$50M Wellcome Leap Program
Multi-Channel Psych: Revealing Mechanisms of Anhedonia

Depression is a complex biological illness. We need treatments to match.

The latest worldwide survey of global health underscores the devastating impact of depression.[i] Depression was ranked as the 3rd highest cause of disability across **all** illnesses, resulting in approximately 43 million years lost to disability (YLD). In only a single year, 264 million people suffer from depression, and 800,000 lives are lost to suicide. Narrowing in on the United States, almost 7% of adults experience an episode of depression each year, costing an estimated $210.5 billion due to the combination of treatment costs and productivity loss. Consistent with this enormous disease burden, the NIH has spent over $22 billion on depression research over the last 20 years – more than for any other mental illness, including addiction, schizophrenia, or autism.[ii] But despite this massive investment, only 1 in 3 patients substantially responds to currently available medication or psychotherapy treatments.[iii,iv]

Why are we stuck?

The modern practices of psychiatry and psychology are grounded in neuroscience and biology. We understand that synaptic connections serve as the currency of neural communication, and that strengthening or weakening these connections can facilitate learning new behavioral strategies and ways of looking at the world. Through studies in both animal models and humans, we have discovered that emotional states are encoded in complex neural network activity patterns, and that directly changing these patterns via brain stimulation can shift mood. We also know that disruption of these delicately balanced networks can lead to neuropsychiatric illness.

Based on this understanding that psychiatric symptoms are rooted in biology, all existing drug therapies for depression target biological mechanisms.[v] Selective serotonin reuptake inhibitors (SSRIs) bind to the serotonin transporter, leading to increased serotonin concentration in the synaptic cleft and a cascade of downstream functional and structural consequences.[vi] Although the exact mechanism of action of the fast-acting antidepressant ketamine is still being investigated, it is known to be an NMDA-receptor antagonist.[vii] Brexanolone, which is the newest FDA-approved antidepressant for the indication of post-partum depression, is a neuroactive steroid that is a positive allosteric modulator of the GABA receptor.[viii] We have now even solved the crystal structures of psychiatric drugs binding to their targeted receptors.[ix] Since at least the 1960's, with the first indications that alterations in levels of catecholamines such as dopamine can lead to depressed mood[x], we have known that depression is biologically based, and that treatments need to address these underlying biological problems.

Yet, these biologically based treatments are not being matched to the biology of the human beings they're being used in. According to standard treatment guidelines currently recommended by the American Psychiatric Association[xi], the first-line pharmacotherapeutic treatment for depression is a randomly selected SSRI. And if that doesn't work, the next step is switching to another randomly selected SSRI, followed by augmentation with an additional agent or switching to an alternative medication class. It is a brute force process guided almost

exclusively by qualitative data and subjective self-report. And the impact of each new medication change can take between 2-6 months to assess. This current state of affairs leads to time lost for both patients and their loved ones, unnecessary side effects, discouragement, and – perhaps most importantly – continued progression towards end-stage illness.

What needs to change?

To make meaningful change, we need to match treatments to the specific biology of the people receiving them. But when field experts are presented with this challenge, three gauntlets are typically thrown down. First, there is a lack of easy access to the biological substrate of depression – i.e., the brain – which makes it difficult to determine pathologic mechanisms. Unlike in the field of cancer, the brain is not easily biopsied, and even if it could be, the abnormalities leading to symptoms are likely distributed over broad neural networks. Second, it can be difficult to tell when treatments for depression are working due to noise in the system. As opposed to determining quantitatively if a tumor has shrunk, treatment efficacy for depression relies on subjective self-report. But any practicing clinician will tell you that family members often notice changes in symptoms such as psychomotor slowing and affect even before patients do themselves. And the third, most daunting gauntlet is – It's Just Too Complex. Depression is a heterogeneous disorder, with an unknown number of different subtypes that may have different treatment responses. The brain is an incredibly complex organ that is composed of an unknown number of different cell types, intricately networked together to supervise all of the body's functions. The brain is situated in the body, which in turn is situated in the world. And the two major collective traumas of 2020 – the COVID-19 pandemic and systemic racism – have made it all too clear that the body and the world can directly impact the brain, leading to depression. The barriers are evident. So, it is now time for the field to take up the gauntlets together, and take down these obstacles.

Why now?

There is increasing recognition that severe treatment-resistant depression is enriched for anhedonia, a symptom that may help us constrain the complexity associated with investigating the heterogeneous diagnosis of depression by synchronizing our efforts within a restricted target population. Anhedonia, operationally defined as an impairment in the effort-based reward system[see Note 1], is a key symptom of depression and other neuropsychiatric illnesses. It is a negative predictor of treatment response, and can be quantitatively assessed via distal "honest signals"[xii] detected using reproducible neurocognitive tasks that can be translated between humans and animal models. Anhedonia can therefore be used as a quantitative surrogate for efficacy of interventions in treatment-resistant depression. And if we can substantially move the needle on anhedonic depression, we can bring the overall number of treatment-responsive patients from 1 in 3 to 1 in 2.

The potential utility of anhedonic depression as a use case is highlighted by several emerging discoveries related to biological causes of depression. In a small study of severely anhedonic adolescents and young adults with significant suicidality, 21/33 people had an identifiable metabolic abnormality in their cerebrospinal fluid (CSF) on spinal tap compared to 0 healthy comparison subjects, and an existing treatment to correct a metabolic deficiency was available for 12/33.[xiii] Critically, blood metabolite levels were normal, so invasive access to the central

nervous system was essential for detection. Restoration of this metabolite to normal levels led to a clinically significant drop in anhedonic depression and suicidality in 60% of patients.

Another recent study using unbiased hierarchical clustering in a large resting state fMRI connectivity sample found that people with depression can be subdivided into four neurophysiological 'biotypes', defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks.[xiv] Biotype classification was able to prospectively predict response to repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex. Strikingly, the biotype that was least responsive to treatment was defined by the presence of anhedonia, psychomotor slowing, and abnormal connectivity in brain networks that support reward processing and action initiation.

Turning to animal models, significant efforts have focused on dissecting the mechanism of action of the new fast-acting antidepressant ketamine, a treatment that has shown efficacy in severe anhedonic and suicidal depression.[vii] Using technologic advances that allow *in vivo* longitudinal monitoring of individual synaptic spines, a recent study tracked the growing and shrinking of synaptic connections in the prefrontal cortex before and after ketamine treatment.[xv] Contrary to initial expectations, new synaptic connections were not necessary to *generate* ketamine's antidepressant effect in this animal model of anhedonia, but they were necessary to *sustain* behavioral recovery. From this work we can calculate that maintenance of a 10% increase in spines is needed to sustain a non-anhedonic behavioral response. If non-invasive markers of synaptic plasticity can be developed in people, this type of metric could serve as a quantitative benchmark for assessing efficacy of behavioral therapy interventions.

These examples show what is possible, and what remains to be done. Identification of a target population enriched for anhedonia and corresponding to the sickest of the sick may ironically facilitate our success. These are the people we most urgently need to help, because time is ticking – they are progressing inexorably forward on a path towards terminal disease, and early treatment intervention in recurrent depression can reduce the length of each successfully-treated episode by 4-5 months.[xvi] If we can identify specific biological problems underlying anhedonic depression and correct the abnormalities, we can make sorely needed gains. And detection of previously unknown CSF abnormalities, predictive stratification of large patient samples, and identification of possible mechanisms of action underlying fast-acting antidepressants highlight how advances in high-throughput omics, sophisticated analysis of neuroimaging datasets, computational modeling, and precise mechanistic experiments in animals may put us in reach of these goals. However, to succeed, our strategy must shift, because insights and advances across the field are currently scattered and piecemeal in nature, due in part to specialization at particular levels of investigation and lack of communication between experts in different silos (e.g. gene, cell-type, circuit, metabolome, microbiome, animal model, human). While discovering the underlying causes of anhedonic depression across multiple levels of investigation, it is therefore essential to simultaneously build a computational framework to integrate "internal" causes with "external" quantitative correlates of symptoms to develop an explanatory and predictive end-to-end model.

Program goals.

We envision a world in which diagnosing anhedonic depression is as straightforward as

getting a mammogram, and stratification into a treatment plan has the same speed as current algorithms after breast biopsy. This necessitates a general shift of mindset in an important way. Depression can be a terminal illness, just like breast cancer. Rapid, targeted intervention is therefore vital to prevent progression. Initially selecting the treatment with the highest likelihood of working for an individual patient based on their specific biology is therefore of high value, because in addition to decreasing the total time of suffering, key goals include avoiding unnecessary side effects and limiting treatment-associated risks.
To that end, our goals are to achieve:

1. **Rapid patient stratification and treatment matching**: Develop an integrated model of anhedonic depression capturing both internal biological factors and externally-manifested and quantifiable symptom-correlated biometrics and behavioral measures. This model should stratify people into those who will be treatment sensitive and those who will be treatment resistant with 80% accuracy, consistent with the current 20% false negative rate for mammograms.[xvii] The model should also be sufficient to match responsive patients to their appropriate treatment regimen rapidly, including novel or existing behavior modification, psychotherapy, medication, and neurostimulation options. Currently 33% of depressed people have significant symptom reduction with the initial treatment selected, while an additional 21-33% of people require between 2-4 treatment trials to achieve remission.[xviii] Our goal is to **double the number of people who receive an effective treatment on the first try.**
    - The model should capture multiple levels of investigation (e.g. genome, phenome, network connectivity, metabolome, microbiome, reward processing, plasticity levels, HPA axis function).
    - The model should seek to leverage high frequency patient-worn or in-home measurements in addition to those obtained in the clinic, hospital, or laboratory.
    - The integrated model should predict the relationship between genome, metabolome (particularly, but not exclusively, from CSF), microbiome, and resting-state connectivity to anhedonia symptoms, reward processing, and treatment response in depressed individuals.
    - Predictive validity should be verified in new cohorts either held out from existing samples or collected during the study period.
2. **Identification of mechanisms underlying treatment-resistant anhedonic depression**: Define the biological basis of anhedonic depression with the goal of **identifying effective treatments for half of non-responsive patients**, as measured by a decrease of ≥50% on current gold-standard suicidality, depression, and anhedonia scales (HAM-D, BDI, SHAPS). We are particularly interested in developing patient-personalized data-driven "Intensive Care" treatment regimens – inclusive of both new and existing lifestyle, drug, psychotherapy, and device interventions – that reduce suicide risk in the top quintile of patient severity. High density behavioral measures should be used in this high-risk population to intensively track symptoms and environmental factors (exercise, sleep, social interactions, etc.) in those who are the most likely to progress to terminal illness, with a goal of developing patient-controlled "alarms" to trigger suggestions to seek help or more intensive interventions. Our intent is to have the same impact on the survivability of severe, treatment-resistant depression that advances in diagnostics and treatment

have had on the survivability of breast cancer. Namely, we want 85% of people to survive their suicidal anhedonic depression for at least 5 years– and perhaps a full lifetime– after diagnosis.[xix]

Note that a cross-disciplinary and cross-institutional collaborative effort focusing on anhedonic depression will allow us to build bridges between experts in different areas, and synchronize investigations across levels (e.g. genes, molecules, cells, animal models, humans) from the very beginning of the program. Thus, it is **not necessary or desired** to form a large consortium or team to address all facets of the program goals (see Thrusts below), since the strength of this approach will manifest through program-level integration of efforts from individuals and small agile teams with deep and sometimes narrow expertise. Across all projects, Wellcome Leap will facilitate iterative and collaborative integration of findings to refine models and improve and validate predictive measures, and adapt approaches as our teams make progress together towards our shared goals.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over 3 years (with a potential additional one-year option) in one or more of the following thrust areas. Proposers should clearly relate work in these thrust areas to one or more of the program goals.

Thrust Area 1: Identify biological markers of mechanistic causes of anhedonic depression

To date, patient stratification to aid in treatment selection has not been performed in routine clinical practice. In the few instances where biological measures have successfully been used to predict treatment response, large sample sizes have typically been required, limiting the ability to deliver individualized care. On the other end of the spectrum, spinal taps have recently been proposed as a potential tool for detection of metabolic deficiencies underlying severe anhedonic depression, but the invasive nature of the procedure, lengthy turnaround times for test results, and lack of available laboratory tests for rare abnormalities limits large-scale adoption and integration into typical clinical practice.

To advance treatments, we need to identify biological markers of anhedonic depression. Objective biological markers can point to disease mechanism, and in some cases can even indicate what needs to be corrected. But a mechanistic understanding of what leads to biomarker alterations in each individual case is necessary to determine the most effective and efficient solutions, since interruptions at many different points in one particular pathway can lead to indistinguishable biomarker outputs.

- We seek performers and small teams specializing in biomarker identification at one or more levels of investigation–i.e., metabolome, genome, epigenome, hormones, connectome/resting state networks, network oscillations, microbiome, and phenome. Although studies in humans will be prioritized, studies in animal models (including rodents, non-human primates, and less conventional model systems) may be considered if they provide an essential translational bridge to achieve program goals.

- We have specific interest in developing methods to measure capacity for synaptic plasticity in anhedonia-relevant brain regions in a) people with anhedonic depression in the depressed vs. recovered state, and b) in people with anhedonic depression compared to unaffected people. Coupling these metrics with direct or indirect measures of neuromodulators including dopamine and serotonin and obtaining ground truth via *in vivo* human recordings will be particularly prioritized. Animal models may be needed to validate these measures.

- Based on evidence that the interface between the periphery and the brain may be a key culprit in depression and potential barrier to its effective treatment, we encourage applications exploring the relationship between anhedonic depression, its treatment, and previously less-explored systems such as the blood-brain/ blood-CSF barrier.

- Note, we are not interested in studies using single-gene knockout mouse models to dissect mechanisms underlying anhedonia. However, we will consider applications that develop and use complex and unique animal model systems for mechanistic tests that support the program goals (e.g. polygenic models, ethologic models).

Thrust Area 2: Quantify symptoms objectively and with high frequency

Obtaining high frequency quantifiable "honest signals"[xii] of subjective symptoms is central to our goals. These honest signals will support our modeling efforts by allowing us to both identify a ground truth for biological causes, and also objectively monitor how symptoms change in response to novel treatments.

- Develop new scalable measurement tools for reliable and high-density quantification of mood (both subjectively reported and objectively quantified via biometrics such as voice, facial expression, etc.), sleep, movement, reward system functioning, effort/motivation/energy levels, social interaction, caloric intake, and HPA axis output in real-world situations. Increasing the frequency of sampling in a more natural environment (i.e. not the lab or the physician's/ therapist's office) is crucial.

    - We specifically encourage the development of non-invasive technology to directly interrogate human brain state. Examples include, but are not limited to, a non-invasive spinal tap equivalent (i.e. reading out CSF metabolites without requiring a lumbar puncture); behavioral or biomarker probes of neural plasticity that can be repeatedly administered to both properly time interventions and monitor their efficacy; and single-session neural monitoring capabilities that define a treatment-predictive brain state within a single subject.

    - Studies that correlate high fidelity technology-intensive measures (e.g. high-resolution fMRI, *in vivo* electrophysiology in humans) with low-cost easily deliverable screening measures are of significant interest.

Thrust Area 3: Develop end-to-end model(s) of anhedonic depression

Finally, we need to integrate these internal and external factors – the internal biological mechanistic causes and their external phenotypic manifestations – to first build and then test end-to-end predictive models of anhedonic depression. A successful end-to-end model will allow us to identify the best treatment(s) for an individual patient with fewer rolls of

the dice – i.e. there will be a shorter time constant to achieve the most effective treatment regimen.

- The overall predictive model architecture should contain and interconnect the levels of granularity captured in Thrusts 1 and 2 – e.g., genes, molecules, cells, systems, environment. Different types of models – e.g., heuristic, machine-learning, circuit, etc. – may be necessary to provide understanding at particular levels. However, these sub-models should then interact, integrate, and therefore ladder up into an overall predictive model. Note, models that cannot integrate with an overarching framework– e.g. circuit models in isolation – are not of interest.

- Once developed, models should be used to test and predict the impact of at least the following factors on a) anhedonia symptoms, b) reward processing, and c) treatment response in depressed individuals: genetic variants associated with abnormal metabolism in neurotransmitter pathways (e.g. MTHFR), synaptic plasticity (e.g. BDNF), or other new pathways of interest identified in Thrust 1; candidate metabolites and resting state biotypes identified in Thrust 1; levels of synaptic plasticity; and high density behavioral and biometric measures from Thrust 2.

- We anticipate that these models will be exercised every 6 months during the performance period. Output and learnings will then be fed back into the program to both inform ongoing work in Thrusts 1 and 2, and flag new channels for investigation.

FOOTNOTES:

[1] Note that while there are many definitions of anhedonia, we are less interested in the investigation of reduced consummatory pleasure, the general experience of pleasure, or the inability to experience pleasure. Rather, as per the description above, we will prioritize investigations of anhedonia as it relates to impairments in the effort-based reward system– e.g. reduced motivation to complete tasks and decreased capacity to apply effort to achieve a goal.

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