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Convergence, preliminary findings and future directions across the four human connectome projects investigating mood and anxiety disorders

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Abstract

In this paper we provide an overview of the rationale, methods, and preliminary results of the four Connectome Studies Related to Human Disease investigating mood and anxiety disorders. The first study, “Dimensional connectomics of anxious misery” (HCP-DAM), characterizes brain-

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Declarations of Competing Interest

The Authors have no conflicts of interest to declare.

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Leonardo Tozzi: Conceptualization, Writing – original draft, Writing – review & editing. **Esther T. Anene:** Writing – original draft, Writing – review & editing. **Ian H. Gotlib:** Writing – review & editing. **Max Wintermark:** Writing – review & editing. **Adam B. Kerr:** Writing – review & editing. **Hua Wu:** Writing – review & editing. **Darsol Seok:** Writing – review & editing. **Katherine L. Narr:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Yvette I. Sheline:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Susan Whitfield-Gabrieli:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Leanne M. Williams:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

symptom relations of a transdiagnostic sample of anxious misery disorders. The second study, “Human connectome Project for disordered emotional states” (HCP-DES), tests a hypothesis-driven model of brain circuit dysfunction in a sample of untreated young adults with symptoms of depression and anxiety. The third study, “Perturbation of the treatment resistant depression connectome by fast-acting therapies” (HCP-MDD), quantifies alterations of the structural and functional connectome as a result of three fast-acting interventions: electroconvulsive therapy, serial ketamine therapy, and total sleep deprivation. Finally, the fourth study, “Connectomes related to anxiety and depression in adolescents” (HCP-ADA), investigates developmental trajectories of subtypes of anxiety and depression in adolescence.

The four projects use comparable and standardized Human Connectome Project magnetic resonance imaging (MRI) protocols, including structural MRI, diffusion-weighted MRI, and both task and resting state functional MRI. All four projects also conducted comprehensive and convergent clinical and neuropsychological assessments, including (but not limited to) demographic information, clinical diagnoses, symptoms of mood and anxiety disorders, negative and positive affect, cognitive function, and exposure to early life stress. The first round of analyses conducted in the four projects offered novel methods to investigate relations between functional connectomes and self-reports in large datasets, identified new functional correlates of symptoms of mood and anxiety disorders, characterized the trajectory of connectome-symptom profiles over time, and quantified the impact of novel treatments on aberrant connectivity.

Taken together, the data obtained and reported by the four Connectome Studies Related to Human Disease investigating mood and anxiety disorders describe a rich constellation of convergent biological, clinical, and behavioral phenotypes that span the peak ages for the onset of emotional disorders. These data are being prepared for open sharing with the scientific community following screens for quality by the Connectome Coordinating Facility (CCF). The CCF also plans to release data from all projects that have been pre-processed using identical state-of-the-art pipelines. The resultant dataset will give researchers the opportunity to pool complementary data across the four projects to study circuit dysfunctions that may underlie mood and anxiety disorders, to map cohesive relations among circuits and symptoms, and to probe how these relations change as a function of age and acute interventions. This large and combined dataset may also be ideal for using data-driven analytic approaches to inform neurobiological targets for future clinical trials and interventions focused on clinical or behavioral outcomes.

1. Introduction

The Human Connectome Project (HCP) has been successful in obtaining phenotypic and brain data across the lifespan in healthy individuals (Bookheimer et al., 2019; Harms et al., 2018; Somerville et al., 2018; Van Essen et al., 2013). The original HCP, however, did not include patients with illness. Therefore, several Connectome Studies Related to Human Disease (CRHD) were launched to investigate populations with various types of neurological and psychiatric conditions. Here, we provide an overview of the four CRHD investigating mood and anxiety disorders: “Dimensional connectomics of anxious misery” (HCP-DAM), “Human connectome Project for disordered emotional states” (HCP-DES), “Perturbation of the treatment resistant depression connectome by fast-acting therapies”

(HCP-MDD) and “Connectomes related to anxiety and depression in adolescents” (HCP-ADA).

Mood and anxiety disorders encompass diagnoses of major depressive disorder (MDD), generalized anxiety disorder (GAD) and persistent depressive disorder (PDD). These disorders commonly co-occur with traumatic stress and post-traumatic stress disorder (PTSD). Combined, they directly affect over 800 million people worldwide and represent the leading cause of disability and lost days of work and the highest rate of suicide of any disorder (James et al., 2018). The National Institute of Mental Health’s (NIMH) Research Domain Criteria framework (RDoC) provides an organizational framework for investigating the neurobiological dimensions that may account for the heterogeneity within and across these mood, anxiety and related traumatic stress disorders (Insel et al., 2010). In particular, RDoC defines neurobiological systems for positive and negative valence that include constructs related to reward, loss and threat, cognitive systems, as well as cross-cutting resting-state functions.

Each of the four CRHD projects investigating mood and anxiety disorders acquired data across different units of analysis to quantify these constructs and will share them with the research community. The goals of each specific project are complementary, as each elucidates a complementary facet of the biology underlying mood and anxiety disorders. In brief, the HCP-DAM aims to characterize brain-symptom characteristics of a transdiagnostic sample featuring anxious misery disorders (for details, see Seok et al., 2020). The goal of HCP-DES is to test an hypothesis-driven model of brain circuit dysfunction in a sample of untreated young adults with symptoms of depression and anxiety (for details, see Tozzi et al., 2020b). The HCP-MDD investigates individuals with depression who have been unresponsive to standard psycho- or pharmacotherapies and focuses on quantifying the perturbations of the structural and functional connectome caused by three fast-acting interventions: electroconvulsive therapy (ECT), serial ketamine therapy, or total sleep deprivation (TSD) (Loureiro et al., 2020; Sahib et al., 2020a, 2020b, 2020c; Vasavada et al., 2021). Finally, the goal of HCP-ADA is to gain a more comprehensive understanding of anxiety and depression subtypes in adolescence and their developmental trajectories in order to facilitate early, personalized intervention for at-risk youth (for details, see Hubbard et al., 2020).

Although the scientific aims of the four projects are different, they all use standardized HCP magnetic resonance imaging (MRI) protocols and a comprehensive set of overlapping clinical and neuropsychological assessments (Barch et al., 2013; Harms et al., 2018; Marcus et al., 2013). Therefore, despite having independent goals, the four CRHD projects investigating mood and anxiety disorders characterize participants using comparable instruments. Taken together, these data provide a rich collection of biological, clinical, and behavioral phenotypes in a large combined sample that spans peak ages for onset of emotional disorders. This data resource will enable researchers to study the heterogeneity of mood and anxiety in the context of underlying circuit dysfunction, to map cohesive relations among circuits and symptoms, and to probe how these relations change in time as a function of age and acute interventions, as well as address as yet undetermined hypotheses.

Our goal in this paper is to provide an overview of the rationale, methods, and preliminary results of the four CRHD projects investigating mood and anxiety disorders. In particular, we focus on their commonalities and on the overlapping measures they administered to provide a theoretical framework that could guide future analyses across the projects by others in the field.

2. Methods

2.1. Design

Of the four CRHD projects presented, HCP-DAM and HCP-DES were designed to facilitate harmonization with the HCP Healthy Young Adult dataset (Van Essen et al., 2013); the project involving minors (HCP-ADA) was designed to facilitate harmonization with the HCP Development dataset (Somerville et al., 2018) and HCP-MDD was designed to facilitate harmonization with the HCP Aging Lifespan Project (Harms et al., 2018). The Healthy Young Adult dataset contains imaging and behavioral data for 1200 healthy young adults aged 18 to 35 years, and the HCP Development dataset is an ongoing effort to obtain imaging and behavioral data from 1300 + healthy children, adolescents, and young adults, while the HCP Aging dataset includes 1200 subjects, Age 36–100 +. It is worth noting that, both in the four CRHD projects and in the original HCP project, there is overlap in the populations targeted around the ages of 18–19, when late adolescence blends with early adulthood, and there are overlaps in the age ranges with the HCP Lifespan Development and Aging studies across all age ranges. The four CRHD projects described here were conducted at different sites. The site for HCP-MDD also acquired data for the multisite HCP Lifespan Development and Aging projects. In the following section, we provide a brief overview of the inclusion and exclusion criteria, and the timelines and measures collected in the four projects while highlighting their most salient differences and commonalities.

2.2. Participants

Written informed consent was provided by each participant and each project was approved by the Institutional Review Board for ethical research at each of the respective study institutions.

2.2.1. Convergent exclusion and inclusion criteria—For a summary of these inclusion and exclusion criteria for participation in each study see Table 1.

In each of the projects, exclusion criteria included MRI contraindications (impairing claustrophobia, aneurysm clips, shunts, non-removable body piercings, non-removable cochlear or ear implants, permanent dentures or dental implants, joint replacements or prosthesis, pacemakers, defibrillators, or other implanted metal devices), histories of certain neurological or cognitive disorders and events (amyotrophic lateral sclerosis, brain aneurysms, brain injury, brain tumors, cerebral palsy, Chiari malformation, dementia, encephalopathy, multiple sclerosis, Parkinson’s disease, recurrent epilepsy or seizures, stroke, or transient ischemic attacks), histories of exclusionary psychiatric conditions (bipolar I, schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis,

autism spectrum disorder) or any other factors that in the investigator's judgement may have affected patient safety or compliance.

Healthy controls were ineligible if they met criteria for a DSM-5 psychiatric disorder, assessed by the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2015), the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) for HCP-DES, HCP-DAM and HCP-MDD, and the equivalent Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS; Kaufman et al., 1997) for HCP-ADA. Addiction, operationalized as clinically significant substance dependence to alcohol, recreational drugs, or prescription medications was an exclusion criterion.

Each project recruited participants from the general population using a wide range of methods including flyers, online advertisements, social media and brochures in clinics. Each project strived to recruit a racially and ethnically diverse sample to reflect the diversity of their location (Philadelphia Area, San Francisco Bay Area, Los Angeles Area and Greater Boston Area).

In addition to these commonalities in recruitment processes, as well as in eligibility criteria, each project has a unique sample with characteristics relevant to its specific aims. These are outlined in the following subsections.

2.2.2. HCP-DAM participants—The HCP-DAM sample consists of 200 participants who were experiencing symptoms of anxious misery and 50 healthy controls (n = 250), with an age range of 18–60 years. In this study, there was no requirement for participants to cease taking any routine psychotropic medications, resulting in a sample with 73% on no psychotropics and 27% on stable psychotropic medication. Participants were enrolled into either a healthy control or anxious misery group. Group assignment was based on participants' raw Neuroticism score on the Neuroticism-Extraversion-Openness Five-Factor Inventory (NEO FFI) (McCrae et al., 2007, p. 3). Neuroticism was selected as an eligibility criterion because it captures general elements of psychopathology that are shared by participants diagnosed with depression, anxiety, and trauma-related disorders (Andrews et al., 1990; Khan et al., 2005). Importantly, it also does not overlap with the diagnostic criteria of any Axis I disorder in the DSM-5, helping to ensure a transdiagnostic dataset. Based on previously collected data from a sample of 635 adults (McCrae et al., 2007, p. 3), clinical participants were required to have raw Neuroticism scores at least 1 standard deviation above the mean (raw score ≥ 26.2 for males and ≥ 30.1 for females), and healthy controls were required to have raw neuroticism scores at least one standard deviation below the mean (by sex).

2.2.3. HCP-DES participants—The HCP-DES sample includes 250 individuals defined as clinical participants based on their current or recent experience of symptoms of emotional disorders that span multiple diagnoses of depression and anxiety and interfere with their capacity to function, in addition to 50 individuals who are not experiencing such symptoms. Symptoms were assessed in five categories: anhedonia, anxious arousal, concentration, rumination, and tension, using previously validated self-report items suited to the target sample of interest (Grisanzio et al., 2018). Clinical participants were required to

report experiencing at least one of these five symptoms “often” or “almost always/always” in the last two weeks and to indicate that their symptoms caused them significant distress and/or impairment. Healthy controls reported that symptom-related statements applied to them only “occasionally” or “rarely/never” in the last two weeks and did not cause significant distress or impairment. Finally, all participants were required to not be taking any psychotropic medications for a mental health problem (including, SSRIs, benzodiazepines, etc.) or receiving therapy by a trained mental health professional (social worker, clinical psychologist, psychiatrist, etc.).

2.2.4. HCP-MDD participants—*HCP-MDD* obtained data from three separate cohorts of patients with major depression ($N = 180$) and nondepressed controls ($N = 51$) between the ages of 20–64 years. Patients were assessed before and after receiving one of three rapidly acting interventions, including ECT ($n = 34$), ketamine infusion ($n = 60$) or TSD ($n = 60$). A sub-sample of controls were assessed either after receiving TSD ($n = 16$) or after receiving no intervention ($n = 17$).

ECT patients were recruited from among those individuals who were already scheduled to receive ECT as part of their routine care at the Resnick Neuropsychiatric Hospital at UCLA, and ketamine patients were also recruited through clinicaltrials.gov (NCT02165449). Interested participants were prescreened via a phone or online survey and were scheduled for an in-person screening if they met preliminary eligibility criteria.

The study design was naturalistic such that assignment of patients to the brain stimulation (ECT), pharmacological (ketamine), or behavioral (TSD) interventions was based on clinical decisions rather than on randomization. All patients who met DSM-5 criteria for Major Depressive Disorder had recurrent depression, with the existing episode lasting for at least 6 months. Patients had also previously failed to achieve therapeutic response to at least two trials of antidepressant medication of sufficient dose/duration. Additional exclusionary criteria for patients receiving ketamine included psychotic reactions to medication or illicit substances and rapid cycling of mood. Any history of convulsions or withdrawal seizures were exclusionary for both ketamine and TSD. Patients in the ECT group were tapered from psychotropic medications (> 24 h) prior to receiving baseline assessments and beginning ECT treatment. Patients in the ketamine and TSD groups were allowed to continue antidepressant medication if they were stable for > 6 weeks prior to study entry. If prescribed, benzodiazepines were withheld 24 h prior to receiving ketamine infusions or 72 h prior to TSD, including before baseline and post-treatment MRI/behavioral/clinical assessments. Any neuromodulation or ketamine treatment within the 6 months prior to study entry was an exclusion criterion. Finally, patients who were determined to be actively suicidal based on a score of 4 for item 3 of the Hamilton Depression Rating Scale and/or on clinical judgment were excluded.

2.2.5. HCP-ADA participants—HCP-ADA collected data from 225 adolescents, scanned at ages 14–17 years. This age range was selected for two primary reasons. First, in this age range, most participants had entered puberty (Parent et al., 2003; Patton and Viner, 2007). Second, relevant brain responses (i.e., emotional and reward system neural activations) and individual differences in these responses are at their apex within this age

range (Somerville et al., 2010). To be included, patients had to have at least one clinical diagnosis of depression, anxiety, or trauma-related disorders according to the DSM-5.

2.3. Brain imaging protocols

2.3.1. Acquisition—For a summary and comparison of imaging sequences across the four projects, see Table 2. Overall, sequences were largely comparable. Because of this, here we only give a brief overview of the most significant similarities and discrepancies across studies, and do not break down this section project by project.

Three of the studies used Siemens Prisma 3T scanners and HCP-DES used a GE Discovery MR750 3T. High-density head receive arrays were used for all studies, including a 64-element head/neck array (only 52 head elements used) and a 32-element head array, all supporting high acceleration factors for the acquisition of the MRI imaging sequences. The peak gradient amplitude specification for the Siemens Prisma was higher than for the GE MR750, 80 mT/m compared to 50 mT/m, but sequence timing parameters were comparable between platforms, even for the DWI acquisition.

All studies collected high-resolution structural T1-weighted and T2-weighted 3D. The structural images were all acquired with comparable contrast preparation, resolution and field of view. Three of the studies (HCP-DAM, HCP-MDD, HCP-ADA) used sequences with prospective motion correction, including an overscan allowance to account for TRs with significant detected motion.

Multiband fMRI and diffusion-weighted images (DWI) were acquired using both AP and PA EPI acquisition schemes. Spin-echo EPI acquisitions were interspersed through the study in order to retrospectively calculate fieldmaps which were used for geometric correction of the fMRI and DWI data.

Parameters for the fMRI acquisition all used highly accelerated multiband EPI acquisitions, although HCP-DES differed in some respects. The multiband factor for the HCP-DES was 6 rather than 8 as in all the other studies due to the steep increase in noise-amplification for the 8x acceleration case compared to the 6x acceleration on the HCP-DES GE system. The voxel resolution for the HCP-DES study was increased to 2.4 mm isotropic in order to preserve comparable TR timing with other HCP studies. This resulted in a 73% larger voxel volume for HCP-DES compared to the studies with 2 mm voxels, which together with the lower multiband factor provided a relative increase in SNR.

Diffusion-weighted images were also acquired similarly across sites. The HCP-DES had a lower number of diffusion directions by shell (75/75 compared to 92/93 at the other sites). As shown by Tournier et al. (2013), 75 directions is still sufficient to characterize the diffusion-weighted signal with up to a 10th order spherical harmonic, and that for their data with $b = 3000$ s/mm2, there was little model accuracy to be gained beyond an 8th order spherical harmonic. While the higher number of 91 directions is the minimum to characterize the signal with a 12th order spherical harmonic, it is expected the higher order coefficients would be insignificant, and that fitting a 12th order spherical harmonic with the minimum required number of directions would also be poorly determined.

2.3.2. Harmonization with previous HCP studies—Sequences for the four projects were designed to align as closely as possible with those used in the HCP-Young Adult, HCP-Lifespan and HCP-Development. It is important to note that in the original HCP, data were acquired on a 3T Siemens Skyra scanner that was extensively customized (Van Essen et al., 2012); therefore, slight deviations from the original protocols were inevitable. At sites using Siemens scanners, sequence parameters did not change or changed only minimally. Due to a software upgrade, TR changed slightly for fMRI (0.80 s from 0.72 s) and diffusion MRI (3.20 s from 5.52 s). Another change was that multi-echo gradient echo and vNavs were introduced for T1w and T2w scans. In the HCP-DES project, data acquisition was done on a 3T GE Discovery scanner. Because of the differences in hardware and software between scanners from different vendors, sequences in this project had greater discrepancies from the original protocols. Nevertheless, the changes were made with the goal of obtaining data that would be most similar to those collected on Siemens systems, especially in terms of preserving the fundamental advances made by the HCP in scanning technology, such as multiband acquisition. Prior to the start of the project, extensive effort was expended to ensure that data collected by HCP-DES would be comparable in quality to those from the original projects; in fact, this was shown to be the case when examining pilot data from the study (Tozzi et al., 2020).

2.3.3. Resting state fMRI—All sites collected resting state fMRI data obtained by having participants stare at a white cross on a black background. However, the total time collected varied across projects: HCP-MDD collected ~12 min (two 6:41 runs of 488 frames each) per session where subjects were scanned at multiple time points, whereas HCP-DES, HCP-DAM, and HCP-ADA collected ~20 min (HCP-DES collected four 5:12 runs of 428 frames while both HCP-DAM and HCP-ADA collected four 5:46 runs of 420 frames).

2.3.4. Task fMRI—The tasks used to collect task fMRI data overlapped across the four projects in terms of the neural circuits and regions that the tasks were designed to engage. In particular, tasks probing the RDoC domains of Negative Valence (negative emotion processing), Positive Valence (reward), and Cognitive Systems (cognitive control) were consistently used to collect fMRI data across projects. For this reason, here we only give a brief summary of the tasks used in the studies, and do not break down this section project by project. An overview of the tasks implemented in each project is presented in Table 3, showing which ones were identical across them. For brevity, the Table shows only measures that were collected across two or more studies; see Supplementary Materials for a table that includes all measures. Below, the full list of tasks and the projects in which they were used are provided.

HCP-emotion processing task: The HCP-Emotion Processing task is designed to assess the processing of emotional faces. The original version of this task was adapted from Hariri et al. (2002). In this version of the task, participants are presented with blocks of trials that ask them to decide either which of two faces presented on the bottom of the screen match the face at the top of the screen, or which of two shapes presented at the bottom of the screen match the shape at the top of the screen. The faces have either angry or fearful expressions. Trials are presented in blocks of 6 trials of the same task (face or shape), with the stimulus

presented for 2 s and a 1 s ITI. Each block is preceded by a 3s task cue (“shape” or “face”), so that each block is 21s including the cue. Each of the two runs includes 3 face blocks and 3 shape blocks. This task was consistently collected across all four projects, although some differences are noteworthy. First, HCP-DAM, HCP-MDD, and HCP-ADA used two runs of the task, whereas HCP-DES implemented one run. Second, HCP-DAM, HCP-MDD, and HCP-ADA used a variant of the task. In these projects, happy, sad, and neutral faces were used in addition to angry and fearful faces. In addition, shape stimuli that were used as a control for facial emotion stimuli were replaced with fruit and vegetable stimuli (Loureiro et al., 2020; Seok et al., 2020; Siless et al., 2020). The number of frames in each run of the task was HCP-DAM: 290, HCP-DES: 192, HCP-MDD: 338 and HCP-ADA: 405. The primary behavioral outcomes of this task were the number of faces and shapes correctly matched and the reaction times to each trial.

HCP-incentive processing task: The HCP-Incentive processing task is designed to probe the function of brain structures involved in reward. The original version of this task was adapted from Delgado et al. (2000). A question mark is presented on screen, and participants must guess whether the number obscured by the question mark (which can range 1–9) is greater than or less than five. If the participant guesses correctly, a green arrow pointing upwards with text indicating “+ $1.00 ″ is shown. If the participant guesses incorrectly, the participant sees a red arrow pointing downwards with text indicating “−$0.50 ″. If the number was five, a gray double-headed arrow is presented, indicating that money was neither gained nor lost. If the participant does not respond within the time allocated for the trial (1.5s after the question mark is presented), then the text “no response” is presented, along with an indication that no money is gained or lost that round. Two runs of this task were collected in HCP-DAM and HCP-ADA. HCP-DES administered one run and adopted a variant of the task from the HCP-Development study. This modified version includes small and large gain and loss outcomes (Somerville et al., 2018). The number of frames in each run of the task was HCP-DAM: 290, HCP-DES: 304 and HCP-ADA: 215. The primary behavioral outcomes of this task were the number of guesses made and the reaction times to each trial.

Emotional interference task: The Emotional Interference Task captures deficits in cognitive control in the presence of negatively valenced emotional distractors. It was adapted from Fales et al. (2008). Participants are instructed to indicate through a button press whether two pictures on either the horizontal or the vertical axes are identical or different. After a cue indicating which axis to attend to, four images are briefly shown on the top, bottom, left, and right of the screen, and participants are given a short period to respond. Images are either human faces or houses, and faces can have either a neutral or a fearful expression. Four runs of this task were collected in HCP-DAM and in HCP-ADA. The number of frames in each run of the task was HCP-DAM: 290 and HCP-ADA: 280. The primary behavioral outcomes of this task were the number of images correctly identified and the reaction times to each trial.

Conditioned approach response inhibition task: The Conditioned Approach Response Inhibition Task (CARIT) measures inhibitory control processes and the modulation of

inhibitory control by reward history (Davidow et al., 2019). It is a classic Go/NoGo task in which the NoGo targets have special "conditioned" qualities. During the task, participants view shape stimuli and are instructed to press a button as quickly as possible ("Go") to every shape except for the circle and the square. One run of this task was administered in HCP-MDD (Sahib et al., 2020b). This version of the CARIT task is identical to that of the HCP-A Lifespan project, although the HCP-D Lifespan project incorporated a conditioned reward component (Bookheimer et al., 2019). The number of frames in each run of the task was HCP-MDD: 300. The primary behavioral outcomes of this task were the number of successful response inhibitions and the reaction times to each trial.

N-back continuous performance task: This task was developed to probe working memory function in depression (Korgaonkar et al., 2013). Participants are instructed to attend to yellow but not to white letters and to press a button when the same yellow letter appears twice in a row. Stimuli are presented under three conditions: 30 sustained attention stimuli in which yellow letters appear twice in a row and participants respond to the consecutive yellow letter; 50 working memory stimuli in which yellow letters appear randomly and not consecutively; and 40 perceptual baseline stimuli in which white letters are presented. One run of this task was administered in HCP-DES. The number of frames in each run of the task was HCP-DES: 422. The behavioral primary outcomes of this task were the number of letters correctly identified and the reaction times to each trial.

2.4. Computerized tests of behavioral performance

All four projects administered an extensive behavioral test battery to assess cognitive and emotional functions. Even if some of the instruments diverged, measures collected at each site were largely overlapping; specifically, either they used exactly the same assessments or they used different assessments targeting the same underlying psychological constructs. Because of this, here we only give a brief summary of the behavioral tests used in the studies, and do not break down this section project by project. An overview of the behavioral measures implemented in each project is presented in Table 3, also showing which ones were identical across them. For brevity, the Table shows only measures that were collected across two or more studies; see Supplementary Materials for a table that includes all measures.

The NIH Toolbox Cognition was used consistently by all sites (Weintraub et al., 2013). In particular, all sites administered the same tests measuring Executive Function (Dimensional Change Card Sort Test), Attention and Executive Functioning (Flanker Inhibitory Control and Attention Test), Processing Speed (Pattern Comparison Processing Speed Test) and Working Memory (List Sorting Working Memory Test). In addition, three of the four sites (HCP-DAM, HCP-DES and HCP-MDD) also administered measures of Episodic Memory (Picture Sequence Memory Test) and Language (Picture Vocabulary Comprehension Test). Finally, two of the sites administered a second measure of Language: the Oral Reading Recognition Test (HCP-ADA and HCP-MDD).

In addition to the NIH toolbox, three sites collected measures from the Penn Computerized Neurocognitive Battery (HCP-DAM, HCP-MDD, HCP-ADA) (Moore et al., 2015).

In particular, all three sites administered a measure of nonverbal reasoning ability (Penn Progressive Matrices) and a test of facial emotion recognition (Penn Emotion Recognition Test). Other measures from the Penn Computerized Neurocognitive Battery were administered by individual sites. For example, the Penn Working Memory Test and Penn Matrix Analysis Test were administered only by HCP-ADA. The Penn Trail Making Test and the Penn Delayed Discounting task were administered only by HCP-DAM. Finally, HCP-MDD also administered an autobiographical memory test (Loureiro et al., 2020).

Importantly, instead of the Penn Computerized Neurocognitive Battery, HCP-DES administered the computerized WebNeuro battery, which has been normed across the lifespan (Silverstein et al., 2007). WebNeuro assesses constructs complementing those assessed using the Penn Computerized Neurocognitive Battery, including tests of facial emotion identification and implicit emotion priming, span of visual memory (equivalent to digit span), switching of attention (equivalent to Trail Making), continuous performance, verbal learning and memory, GoNoGo and executive Maze.

2.5. Symptom measures

All sites administered questionnaires assessing symptoms of depression and anxiety. Because of its focus on adolescents, HCP-ADA used different assessments than the other three projects, although they targeted the same constructs. Because of the similarities in the self-report measures from the four projects, here we summarize them without breaking down this section project by project. An overview of the self-report measures implemented in each project is presented in Table 3, also showing which ones were identical across them. For brevity, the Table shows only measures that were collected across two or more studies; see Supplementary Materials for a table that includes all measures.

First, all sites conducted a structured diagnostic interview for psychiatric disorders: the Structured Clinical Interview for DSM-5 (First MB, Williams JBW, Karg RS, Spitzer RL, 2015) (HCP-DAM and HCP-MDD); the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) (HCP-DES); and the Kiddie Schedule for Affective Disorders and Schizophrenia, both child and parent versions (K-SADS; Kaufman et al., 1997) (HCP-ADA).

With respect to depression and anxiety symptoms, the Hamilton Depression Scale was also administered at all “adult” sites (Hamilton, 1986). Other measures were administered across only two sites, although they probed largely overlapping symptoms, such as the Quick Inventory of Depression Symptoms (Rush et al., 2003), the depression, anxiety and stress scale (Parkitny and McAuley, 2010) (HCP-MDD and HCP-DES), the Mood and Anxiety Symptom Questionnaire (Wardenaar et al., 2010) (HCP-DAM and HCP-DES) and the PROMIS scale (Schalet et al., 2016) (HCP-MDD and HCP-DAM).

Scales specific for anhedonia and behavioral activation/inhibition were administered across all four projects: the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995) and the behavioral activation/inhibition scales (Carver and White, 1994), respectively. All adult sites also assessed rumination using the Ruminative Response Scale (Parola et al., 2017)

The three adult sites also administered the NIH toolbox Emotion, consisting of self-reported measures of negative affect, stress and self-efficacy, psychological well-being and social relationships (Salsman et al., 2013).

Finally, early life stress was also measured at all sites, albeit with different questionnaires: the Stress and Adversity Inventory (Slavich et al., 2019), Holmes-Rahe Life Stress Inventory (Noone, 2017), Stressful Life Events scale (Brugha et al., 1985) and the Early Life Stress scale (Sanders and Becker-Lausen, 1995).

2.6. Longitudinal data collection

Beside the main data collection visit, all 4 projects also followed up with participants.

In HCP-DES, every 3 months for one year after the baseline visit (4 times total), clinical participants completed an online questionnaire assessing symptoms, treatments, and life events. The Patient Health Questionnaire (PHQ-9), General Anxiety Disorder (GAD-7), and Satisfaction with Life Scale (SWLS) were also included. One year after the baseline assessment, clinical participants also completed a diagnostic interview over the telephone (MINI) and cognitive testing remotely (WebNeuro).

In HCP-ADA, two follow-up sessions were conducted 6 (online) and 12 months (in person) after the first imaging session. In these follow-up sessions, the same clinical assessments that were included at baseline were administered.

In HCP-DAM, follow-up visits were conducted at 6 months in person and 12 months over the telephone. In the in-person visit, one additional MRI session was conducted, consisting of fMRI resting state and tasks (HCP-Emotion Processing, HCP-Incentive Processing, Emotional Interference). They also received an interim episode and treatment history assessment, medical history, and were administered the Montgomery-Asberg Depression Rating Scale (MADRS) as well as self-reports for mood and anxiety and life stress. At 12 months they completed a phone assessment for mood and anxiety symptoms, interim episode and treatment history and medical history.

Due to its testing of multiple interventions, HCP-MDD had a complex longitudinal organization, summarized in Fig. 1.

Briefly, HCP-MDD included three interventions that are each known to elicit rapid and pronounced antidepressant effects in patients resistant to first line treatments: ECT, Ketamine, and TSD (Francesco and Enrico, 2009; Kho et al., 2003; Kraus et al., 2017; Wirz-Justice and Van den Hoofdakker, 1999). Because peak response to each intervention varies across time (hours to weeks), baseline and longitudinal follow-up assessments were performed at different time points depending on whether patients received ECT, ketamine infusion, or TSD. For ECT, MRIs and clinical/behavioral assessments were conducted again within one week of completing the ECT index series (approximately 3,4 weeks following treatment initiation, with ECT administered 2,3 times weekly). Also, ECT patients received a final study visit when possible either three months after ECT treatment ended or upon symptom recurrence, whichever occurred first. For ketamine, a subanesthetic dose (0.5 mg/kg) of ketamine diluted in 60cc saline was delivered intravenously via pump over 40

min. Post-treatment MRIs and clinical/behavioral assessments occurred 24 h after patients completed four serial ketamine infusions that were also administered 2,3 times weekly. Supplemental MRI and clinical/behavioral follow-up assessments were also obtained for a majority of ketamine subjects 24 h after they had received their first ketamine infusion, and five weeks after their fourth infusion or upon symptom recurrence, whichever occurred first. For TSD, follow-up MRI scans and clinical/behavioral assessments took place directly after the overnight sleep deprivation session, occurring 23–25 h after baseline and at least 36 h of wakefulness. TSD patients completed clinical assessments 1-week after sleep deprivation though MRIs were not collected at this time point. Nondepressed controls were scanned at either a single session, or before and after receiving TSD or no intervention.

3. Data sharing

Currently, some clinical and behavioral data collected from the four CRHD projects have already been uploaded to the NIMH Data Archive (NDA). With respect to the neuroimaging data, each study is tasked with an intensive pipeline to transfer them to the Connectome Coordination Facility. CCF will release all original (raw) imaging data screened according to quality assurance protocols and plans to release data using protocols equivalent to those for HCP-Development and HCP-Aging Lifespan projects.

The timelines for the release of all data will be determined by the CCF and NDA. Via coordination with the CCF and NDA, project data has already been released for one existing CRHD project (Demro et al., 2021). Release of data for the current projects will begin in the first quarter of 2022, with all data expected to be fully available through the NDA no later than mid 2024. The release date will take into account unexpected factors that affected the timelines of the projects, such as the COVID-19 pandemic.

4. Recently published findings

Across the four projects we have focused the first round of analyses on developing and validating methods suited to large connectome datasets, on mapping cross-sectional relations between connectome profiles and symptoms, on characterizing the trajectory of connectomes and connectome-symptom profiles over time and the impact of novel treatments on modifying disordered connectivity. The preliminary findings from these areas of focus are outlined in the following subsections.

4.1. Mapping novel relations between symptoms and functional connectivity

In clinical participants, a primary goal for all four projects is to relate symptoms of depression and anxiety to functional connectivity measures. This effort is motivated by an extensive body of evidence suggesting that functional connectivity is disrupted in mood disorders and that the extent of disruption is related to specific symptoms (Helm et al., 2018).

Across projects, investigators pursued two complementary methodological approaches to this goal: one motivated by a theoretical framework based on prior evidence and targeting

brain circuits shown to be particularly affected in depression and anxiety (for a review, see Williams, 2016); and the other using whole-brain data-driven analyses.

4.1.1. Reduced default mode network connectivity might characterize a biotype of major depressive disorder—As one example of an approach targeting specific brain circuits, HCP-DES investigators conducted a meta-analysis in which they quantified default mode network connectivity in 618 individuals with major depression and 683 controls scanned across 10 sites. This analysis was motivated by previous by conflicting findings of large studies and meta-analyses reporting both increased and decreased default mode connectivity in major depression (Yan et al., 2019; Kaiser et al., 2015). In our theoretical framework, a working hypothesis was that increased versus decreased connectivity of the default mode and its sub-networks reflects distinct dysfunctions associated with components of rumination, self-referential and autobiographical processing, and contributes to different treatment response profiles (Williams et al., 2016). The authors found that functional connectivity between the core posterior to anterior connection of the default mode circuit was slightly but significantly reduced in MDD compared to controls (Tozzi et al., 2021b). This HCP-DES meta-analysis suggested that there are subtypes of depression that are characterized by different levels of default mode network connectivity, consistent with our working hypothesis. Such reduced connectivity has been implicated in poorer remission on first-line antidepressants (Goldstein et al., 2018; Korgaonkar, 2020) and in more persistent (or recurrent) depression (Yan et al., 2019).

4.1.2. Different symptoms might impact the functional connectome at different scales of brain organization—A first data-driven study conducted on the HCP-DAM dataset used a dimensional approach inspired by the NIMH Research Domain Criteria Initiative (Insel et al., 2010) to investigate correlations between symptoms of disorders of “anxious misery” and resting state functional connectivity. The authors focused on six specific domains (anxiety sensitivity, anxious arousal, rumination, anhedonia, insomnia, and negative affect) using three different approaches: seed-based correlation analysis (SCA), support vector regression (SVR), and Brain Basis Set modeling (BBS) (Seok et al., 2021). The Authors performed hyperparameter tuning and feature selection for these multivariate methods using cross-validation, and then evaluated the model performance on a held-out test set. For anhedonia and anxiety sensitivity, seed-based correlation analysis produced optimum results. These symptoms were best modeled using single connections: dorsolateral prefrontal cortex-amygdala and orbitofrontal cortex-ventral striatum, respectively. Anxious arousal and insomnia, on the other hand, were best modeled using SVR, which utilized a small subset of all functional connections in the brain (~5%). In particular, anxious arousal was associated with hyperconnectivity between sensory regions and regions in the association cortex. Insomnia was associated with hyperconnectivity between the default mode network and multiple cortical areas, including the primary sensory cortex, salience network, and limbic nodes. Finally, multivariate methods produced stronger results for negative affect and rumination, for which modeling of a much larger set of connections (38,000) was necessary. These findings indicate that symptom dimensions differ in the degree to which they impact different scales of brain organization (Seok et al, 2021). Importantly, and consistent with findings from the larger HCP healthy dataset (Tozzi et

al., 2021a), the authors also pointed out that validation of findings using independent data is crucial for establishing the generalizability of multivariate models of brain-symptom relations.

4.2. Identifying structural and functional brain correlates of longitudinal changes in symptoms

A third body of findings to emerge from the four projects pertains to how longitudinal changes in depression and anxiety symptoms are related to brain structure and function. The overarching goal of these studies was to identify brain imaging measures at baseline that predict the trajectory of depression and anxiety symptoms over time.

4.2.1. Impairments of reward circuits in depressed and anxious adolescents predict symptom trajectories—In adults, depression and anxiety have been found to be characterized by reduced volume in several subcortical structures (Zhao et al., 2017). In youth, depression and anxiety are often comorbid (Axelson and Birmaher, 2001), but the structural correlates of this comorbidity have not been investigated as extensively as they have been in adults. In a longitudinal study, HCP-ADA investigators tested the hypothesis that depressed-anxious youth will have reduced nucleus accumbens, putamen, amygdala, and hippocampal volumes relative to healthy adolescents. Second, they leveraged an incentive-processing task to test whether depressed–anxious adolescents would show reduced reward-related activation in the accumbens compared to healthy youth. Finally, they assessed whether they could predict depression scores after six months based on accumbens volume and activation. The study found that, relative to healthy youth, depressed-anxious adolescents had reduced nucleus accumbens volume and activation, independent of medication (Auerbach et al., 2021). Importantly, reduced nucleus accumbens volume predicted an increase in depressive symptoms over six months (Fig. 2).

4.2.2. Maladaptive coping strategies and brain structure interact to predict symptom changes during environmental stressors—The COVID-19 global pandemic was a stressful life event that resulted in more than 4 million deaths (https://covid19.who.int/) and substantial increases in rates of depression and anxiety (Xiong et al., 2020). The ability to cope adaptively with stressful events is related to the capacity to regulate emotions, which in turn influences the development of anxiety and depression symptoms (Stanisławski, 2019). These symptoms have also been linked with the structural integrity of the brain regions involved in emotion regulation (see Introduction in Holt-Gosselin et al., 2021). A recent study used longitudinal data from HCP-DES to investigate whether coping strategies and gray matter content of brain regions involved in emotion assessed pre-pandemic could predict the severity of anxiety and depression symptoms during the pandemic. The authors found that maladaptive coping strategies and lower insula thickness were associated with an increase in anxiety symptoms in patients after the onset of the COVID-19 pandemic (Holt-Gosselin et al., 2021).

4.3. Fast-acting therapies differentially impact functional connectivity in treatment-resistant depression

Fewer than half of patients with major depressive disorder remit within the first 3 months of treatment with first-line antidepressants (Trivedi et al., 2006), and ~30% remain unresponsive to ≥ 2 pharmacotherapies (McGrath et al., 2006; Mrazek et al., 2014, pp. 1996–2013). One of the goals of HCP-MDD was to examine the effect of novel fast-acting interventions – ECT, ketamine and TSD – on treatment-resistant depressed patients. In the study, all three interventions led to rapid improvements in depressive symptoms. Each intervention was also associated with unique systems-level perturbations in the structural and functional connectome. Examples of these findings are described below.

4.3.1. Ketamine and functional connectivity—Ketamine is an antagonist at the N-methyl-D-aspartate receptor that has rapid antidepressant effects which can last for weeks (Zarate et al., 2006; Abdallah et al., 2015). To date, few studies have assessed the impact of serial ketamine infusion on functional connectivity and brain activation, many of which have come from HCP-MDD. For example, in one study, investigators from HCP-MDD showed that ketamine alters the functional connectivity between limbic regions and large-scale resting state networks whose dysfunction is implicated in MDD (default mode, central executive, and salience networks). Early changes in network function were also associated with clinical improvements (Vasavada et al., 2021) (Fig. 3). Using a data-driven functional connectomics approach, other results from HCP-MDD suggest that functional connectivity of cortico-striatal-cerebellar loops is a potential biomarker for response to ketamine treatment (Sahib et al., 2020c). Further, ketamine leads to changes in the functional connectivity of inhibitory control networks, including functional coupling of cerebro-cerebellar circuitry, that are associated with therapeutic (Sahib et al., 2020b; Loureiro et al., 2021). Focusing on HCP-MDD results using task fMRI, ketamine leads to reductions in amygdala reactivity during task-elicited emotion recognition (Loureiro et al., 2020).

4.3.2. TSD and functional connectivity—One night of partial or total sleep deprivation elicits rapid improvements in mood in 40–60 % of patients with major depression (Wu and Bunney, 1990; Dallaspezia and Benedetti, 2011). However, the brain systems-level mechanisms contributing to these effects, which could overlap with other fast-acting antidepressant therapies, remain poorly understood. Using data-driven whole brain functional connectivity (FC) analysis methods, HCP-MDD found that both patients and controls show significant changes in functional connectivity in visual, default mode, dorsal attention, auditory, and motor brain networks following > 24 h of sleep deprivation. Similar to results for pharmacological perturbation with low-dose ketamine infusion (Sahib et al., 2020c), HCP-MDD further observed that TSD acts to modulate cortico-hippocampal-cerebellar functional circuitry in patients with depression who show improvements of 30% or more in depressive symptoms (manuscript in review). Notably, TSD, like ketamine, also perturbed visual networks (Sahib et al., 2020c) suggesting some overlap in response mechanisms.

4.3.3. ECT and functional connectivity—ECT produces fast-acting and high response rates in patients with major depression failing standard pharmacological therapies (UK ECT Review Group, 2003). Prior imaging studies attempting to understand the mechanisms of rapid therapeutic response have reported ECT-related increases in the volume of the hippocampus with relative consistency, though global changes in hippocampal structure are typically not found to associate with clinical improvement (Oltedal et al. 2018; Wilkinson et al. 2017; Takamiya et al. 2018; Enneking et al. 2020). However, HCP-MDD has demonstrated that response to ECT is likely associated with more regionally specific changes in hippocampal structural and functional plasticity (Leaver et al., 2020). Further, HCP-MDD has shown that imaging biomarkers of treatment response are more accurately predicted when accounting for pre-treatment symptom heterogeneity (Wade et al., 2021). Finally, in HCP-MDD, ECT was found to have a similar effect as ketamine in reducing in amygdala reactivity during task-elicited emotion recognition (Loureiro et al., 2020), suggesting similar modulation of negative valence systems with both fast-acting therapies.

5. Discussion

Here we have reviewed a unique set of four CRHD projects investigating mood and anxiety disorders and the preliminary promising findings from these projects. These projects generated rich and complementary datasets that used cutting-edge HCP protocols for acquiring structural MRI, diffusion-weighted MRI, resting state fMRI and task fMRI, as well as phenotypic information derived from tests of behavioral performance and self-reported symptoms. Because data for these four projects is collected using substantially overlapping measures and protocols, they offer a combined opportunity to overcome several limitations that have plagued neuroimaging research focused on characterizing the neural circuit basis of mood and anxiety disorders, how they change over time and their response to treatment.

Neuroimaging research in depression and anxiety has been limited by a focus on narrowly defined diagnostic groups, insufficient sample sizes, inconsistent or suboptimal MRI protocols, and inconsistent characterization of phenotypic variables. Pooled analysis has also been limited to meta-analyses with no data harmonization, which are constrained by variation among studies in methods, by a lack of spatial specificity, and other confounds. Finally, prior research has also mostly evaluated behavior and self-reports in individuals with a single diagnosis, such as MDD, GAD, PDD, and PTSD, but has rarely harmonized such measures across the spectrum of mood and anxiety disorders.

Once data from the four CRHD projects is released, there will be the opportunity for pooling of complementary data across the four projects. These data will contribute to ongoing research for the development of a brain-based taxonomy for classifying psychopathology of mood and anxiety disorders, identifying treatment targets, and elucidating underlying mechanisms.

5.1. Common findings

One common insight that emerges across projects is that deconstructing the functional brain circuit dysfunctions that underlie specific symptoms of depression, going beyond the

umbrella diagnostic category, requires us to probe both the whole functional connectome and specific established circuits in the same datasets. Multivariate methods analyzing the whole functional connectome showed promise for characterizing broad, transdiagnostic symptom constructs. For example, convergent findings from HCP-DAM and HCP-DES suggest that the neural correlates of rumination are not constrained within individual networks or regions, but rather, distributed across the brain. Importantly, however, the use of multivariate methods brings the risk of overfitting the data, which makes it necessary to use large held-out datasets to validate results.

One promising complementary approach is the focused investigation on specific functional connections or regions within a circuit, informed by prior data and neuroanatomy. Across projects we found that the structural integrity of specific regions is important in determining the trajectory of depression and anxiety in adolescents and young adults. Within the reward circuit, reduced volume of the nucleus accumbens predicted worsening of depressive symptoms over 6 months in adolescents in the HCP-ADA sample. In young adults in HCP-DES, reduced thickness of the insula contributed to worsening anxiety symptoms over a similar time period during the pandemic.

Findings for treatment also highlight the theme of probing both specific circuit regions and complementary data-driven systems-level circuit analyses. In HCP-MDD, both ketamine and ECT reduced emotion-elicited amygdala reactivity. Given that reactivity of the amygdala and interconnected regions predicts non-response to typical antidepressants (Williams et al., 2015; Victor, 2013), these HCP-MDD findings indicate that targeting brain circuit regions with established tasks can yield promising candidate biomarkers of differential response to novel treatments. Similarly, ketamine induced rapid changes in functional connectivity of inhibitory control networks that are also differentially affected by typical antidepressants (Tozzi et al., 2019). At the systems level, ketamine response involved changes in connectivity of cortico-striatal-cerebellar loops consistent with the putative glutamatergic effects of this novel rapid-acting intervention.

An intriguing observation that emerged across the four projects is that the circuit dysfunctions associated with diagnostic symptoms and course of illness are not necessarily the same as those that predict clinical remission or response to treatment. This suggests that it will be important to identify the neurobiological characteristics unique to a subset of patients who exhibit the same symptoms within a pre-treatment baseline state and, concurrently, to identify whether the same or a different set of characteristics predicts and drives treatment response.

5.2. Future directions for the four projects

Because of the depth and breadth of the resource provided by the four CRHD projects described here, several scientific and methodological advances will be possible.

Future studies will be able to address in more detail a major challenge in using neuroimaging to characterize the neural circuit basis of depression and anxiety; namely, the availability of sufficiently precise phenotype information. Typically, neuroimaging studies have been required to rely on broad descriptive categories such as the presence or absence of

a diagnosis. The availability of common and more detailed assessments across projects will allow for future investigators to characterize subjects based on individual symptoms as well as on objective behavioral measures. Such data will facilitate dimensional analysis of how specific circuits and circuit dysfunctions relate to specific clinical phenotypes. These data will also facilitate the identification of subgroups that are homogenous in terms of symptom-behavior profiles, and may cut across traditional diagnostic boundaries, to determine if there is a natural neurobiological underpinning to such subgroups. Taking this a step further, future investigations could leverage the overlap in self-report item response and behavioral data across the four projects to generate develop new transdiagnostic constructs that might account for the phenotypic heterogeneity of depression and anxiety across the lifespan and provide new targets for probing it with neuroimaging. It is difficult to address such questions in a robust way without large samples. In this context, identical measures that were collected across all sites represent “low hanging fruit” for the first analyses integrating data across the projects. Examples of these measures are resting state fMRI, HCP-Emotion processing task fMRI, diffusion MRI, NIH toolbox emotion and cognition measures, depression severity measured by the Hamilton Depression Rating Scale, anhedonia measured by the Snaith-Hamilton Pleasure Scale and motivational systems measured by the BIS/BAS scales.

Future investigations will also be able to take advantage of the present 4-project CRHD resource by performing unified post-processing of data across all sites to extract phenotypes of interest. This will allow for more systematic characterization of subtypes of depression and anxiety defined by imaging measures rather than by symptom-behavior phenotypes. The imaging resource represented by the four projects allows for identification and validation of imaging subtypes defined by variations in brain structure, white matter tracts and by brain function at rest as well as during tasks. It remains unknown whether the remarkable heterogeneity of depression and anxiety may arise from distinct forms of neural circuit dysfunction. No study has yet tested this possibility by combining structural, diffusion, resting function and task-evoked functional imaging data derived from the same subjects, and then determining if imaging-derived subtypes adequately account for clinical heterogeneity. Certainly, seminal prior studies focused on a single imaging modality, such as resting state fMRI, highlight the promise for characterizing robust and clinically meaningful imaging subtypes (or ‘biotypes’) (Drysdale et al., 2017; Williams, 2016).

Methodologically, robust characterization of phenotypes and biotypes for depression and anxiety, and their integration, will rely on complementary insights that are gained from interrogation of the data using both theoretically motivated and data-driven approaches. As highlighted in our preliminary findings, appropriate regularization and testing on independent datasets are crucial steps in achieving robust results from data driven machine learning techniques, and the opportunity to utilize data across the four projects would accelerate progress in this area. Robust characterization of mood and anxiety disorders will also rely on knowing that associations between clinical, behavioral and neuroimaging data are robust across sites and scanners. Our four CRHD datasets will allow for progress to be made in determining the extent to which both phenotype and imaging data may generalize across sites and how possible site effects may be quantified and taken into account.

The vast majority of our current imaging knowledge about depression and anxiety is based on single snapshots in time. Gaining a more granular understanding of the extent to which imaging types and imaging-phenotype associations change over time is essential to understanding why the peak onset of depression and anxiety occurs in adolescence and why in some people it continues to have a chronic and/or ongoing remitting/relapsing course well into adulthood. By providing common imaging and phenotype data across early adolescence through mid-adulthood, data from our projects provide investigators with a means to generate insights about which aspects of imaging and associated phenotypes are common and which are distinct across these phases of the lifespan.

Use of the four datasets to lay the foundations for how phenotypes and imaging-derived biotypes are associated is also essential to facilitating ongoing discoveries about how these subtypes may be utilized as biomarkers for predicting response to novel antidepressant therapies. Related, such foundations also provide a means for reliably determining which circuit and clinical dysfunctions are modifiable by which interventions and which are not, and whether change in imaging-derived biotypes produces alleviation of clinical symptoms and distress.

Looking further ahead, insights gained from detailing imaging and phenotype associations that account for heterogeneity in mood and anxiety disorders across the present four CRHD projects will provide means from which to determine which of these associations are also characteristic of other disorders, either by comparing these datasets to others acquired using HCP protocols, or in new projects yet to be launched.

Although using data across the four datasets is clearly a promising avenue for future research, we should note two limitations of this approach. First, even though similar behavioral and questionnaire measures have been collected, in many cases these were not identical. In hindsight, reaching a consensus before starting the projects about which measures to collect would have improved harmonization. Of course, this was not possible because the projects were funded and started at different times and targeted different populations. In cases such as this, future studies should develop novel approaches to link convergent constructs that are assessed by different instruments across datasets so that the data collected by different projects can be integrated. Second, although the same types of imaging data were collected across sites, there were site differences in hardware and sequence parameters. If these data are to be analyzed together, it will be necessary to use tools that allow investigators to correct for site effects, such as ComBat (Fortin et al., 2017; Yu et al., 2018). Third, similar to what we outlined above, it would be beneficial for future studies to reach consensus on which imaging measures to collect before starting acquisition. In particular, the four studies used variants of the same fMRI tasks or used different tasks targeting the same construct. Future research using these four and other HCP datasets might compare results of these design choices to identify an optimal harmonized battery of tasks for use in subsequent work.

Conclusion

In sum, the four CRHD projects investigating mood and anxiety disorders have collected convergent structural and functional neuroimaging data as well as behavior and self-reports in large samples across much of the lifespan, from adolescence to adulthood. Investigators involved in these projects have already developed new methods for clinical neuroimaging applications, mapped novel relations between symptoms and functional connectivity, and identified structural and functional brain correlates of changes in symptoms during adolescence and after treatment with antidepressant therapies. Integrating data across these datasets will provide an invaluable resource for the development of a brain-based taxonomy of mood and anxiety disorders across the lifespan and the identification of novel treatment targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

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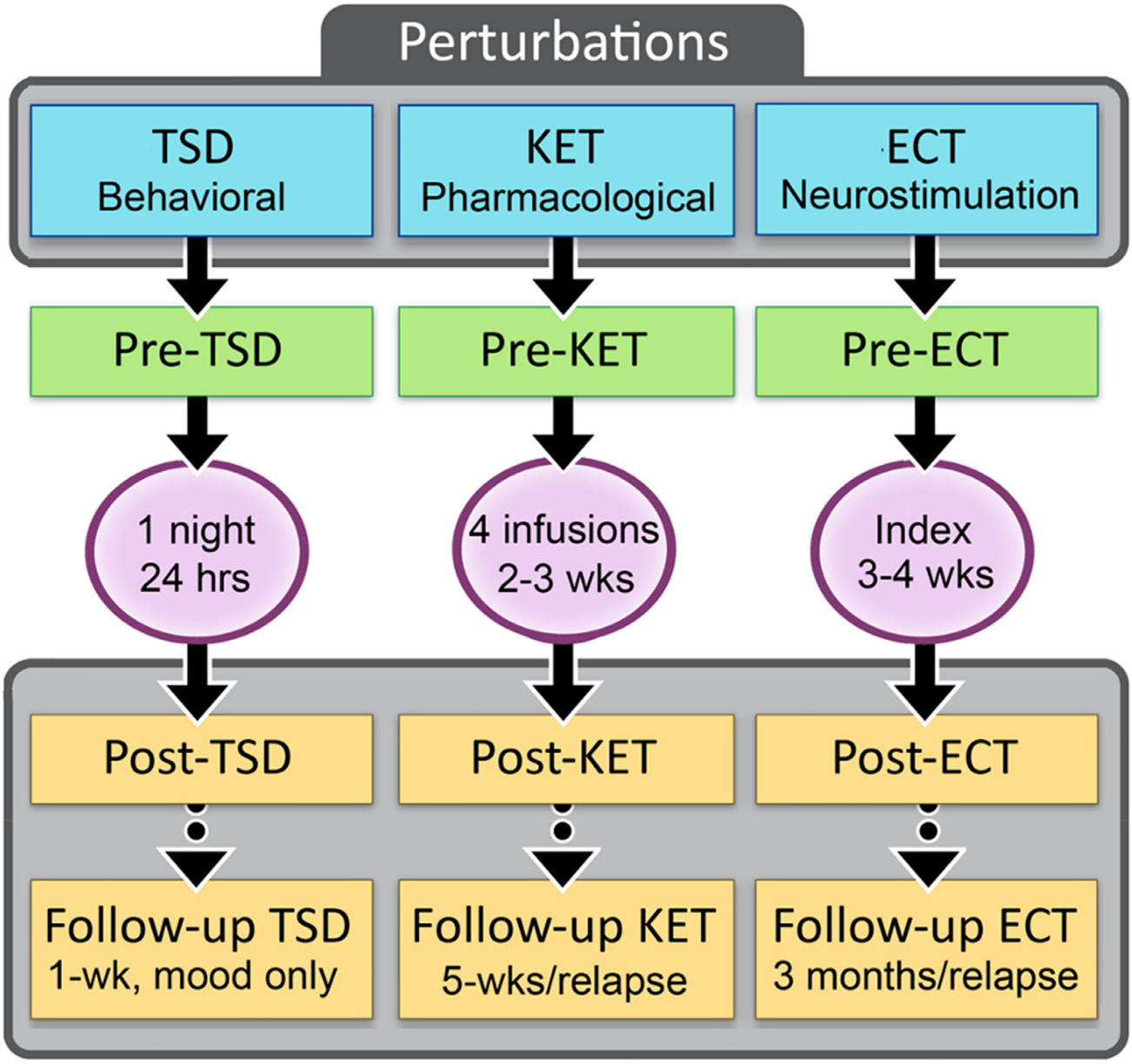

Fig. 1. Schematic showing the timing of the pre- and post-treatment MRI and clinical/behavioral assessments for each intervention in HCP-MDD.

Imaging and behavioral assessments were also collected after patients received their first ketamine infusion. HCP-MDD: "Perturbation of the treatment resistant depression connectome by fast-acting therapies"; TSD: total sleep deprivation; KET: ketamine; ECT: electroconvulsive therapy.

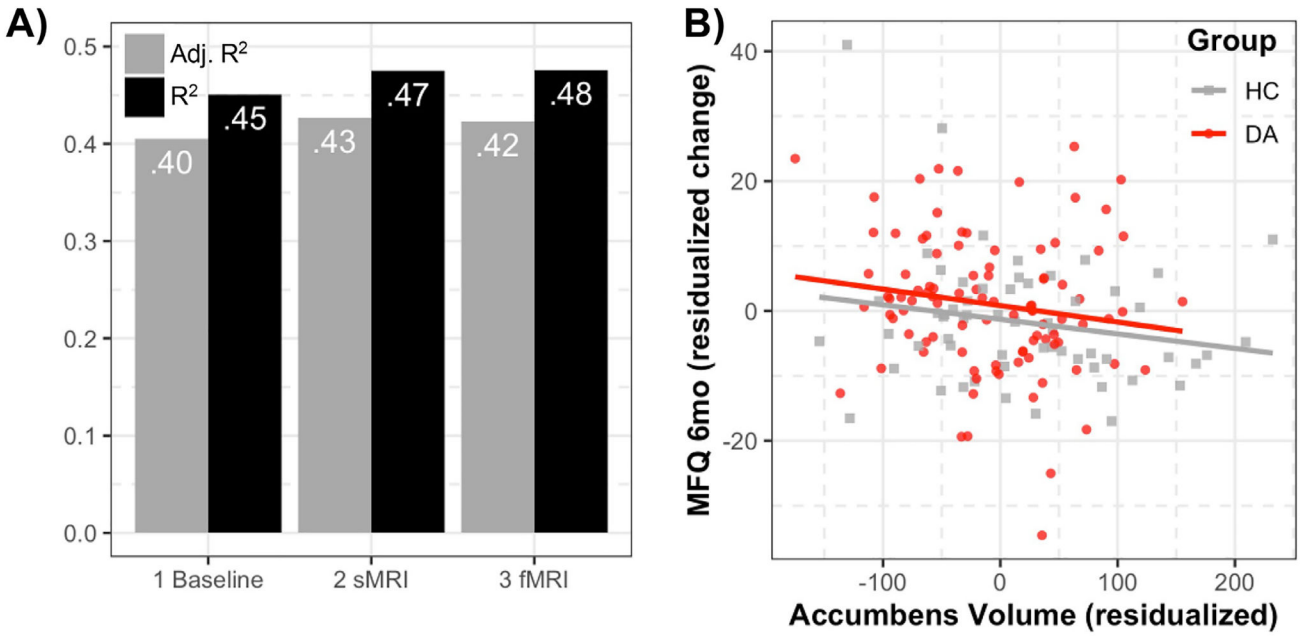

Fig. 2. Reduced nucleus accumbens volume predicted an increase in depressive symptoms over six months in HCP-ADA.

A: Adjusted R^2 (gray) and R^2 (black) values for the three models tested in the multimodal prediction section predicting MFQ (Mood and Feelings Questionnaire) depression scores at the 6-month follow-up. The first model includes baseline MFQ scores and all covariates. The second model adds average accumbens volumes (sMRI). The third model adds average accumbens Reward versus Baseline activation (fMRI). Panel B displays the association between residualized accumbens volumes and residualized MFQ (Mood and Feelings Questionnaire) depression scores from the 6-month follow-up, also residualized for all covariates including baseline depression. These represent results from the multimodal prediction model 2 (sMRI) indicating that smaller accumbens volume predict worsening depression symptoms at 6-month follow-up. HCP-ADA: “Connectomes related to anxiety and depression in adolescents”; HC = healthy controls; DA = depressed–anxious. Used from Auerbach et al. (2021) with permission.

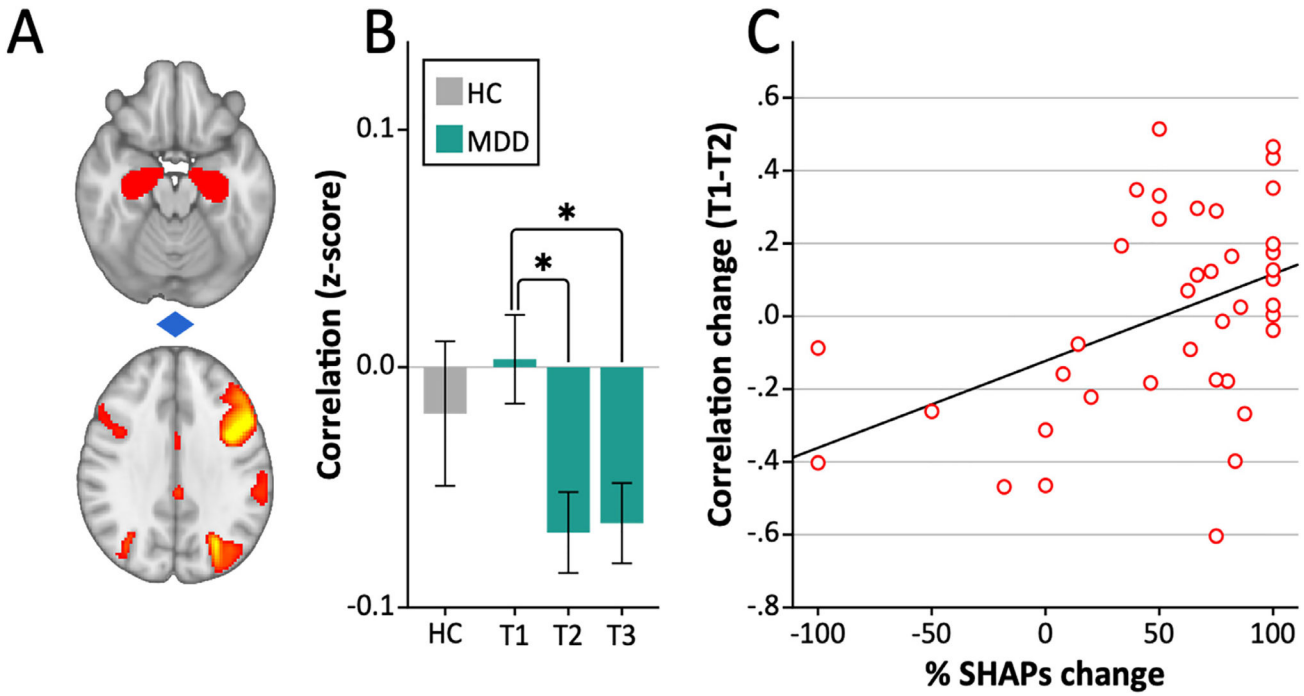

Fig. 3. Systems-level connectome perturbations following ketamine infusion in HCP-MDD.

A: Functional connectivity between the hippocampus and the central executive network (CEN) at B: Baseline (T1), and after single (T2) and serial ketamine infusions (T3) in patients with major depression (MDD, $n = 44$) and controls (HC, $n = 33$). C: Correlation between change in right hippocampal-CEN functional connectivity and % change in anhedonia measured with the Snaith–Hamilton Pleasure Scale (SHAPS) ($r = 0.44$, $p <$. 005). Data from Vasavada et al. (2021). HCP-MDD: "Perturbation of the treatment resistant depression connectome by fast-acting therapies".

Table 1

Sample information, inclusion and exclusion criteria for each of the four connectome studies related to human disease investigating mood and anxiety disorders.

HCP-DAM: “Dimensional connectomics of anxious misery”; HCP-DES: “Human connectome project for disordered emotional states”; HCP-MDD: “Perturbation of the treatment resistant depression connectome by fast-acting therapies”; HCP-ADA: “Connectomes related to anxiety and depression in adolescents”.

	Site	Age	N controls	Inclusion criteria for controls	N clinical	Inclusion criteria for clinical	Exclusion criteria
HCP-DAM	University of Pennsylvania	18–60	50	Must not meet criteria for a DSM-5 psychiatric disorder	200	Neuroticism ≥ 1 standard deviation above the mean of controls	MRI contraindications, history of neurological disorders, histories of exclusionary psychiatric conditions, factors affecting safety or compliance, alcohol/substance dependency, suicidality
HCP-DES	Stanford University	18–35	50	Must not meet criteria for a DSM-5 psychiatric disorder, no significant anhedonia, anxious arousal, concentration, rumination, or tension	250	Significant anhedonia, anxious arousal, concentration, rumination, or tension, untreated	
HCP-MDD	University of California Los Angeles	20–64	51	Must not meet criteria for a DSM-5 psychiatric disorder	180	Recurrent depression, existing episode lasting at least 6 months, failed to respond to at least two antidepressants, no neuromodulation or ketamine within the previous 6 months	
HCP-ADA	Northeastern University	14–17	-	-	225	Diagnosis of depression and/oranxiety	

Table 2

Magnetic resonance imaging acquisition parameters for each of the four connectome studies related to human disease investigating mood and anxiety disorders.

HCP-DAM: “Dimensional connectomics of anxious misery”; HCP-DES: “Human connectome Project for disordered emotional states”; HCP-MDD: “Perturbation of the treatment resistant depression connectome by fast-acting therapies”; HCP-ADA: “Connectomes related to anxiety and depression in adolescents”.

	HCP-ADA	HCP-DAM	HCP-MDD	HCP-DES
Scanner	Siemens Prisma 3T	Siemens Prisma 3T	Siemens Prisma 3T	GE Discovery MR750 3T
Head coil elements	64 (52 used)	64 (52 used)	32	32
Max. gradient strength (mT/m)	80	80	80	50
T1w				
Resolution(mm)	.8 × .8 × .8	.8 × .8 × .8	.8 × .8 × .8	.8 × .8 × .8
FoV (mm)	256 × 240 × 167	256 × 240 × 167	256 × 240 × 167	256 × 256 × 184
TE (ms)	2.18	2.22	1.81/3.6/5.39/7.18	3.548
TR (ms)	2400	2400	2500	2840
TI (ms)	1040	1000	1000	1060
Slice oversampling (%)	23.1	23.1	7.7	0
Max. vNav reacquisition	24 (~60 s)	–	30	PROMO (Rescan=300 s)
Bandwidth (Hz/px)	220	220	740	195
Parallel imaging	2	2	2	2 × 1.25
Flip angle	8	8	8	8
Fat suppression	water excitation	water excitation	water excitation	–
T2w				
Resolution(mm)	.8 × .8 × .8	.8 × .8 × .8	.8 × .8 × .8	.8 × .8 × .8
FoV (mm)	256 × 240 × 167	256 × 240 × 167	256 × 240 × 167	256 × 256 × 184
TE (ms)	564	563	564	~75 (subject-specific)
TR (ms)	3200	3200	3200	2500
Slice oversampling (%)	0	0	7.7	0
Max. vNav reacquisition	18 (~60 s)	not specified	25	PROMO (Rescan=300 s)
Bandwidth (Hz/Px)	744	744	744	781
Parallel imaging	2	2	2	1.9 × 1.9

	HCP-ADA	HCP-DAM	HCP-MDD	HCP-DES
EPI				
PE direction	AP/PA	AP/PA	AP/PA	AP/PA
dMRI				
b-values (s/mm2)	1500/3000	1500/3000	1500/3000	1500/3000
Diffusion directions by shell	91/92 (+14 b0)	92/93	92/93	75/75 (+10 b0)
Multiband factor	4	4	4	4
TR (ms)	3230	3230	3230	3200
TE (ms)	89.2	89.2	89.2	82.3
Resolution (mm)	1.5 × 1.5 × 1.5	1.5 × 1.5 × 1 × 5	1.5 × 1.5 × 1.5	1.5 × 1.5 × 1.5
fMRI				
TR (ms)	800	800	800	710
TE (ms)	37	37	37	30
Multiband factor	8	8	8	6
Resolution (mm)	2 ×2 ×2	2 ×2 ×2	2 ×2 ×2	2.4 × 2.4 × 2.4
Matrix size	104 × 104 × 72	104 × 104	104 × 104 × 72	92 × 92 × 60
FOV (mm)	208 × 208 × 144	208 × 208 × 144	208 × 208 × 144	220.8 × 220.8 × 144
Voxel Volume (mm^3)	8	8	8	13.824

Table 3

Common fMRI tasks, behavioral measures and questionnaires across the four connectome studies related to human disease investigating mood and anxiety disorders.

For each measure, the studies in which it was collected are marked with an X. For brevity, only measures collected in at least two studies are shown. For tables of all measures collected see Supplementary Materials. HCP-DAM: “Dimensional connectomics of anxious misery”; HCP-DES: “Human connectome Project for disordered emotional states”; HCP-MDD: “Perturbation of the treatment resistant depression connectome by fast-acting therapies”; HCP-ADA: “Connectomes related to anxiety and depression in adolescents”.

Domains	Measures	HCP-ADA	HCP-DAM	HCP-MDD	HCP-DES
MRI	Structural MRI (T1w and T2w)	X	X	X	X
	Diffusion MRI	X	X	X	X
	Resting state fMRI	X	X	X	X
	HCP-Emotion Processing task fMRI	X	X	X	X
	HCP-Incentive Processing task fMRI	X	X		X
	Emotional Interference task fMRI	X	X		
Cognitive	NIH Dimensional Change Card Sort	X	X	X	X
	NIH Pattern Comparison	X	X	X	X
	NIH Flanker Inhibitory Control and Attention Test	X	X	X	X
	NIH List Sorting Working Memory Test	X	X	X	X
	NIH Oral Reading Recognition Test	X		X	
	Penn Word Memory Test	X	X		
	Penn Progressive Matrices	X	X	X	
	NIH Picture Sequence Memory Test		X	X	X
	NIH Picture Vocabulary Test		X	X	X
Diagnostic	The Structured Clinical Interview for DSM-5		X	X	
	PTSD Checklist Civilian Version		X		X
Mood and anxiety	Hamilton Depression Rating Scale	X	X	X	X
	Depression Anxiety Stress Scales			X	X
	Quick Inventory of Depressive Symptoms-Self Report			X	X
	Mood and Anxiety Symptom Questionnaire short form		X		X
	Ruminative Thought Style Questionnaire		X	X	X
	Stress and Adversity Inventory	X		X	

Domains	Measures	HCP-ADA	HCP-DAM	HCP-MDD	HCP-DES
	Snaith-Hamilton Pleasure Scale	X	X	X	X
Functioning	Social Functioning and Adjustment Scale		X		X
	Columbia-Suicide Severity Rating Scale	X	X		
Temperament	Behavioral Inhibition Scale	X	X	X	X
	Behavioral Activation Scale	X	X	X	X
	Five Factor Personality Inventory-Neuroticism subscale	X	X		
Emotion	NIH Psychological Well-Being	X	X	X	X
	NIH Social Relationships	X	X	X	X
	NIH Stress and Self-Efficacy	X	X	X	X
	NIH Negative Affect	X	X	X	X
Demographics and sample characteristics	Fagerstrom Test For Nicotine Dependence		X	X	X
	Diagnostic and Statistical Manual of Mental Disorders -V Alcohol Use Disorder		X		X
	Diagnostic and Statistical Manual of Mental Disorders-5 Substance Use Disorder		X		X
	Phenotypes and eXposures			X	X
	Demographic Questionnaire	X	X	X	X
	Medical History	X	X	X	X
	PhenX Alcohol			X	X
	PhenX Tobacco			X	X
	Handedness	X	X	X	X
	Substance use		X	X	