinical populations, pervasive methodological limitations, and huge expense for these technologies. But in the words of Bruce Cuthbert, “we believe it will go swimmingly. Though we may swim slowly.”

The Patient Experience in the Depression Clinic of Tomorrow

Together, the suggestions above give a roadmap towards the Depression Clinic of Tomorrow and a vision of what it might look from the eyes of a patient entering that clinic. Imagine that a patient walks in the clinic door having uploaded a series of questionnaires, reaction times, and judgments from on-line assessments. A clinician, after interviewing the patient and viewing the assessments, concludes that the patient experienced early trauma, leading to possible learned helplessness. But how ingrained that learned helplessness is, and whether it can be modified behaviorally is not clear. So, the clinician orders a quick behavioral and fMRI assessment of the patient to determine the extent of connectivity among regions associated with threatening stimuli and the reactivity of regions associated with adaptive avoidance responses, to assess the level of the patient's pathology. The clinician observes that the patient retains the motivation to escape behaviorally from initial mild threat stimuli, and that initially their escape systems activate, but gradually with

increasing threat these systems appear to decrease in activity. Comparing the data to norms for healthy individuals, the clinician concludes that the patient has but a mild case of learned helplessness that can easily be deconditioned. The patient is sent home with a smart-phone downloadable application in which he is rewarded for escape from repeated threat. Three weeks later another imaging session confirms decreased habituation in the patient's escape system and the patient is on the road to recovery.

I personally look forward to being part of constructing the Depression Clinic of Tomorrow, and sincerely thank Forgeard et al. for helping the field to move in the directions necessary to make this clinic a reality.

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