Title:

Addressing heterogeneity (and homogeneity) in treatment mechanisms in depression and the potential to develop diagnostic and predictive biomarkers

Running title:

Biomarkers in depression

Authors:

Cynthia H.Y. Fu [1-2], Yong Fan [3], Christos Davatzikos [3]

Affiliations:

1. School of Psychology, University of East London, London, UK

2. Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

3. Center for Biomedical Image Computing and Analytics, Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

Corresponding author:

Professor Cynthia H.Y. Fu, School of Psychology, University of East London, Arthur Edwards Building, Water Lane, London E15 4LZ, United Kingdom

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Abstract

It has been 10 years since machine learning was first applied to neuroimaging data in psychiatric disorders to identify diagnostic and prognostic markers at the level of the individual. Proof of concept findings in major depression have since been extended in international samples and are beginning to include hundreds of samples from multisite data. Neuroimaging provides the unique capability to detect an acute depressive state in major depression, while we would not expect perfect classification with current diagnostic criteria which are based solely on clinical features. We review developments and the potential impact of heterogeneity, as well as homogeneity, on classification for diagnosis and prediction of clinical outcome. It is likely that there are distinct biotypes which comprise the disorder and which predict clinical outcome. Neuroimaging-based biotypes could aid in identifying the illness in individuals who are unable to recognise their illness and perhaps to identify the treatment resistant form early in the course of the illness. We propose that heterogeneous symptom profiles can arise from a limited number of neural biotypes and that apparently heterogeneous clinical outcomes include a common baseline predictor and common mechanism of treatment. Baseline predictors of clinical outcome reflect factors which indicate the general likelihood of response as well as those which are selective for a particular form of treatment. Irrespective of the mechanism, the capacity for response will moderate the outcome, which includes inherent models of interpersonal relationships that could be associated with genetic risk load and represented by patterns of functional and structural neural correlates as a predictive biomarker. We propose that methods which directly address heterogeneity are essential and that a synergistic combination could bring together data-driven inductive and symptom-based deductive approaches. Through this iterative process, major depression can develop from being syndrome characterized by a collection of symptoms to a disease with an identifiable pathophysiology.

Major depression is characterized by a persistent low mood or inability to experience usual feelings of pleasure, which is associated with impairments in neurovegetative, psychomotor and cognitive functioning (1, 2). Although melancholia has been recognised throughout millennia, current diagnostic criteria are the result of attempts in the past decades to develop reliable, ontological classifications (3). However, the criteria are based only on observable clinical features because no diagnostic pathophysiology has yet been identified. At the present time, major depression is thus a syndrome, which is characterized by a collection of symptoms, rather than a disease with an identifiable pathophysiology.

There is significant heterogeneity in the symptom profiles that can make up a diagnosis, in the clinical outcomes for a given treatment, and in the longitudinal course for individual patients. Addressing heterogeneity is essential, which includes taking into account potential homogeneous factors. Within the heterogeneity in our current classification criteria, we support a core concept of the illness as a primary disorder in mood, in particular a lowering in mood that is embodied in the individual, though we would not expect perfect classification with current diagnostic criteria (4).

We propose that neuroimaging can aid in identifying potential biotypes by quantifying the heterogeneity, as well as homogeneity, that comprise major depression and the biotypes that can predict clinical outcome. We review development from the initial studies 10 years ago, which had applied machine learning to neuroimaging data to classify major depression and to predict clinical outcome (4–6), to replication and progression in international independent datasets (7–9), and how heterogeneity is being addressed in recent studies (7, 10, 11). We review homogeneous mechanisms in psychological and pharmacological therapies, and we discuss the potential to identify biomarkers to predict clinical response. We propose that multitudinous heterogeneous symptom profiles can arise from a limited number of neural patterns as well as how apparently heterogeneous clinical outcomes can include a common baseline predictor of response and common mechanism of treatment.

We conclude with a proposal for the necessary steps and recent developments to identify neuroimaging-based biotypes: 1) harmonization of longitudinal multisite datasets acquired in different scanners and with different image acquisition protocols (12); 2) modelling the pathological process by multiple regularized transformations from the healthy to the patient population to identify the multiple neuroanatomical patterns that characterise disease heterogeneity (CHIMERA) (13); and 3) characterisation of the neuroanatomical heterogeneity through delineation of the multiple hyperplanes within disease populations (HYDRA) (14).

Heterogeneity in major depression phenotypes

Johannsen (15) introduced the terms: "genotype", which describes the sum of genes in a gamete or zygote; "phenotype", referring what can be readily observed; and "biotype", which represents a given genotype in which biotypes can evolve from each other through small changes in genotype. Our current diagnosis of major depression is a phenotype, and many phenotypic combinations are possible within present diagnostic systems (1, 2). In terms of the symptoms, there are many potential combinations of clinical profiles, and there is significant clinical comorbidity with anxiety disorders (1–3). In terms of the longitudinal course of the illness, it is unknown whether the initial episode will be a single episode, or points to a course of unipolar depression, or is an acute depressive episode of a bipolar disorder (in the present review, 'major depression' refers to 'unipolar depression' in distinction to bipolar disorder). Heterogeneous phenotypes can arise from a common genotype, and seemingly homogeneous phenotypes can arise from different genotypes (15).

Major depression is the leading mental health disorder worldwide, affecting over 350 million people (16). Yet, heritability estimates are around 37% (17), which is relatively low in contrast to bipolar disorder and schizophrenia which have heritability estimates that are

consistently up to 90% from twin and molecular genetic studies (18). The heritability of major depression is polygenic, consisting of hundreds of variants and genes, each providing a small component to the genetic contribution, and samples have generally consisted of people of European ancestry (19). Genetic risk variants are not clinically useful at the level of the individual, and how genetic risk progresses into an acute depressive episode is unknown (20).

The genetic and environmental factors that lead to major depression are expressed in subtle and widespread alterations in brain structure and brain function. Magnetic resonance imaging (MRI) has revealed effects in multiple networks, including in frontolimbic circuits and default mode network (21), which are evident in the first episode (22, 23) and supported by neuropathological abnormalities (24). Multivariate pattern analysis integrates the subtle and spatially distributed alterations into models, learning to categorise the patterns and then to identify them in new data. Applying machine learning, proof of concept data demonstrated the ability to identify major depression at the level of the individual with high sensitivity and specificity from structural MRI and task-based functional MRI data (5, 6, 25), and distinct models predicted clinical response at baseline before the start of treatment with measures of confidence of the accuracy of the predictions (26).

Kambeitz et al. (8) meta-analysis of 33 international samples of major depression (n = 912) and healthy (n = 864) participants demonstrated an overall classification with 77% sensitivity and 78% specificity, based on structural MRI, resting state functional MRI, task-based functional MRI and diffusion tensor imaging. Most studies to date have generated dichotomous classification labels for diagnosis, either major depression or healthy control, primarily due to limited sample sizes of participants with major depression (n = 15-57) (8, 9). In the largest multisite sample to date, Drysdale et al. (7) were able to identify a number of subtype models based on resting state functional MRI data, which were then validated in independent samples. The models were developed from what would be considered a more

treatment-resistant form of depression, that is from participants with major depression (n = 220) with active symptoms which had failed to respond to at least two antidepressant treatment trials and while taking medications. The models were then trained in the full sample of depression (n = 333) and healthy (n = 378) participants and further validated in independent samples of depression (n = 125) and healthy (n = 352) participants.

A common pattern of altered connectivity was evident, which encompassed the ventromedial prefrontal, orbitofrontal and posterior cingulate cortices, insula, and subcortical regions, and distinct patterns of functional connectivity and clinical symptom profiles were revealed in four subtypes with high sensitivity and specificity (82 - 92%). Subtype 1 was associated with anxiety, early and middle insomnia, and anergia; subtype 2 was primarily associated with anergia; subtype 3 with anhedonia and psychomotor retardation; and subtype 4 with the highest levels of anxiety, early and middle insomnia, as well as anhedonia. The subtypes were not accounted for by depressive severity only as there were no significant differences in depressive severity scores in subtypes 1, 3 and 4, although there was a modest decrease in subtype 2. Increased thalamic and frontostriatal connectivity associated with anhedonia and psychomotor retardation was most pronounced in subtypes 3 and 4. Reduced fronto-amygdala connectivity associated with anxiety was most severe in subtypes 1 and 4. Reduced connectivity in anterior cingulate and orbitofrontal regions involved in motivation associated with symptoms of anergia and fatigue were most evident in subtypes 1 and 2. By addressing heterogeneity, Drysdale et al. (7) represent an important step in identifying potential biotypes that comprise major depression.

While the highest levels of sensitivity and specificity in classification have been achieved in the treatment-resistant form of depression (8, 9), these could be confounded by biological effects of treatment resistance and antidepressant medication on brain structure and function (27, 28). From a methodological perspective, Dinga et al. (29) suggest that the clustering algorithm had led to overfitting as their replication analysis could not generate

comparable statistically significant subtypes. However, the samples differ significantly in their clinical characteristics in terms of treatment resistance and depressive state, which are associated with distinct neural correlates (27, 28). Drysdale et al. (7) training sample had been based on treatment resistant depression in an acute episode, while Dinga et al. (29) sample (n = 178) was comprised of major depression, anxiety disorders, as well as comorbid depression and anxiety disorders, in which about half the sample were in remission or had mild symptoms. The training samples, while larger than the majority of studies to date, could have been sufficiently non-overlapping, were underpowered, and might reflect homogeneity in the neural biotypes of less treatment resistant forms of the illness that are in remission or with few symptoms and which present as heterogeneous clinical phenotypes (7, 29).

As a corollary, treatment-resistant depression is currently a clinical diagnosis that refers to a depressive episode that does not improve despite a series of treatments. A predictor model of clinical and sociodemographic data has demonstrated an accuracy of 75% in identifying treatment resistant depression (30). Clinical features in the model though included duration of illness, lifetime duration of hospitalizations and number of depressive episodes, which precludes identification early in the course of the illness. If the treatment resistant biotype is present at the onset of the episode, rather than as a consequence of subsequent treatments, then the biotype might be identifiable early in the illness. Low rates of remission, which is less than one third of treatment trials irrespective of the form of treatment (31,32), indicate that current treatments are insufficient and highlight a subgroup which consistently shows a limited or lack of clinical improvement, suggesting that the pathophysiology of treatment-resistant depression could already be present early in the course of illness.

Common and distinct neural patterns between unipolar major depression and other disorders are another source of heterogeneity. Conjunction analysis of grey matter volumes has observed common reductions in anterior cingulate, dorsomedial and ventromedial prefrontal cortices and insula in unipolar depression and bipolar disorder relative to healthy

controls with additional reductions which included right middle frontal and left hippocampus in unipolar depression relative to bipolar disorder (21). Classification results have demonstrated a contribution of reduced grey matter volumes in the anterior cingulate in unipolar depression relative to bipolar disorder (33), although the datasets were based on different samples (21,33).

In addition to the inherent heterogeneity in the disorder, demographic-related factors, such as age, sex and ethnicity, are potential variables which can be controlled for. Most studies have consisted of ethnically homogeneous samples, either predominantly Caucasian or Chinese, raising the issue of whether the models can be generalised to the wider patient population, although we have found proof of principle from a small community sample of African, Asian and Caucasian patients based on structural MRI (9). Furthermore, applying neuroimaging-based biotypes as a model of major depression for genetic studies could improve the specificity of identifying variants for major depression as well as from a greater ethnic diversity, addressing limitations associated with broader definitions of depression and current genetic studies which have been most often assessed in people of European ancestry (20).

Heterogeneity in methodology is a controllable variable. Task-based functional MRI protocols focused on a cognitive task (25) show lower levels of classification accuracy relative to an emotion-based task (5), which is not unexpected in major depression. Overlooking task effects adds variability that is not random, which degrades the quality of the signal and introduces confounds in meta-analyses of classification biomarkers (8, 34).

Heterogeneity (and homogeneity) in treatment mechanisms

Selective serotonin reuptake inhibitor (SSRI) antidepressants enhance synaptic plasticity, in which the effects on mood might be moderated by environment (35, 36). Pharmacological

treatment is associated with increases in regional cerebral volumes, such as in the hippocampus (37). Hippocampal volume is reduced in major depression, which is evident in the first episode (23). SSRI treatment is associated with increased hippocampal volume (37), and an early increase in hippocampal volume following one week of treatment with a serotonin noradrenaline reuptake inhibitor (SNRI) antidepressant was predictive of clinical response (35), which could reflect enhancement in synaptic plasticity and neurogenesis (36, 37).

Psychotherapy is an effective treatment for an acute depressive episode, is the preferred form of treatment for many individuals with depression, and demonstrates a sustained benefit in preventing a subsequent depressive relapse (39-41). The most common forms of short term psychotherapy are cognitive behavior therapy, behavioral activation, interpersonal therapy, and psychodynamic psychotherapy. Distinct formulations and mechanisms have been proposed, however efficacy has either been comparable or no significant differences have been observed between treatments (42-46). Moreover, our understanding of the neural mechanisms is limited, and there have been remarkably few longitudinal studies of the neural correlates of psychotherapy in depression, about a quarter of the number of pharmacological studies (47, 48).

The theoretical formulation of cognitive behavior therapy (CBT) proposes a cognitive triad of biased negative views of onself, one's future and experiences in the outside world which leads to characteristic affective and behavioural symptoms (49). CBT attempts to intervene in this cycle by addressing negative cognitions: automatic thoughts (eg. "I'm a failure") and dysfunctional attitudes (eg. "I should be happy all the time") that in turn reflect schemas and core beliefs which organize new experiences. Cognitive change is a key mechanism in which modifying maladaptive cognitions leads to an improvement in mood (49, 50). Behavioral activation therapy focuses on behavioural change to increase engagement in constructive reinforcing activities and to reduce engagement in avoidance and withdrawal

behaviours which maintain depression. Behavioral activation refers to the process of changing behaviors in order to engage in positively reinforcing and adaptive activities, which has demonstrated efficacy as a stand-alone component of CBT (43, 51).

Interpersonal therapy (IPT) is based on the premise that maladaptive communication processes impact negatively on mood. IPT seeks to address interpersonal difficulties common in depression, focusing on four main themes: bereavement related to the grief and loss of a significant other; role transition due to a life change which affects relationships, such as a new job or loss of functioning; interpersonal disputes in expectations in relationships with significant others; or interpersonal deficits which could be reflected in social isolation or difficulties in maintaining relationships (52). Short term psychodynamic psychotherapy applies support as well as insight to discuss internalized past relationships, intrapersonal patterns and current relationships. Psychodynamic psychotherapy considers how internalized past relationships and unconscious processes could impact on interpersonal relationships and day to day functioning to improve awareness of such processes which in turn aids in the ability to modify responses and behaviours in current behaviours and relationships (53).

If a particular process is a mechanism, it is necessary to establish the temporal sequence such it is the specific process which leads to improvements in depressive symptoms (54). As a potential mechanism in CBT, a change in cognition would be expected to precede any improvements in depressive symptoms. In support, early changes in cognition during CBT and "sudden gains" (55–57) as well as therapist adherence to techniques and competence (58) are associated with symptom improvements. However, when changes in mood symptoms were taken into account, early changes in cognitive content no longer predicted subsequent improvements (59). Moreover, improvements in depressive symptoms have also been observed to precede changes in cognitions (60). Component analysis suggests that the effectiveness of CBT can be largely ascribed to behavioral activation (43, 50), while

acknowledging a predictive component of cognitive change, though assessed as a nominal contribution (61).

Although heterogeneous mechanisms have been proposed, the effects are small. It is well established that common factors contribute to the efficacy of the different forms of psychotherapy. Therapeutic alliance refers to the relationship between the patient and therapist and has consistently demonstrated a mediating effect in clinical outcome to psychotherapy (62), as well as to pharmacological and placebo treatments (63, 64). Patient outcome expectations describe the prognostic beliefs about effects of engaging in treatment that could be positive, negative or ambivalent, which show a small association with treatment outcome, which may further be mediated by the therapeutic alliance (65). A common role of the therapist in short term psychotherapy is as an advocate for the patient. The CBT therapist is proposed to represent an active, authoritative advocate for change who supports patients to engage in activities and thoughts, which in turn leads to improvements in depressive symptoms (61). The goal of the IPT therapist is to be the patient's ally who reinforces beneficial interpersonal skills and actively reviews adverse outcomes including through role play and rehearsal (52). A range of outcomes has been observed between therapists, in which adherence and competence seem to have a limited effect (66), while therapist adaptiveness and empathy are correlated with clinical outcome (68). How, when and what a therapist responds to in a session reflects their adaptiveness and empathy.

Enhanced synaptic plasticity is a potential common mechanism of antidepressant medication (35, 36) and psychotherapy. Synaptic plasticity is a fundamental mechanism in learning and memory (68, 69), and learning is an important mechanism in psychotherapy, in which the therapist provides an essential component with whom skills are learned. Moreover, we propose that the patient therapist relationship builds upon inherent models of relationships. Even in the absence of a therapist who is physically present, we would expect that inherent models would have an impact on the perceived relationship, such as in internet-based

treatments. We propose that encoding of the relationship is episodic with the repeated sessions of the therapy and that recall of the relationship may be initially explicit.

Furthermore, treatment with CBT (70) as well as treatment with a selective serotonin reuptake inhibitor antidepressant (71, 72) has been associated with normalisation of amygdala responses to sad emotional expressions. Encouragement and validation from another person is associated with a reduction in pain (73), in which the emotional-affective dimensions are encoded in the amygdala (74). While support is an inherent component of the patient therapist relationship in both psychological and pharmacological treatments, learning in the context of the patient therapist relationship is potential mechanism, which would have a greater contribution in psychotherapy. Normalisation of amygdala responses could reflect common effects on mood following psychological and pharmacological treatments, in which learning in the context of the patient therapist relationship is a contributing mechanism.

Heterogeneity in treatment responsiveness and outcomes

Baseline predictors of clinical outcome reflect factors which indicate the general likelihood of response to a variety of forms of treatments and those which are selective for a particular form of treatment. Irrespective of the mechanism of treatment, the capacity for response will moderate the outcome. If there is an inherent capacity, then there would be general predictor of clinical responsivity to current first line treatments (32, 35, 36, 47). The absence of such marker/s would indicate a reduced likelihood of response.

Short term psychological treatments require the therapist to be an active advocate for the patient (49, 52, 53, 75). This could be explicit in the physical presence of the therapist or an inherent implicit presence. Therapeutic alliance is a mediator of treatment outcomes to both pharmacological and psychological treatments (62-65), but how an individual with

depression experiences the interaction with the therapist would be affected in part by their inherent patterns in interactions in close relationships (76, 77). Predisposing patterns in interpersonal relationships would moderate treatment outcome as a general predictor of clinical outcome.

If impairments in inherent models of interpersonal relationships moderate clinical outcome to psychological treatments, then factors which impact on their development would contribute to clinical outcome, such as attachment patterns (76, 77). Spatial and temporal patterns of interactions between an individual and their attachment figures frame how the individual then perceives and responds in other interpersonal relationships, termed 'internal working models' (76). For example, attachment theory describes how interpersonal relationships evolve from relationships with early caregivers to diverse adult relationships, which are malleable and can continue to develop. It is estimated that 55% of healthy adults have a secure attachment pattern, but it is the insecure attachment profile which predominates in depression and specific subtypes have been associated with poorer clinical outcomes (76, 77).

Limited development of inherent models of interpersonal relationships could also be associated with genetic risk load, for example it might be expected that patients with depression with a high genetic risk load for autistic spectrum disorder would prefer an internet based CBT, however, if they have an impaired inherent model of interpersonal relationships, then their ability to interact with and utilise the CBT format would be limited (76), as potentially for any short term therapy which could be transdiagnostic.

Shared features in the forms of therapy include treatment durations, which have mostly been short term in the order of weeks to months, low rates of clinical effectiveness, and the role of the therapist as an active advocate who interacts directly with the patient (32, 78). However, if the ability of the patient to engage with the therapist depends in part on their inherent

models of interpersonal relationships, then impairments in the models would impact on how their relationship develops with the therapist, to which some therapists may be better able to respond and adapt their treatment. This heterogeneity could be evident in part in amygdala responsivity, for example an insecure anxious attachment pattern is associated with increased amygdala response to emotional stimuli (79) and attachment patterns modulate experimentally induced pain ratings in the presence of an observer (80).

Addressing heterogeneity

Being able to identify an acute depressive episode in major depression that is not treatment-resistant, to predict treatment outcome and to predict the course of the illness are key clinical challenges. Model development requires the appropriate data and methodology, which can be summarised, but the quality of the data and methodology are paramount (4, 10). In order to reflect clinical practice and to develop models that are not confounded by treatment, the data would be from a community based medication-free population in an acute depressive episode with first episode or recurrent depression that is not treatment-resistant. Well characterised large datasets are required with consideration of ethical and data sharing issues. We would not expect perfect classification with current diagnostic criteria because clinical presentations do not necessarily reflect specific biological measures and do not identify specific pathophysiologies. We would expect an iterative process in which the neuroimaging-based biomarkers are applied to specify potential pathophysiologies (4).

Methods that directly address heterogeneity are essential. Several studies have begun to use high-dimensional clustering methods to dissect imaging heterogeneity in various diseases (81). While direct clustering of patient data can be informative, it is confounded by variations related to demographics and other factors that are not related to disease pathophysiology. Two semi-supervised learning methods are proposed in an attempt to address this limitation: CHIMERA (13) and HYDRA (14).

CHIMERA is primarily generative, and it assumes that the statistical distribution of imaging features of the (heterogeneous) patient cohort is derived from the statistical distribution of the healthy cohort via a number of transformations that reflect the effects of underlying (heterogeneous) pathophysiologies (Figure 1). Covariates are taken into account explicitly. CHIMERA is probabilistic clustering approach that models the pathological process by a combination of multiple regularized transformations from the healthy control population to the patient population. The populations are considered as point distributions which are matched by a variant of the coherent point drift algorithm. For example, a 40 year old woman with depression would have been a 40 year old healthy woman had she been spared the disorder. This is directly modelled in CHIMERA which seeks to identify the multiple imaging patterns that relate to disease effects in order to characterize disease heterogeneity.

HYDRA takes a similar approach, but from the discriminative angle: it uses a number of support vector machine hyperplanes to separate patients from health controls in which each hyperplane reflects one subtype. Covariates are first regressed out of the data. The subtypes are captured by multiple linear hyperplanes which form a convex polytope that separates two populations in which each face of the polytope defines a disease subtype (Figure 2). Both methods use cross-validation and split-sample analyses to find the optimal number of subtypes.

The potential of these methods to capture neuroanatomical heterogeneity from MRI has been demonstrated in schizophrenia, mild cognitive impairment and Alzheimer's disease (11, 81-83). Data-driven, inductive modelling strategies model the neuroanatomical patterns that make up major depression as a collection of directions of deviation from normal neuroanatomical patterns. These approaches model the pathological processes associated with depression by a combination of multiple regularized transformations from the healthy control population to the patient population, thereby seeking to identify multiple

neuroanatomical patterns that relate to disease effects and to characterize disease heterogeneity. A complementary deductive approach, such as reported clinical symptoms, would apply prior knowledge to identify the linear combinations of neuroanatomical features that correlate with clinical clusters. A synergistic combination could also bring together data-driven inductive and symptom-based deductive approaches such that the clinical measures will be used in CHIMERA and HYDRA to inform the clustering.

Psychological and pharmacological treatments propose distinct heterogeneous mechanisms. Yet, short term psychotherapies advocate an active therapist as a common homogeneous component. If outcomes to short term psychotherapy as well as to antidepressant medication depend in part on inherent models of interpersonal interactions, then this is measurable prior to the initiation of treatment. Measures to date though have been subjective or clinician-rated without a gold standard. Neuroimaging markers offer the potential to characterize the homogeneous as well as heterogeneous mechanisms of clinical effectiveness at the level of the individual with the potential to lead to patient-specific treatments.

In summary, neuroimaging-based biomarkers offer the strongest potential to date in identifying the biotypes that comprise our current symptom-based diagnosis of major depression. Increasing sample sizes from multisite collaborations will provide increased power to identify neural biotypes that comprise the diagnosis. Among purported heterogeneous treatment mechanisms, a common factor is the patient clinician relationship. Learning in the context of this relationship is a potential common mechanism which could modulate amygdala responsivity. The inherent model of interpersonal relationships would moderate clinical outcome, which could be associated with genetic risk load and represented by patterns of functional and structural neural correlates. A predictive biomarker would aid in the stratification of the illness, indicating the most appropriated treatment or combination of treatments, which would improve recovery and disability, as well as increase statistical

power in treatment studies by reducing heterogeneity in samples. Integrating neuroimaging-based biotypes with genetic studies could aid the specificity in identifying variants. It is essential to directly address heterogeneity in developing biomarkers in which a synergistic combination could bring together data-driven inductive and symptom-based deductive approaches.

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CF, YF and CD have nothing to disclose.

Figure Legends

Figure 1.

CHIMERA is a primarily generative method, which assumes that the distribution of measurements from patients (Y, in the figure) is derived from the distribution of controls (X, in the figure), after some (unknown) transformations (T_i) are applied. The latter represent (heterogeneous) disease effects

Figure 2.

The HYDRA method is mostly discriminative, in that it attempts to separate patients and controls as well as possible, using multiple hyperplanes, one for each subtype.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5); 2013.

2. World Health Organization. International Statistical Classification of Diseases. 10th revision, 2nd edition. Geneva: World Health Organization; 2004.

3. Kendler KS. The genealogy of major depression: symptoms and signs of melancholia from 1880 to 1900. Mol Psychiatry. 2017;22(11):1539–53.

4. Fu CHY, Costafreda SG. Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. Can J Psychiatry. 2013 Sep;58(9):499–508.

5. Fu CHY, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SCR, et al. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. Biol Psychiatry. 2008 Apr 1;63(7):656–62.

6. Costafreda SG, Chu C, Ashburner J, Fu CHY. Prognostic and diagnostic potential of the structural neuroanatomy of depression. Domschke K, editor. PLoS ONE. 2009 Jul 27;4(7):e6353.

7. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28–38.

8. Kambeitz J, Cabral C, Sacchet MD, Gotlib IH, Zahn R, Serpa MH, et al. Detecting neuroimaging biomarkers for depression: a meta-analysis of multivariate pattern recognition studies. Biol Psychiatry. 2017 01;82(5):330–8.

9. Sankar A, Zhang T, Gaonkar B, Doshi J, Erus G, Costafreda SG, et al. Diagnostic potential of structural neuroimaging for depression from a multi-ethnic community sample. BJPsych Open. 2016 Jul;2(04):247–54.

10. Davatzikos C. Machine learning in neuroimaging: progress and challenges. NeuroImage. 2019 Aug;197:652–6.

11. Davatzikos C. Quantifying anatomical and functional heterogeneity in big datasets,

using machine learning methods towards a dimensional neuroimaging framework. Biol Psychiatry. 2018 May;83(9):S14–5.

12. Erus G, Doshi J, An Y, Verganelakis D, Resnick SM, Davatzikos C. Longitudinally and inter-site consistent multi-atlas based parcellation of brain anatomy using harmonized atlases. NeuroImage. 2018 01;166:71–8.

13. Dong A, Honnorat N, Gaonkar B, Davatzikos C. CHIMERA: Clustering of heterogeneous disease effects via distribution matching of imaging patterns. IEEE Trans Med Imaging. 2016 Feb;35(2):612–21.

14. Varol E, Sotiras A, Davatzikos C, Alzheimer's Disease Neuroimaging Initiative. HYDRA: Revealing heterogeneity of imaging and genetic patterns through a multiple max-margin discriminative analysis framework. NeuroImage. 2017 15;145(Pt B):346–64.

15. Johannsen W. The genotype conception of heredity. Am Nat Repr Int J Epidemiol 2014 4 989-1000. original: 1911;45:129–59.

16. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryokov S, Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Aug 22;386(9995):743–800.

17. Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, et al. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2013 Apr;18(4):497–511.

18. Geschwind DH, Flint J. Genetics and genomics of psychiatric disease. Science. 2015 Sep 25;349(6255):1489–94.

19. Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019 Mar;22(3):343–52.

20. McIntosh AM, Sullivan PF, Lewis CM. Uncovering the genetic architecture of major depression. Neuron. 2019 Apr 3;102(1):91–103.

21. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. Mol Psychiatry. 2017 Oct;22(10):1455–63.

22. Wang W, Zhao Y, Hu X, Huang X, Kuang W, Lui S, et al. Conjoint and dissociated structural and functional abnormalities in first-episode drug-naive patients with major depressive disorder: a multimodal meta-analysis. Sci Rep. 2017 Dec;7(1):10401.

23. Cole J, Costafreda SG, McGuffin P, Fu CHY. Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. J Affect Disord. 2011 Nov;134(1–3):483–7.

24. Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, et al. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology. 2013 May;38(6):1068–77.

25. Marquand AF, Mourão-Miranda J, Brammer MJ, Cleare AJ, Fu CHY. Neuroanatomy of verbal working memory as a diagnostic biomarker for depression: NeuroReport. 2008 Oct;19(15):1507–11.

26. Nouretdinov I, Costafreda SG, Gammerman A, Chervonenkis A, Vovk V, Vapnik V, et al. Machine learning classification with confidence: Application of transductive conformal predictors to MRI-based diagnostic and prognostic markers in depression. NeuroImage. 2011 May;56(2):809–13.

27. Lui S, Wu Q, Qiu L, Yang X, Kuang W, Chan RCK, et al. Resting-state functional connectivity in treatment-resistant depression. Am J Psychiatry. 2011 Jun;168(6):642–8.

28. Ferri J, Eisendrath SJ, Fryer SL, Gillung E, Roach BJ, Mathalon DH. Blunted amygdala activity is associated with depression severity in treatment-resistant depression. Cogn Affect Behav Neurosci. 2017;17(6):1221–31.

29. Dinga R, Schmaal L, Penninx BWJH, van Tol MJ, Veltman DJ, van Velzen L, et al. Evaluating the evidence for biotypes of depression: Methodological replication and extension of. NeuroImage Clin. 2019;22:101796.

30. Kautzky A, Dold M, Bartova L, Spies M, Vanicek T, Souery D, et al. Refining prediction

in treatment-resistant depression: results of machine learning analyses in the TRD III sample. J Clin Psychiatry. 2018 Feb;79(1).pii. 16m11385.

31. Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J Consult Clin Psychol. 2008 Dec;76(6):909–22.

32. Gartlehner G, Wagner G, Matyas N, Titscher V, Greimel J, Lux L, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. BMJ Open. 2017 Jun;7(6):e014912.

33. Redlich R, Almeida JJR, Grotegerd D, Opel N, Kugel H, Heindel W, et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. JAMA Psychiatry. 2014 Nov;71(11):1222–30.

34. Lee Y, Ragguett R-M, Mansur RB, Boutilier JJ, Rosenblat JD, Trevizol A, et al. Applications of machine learning algorithms to predict therapeutic outcomes in depression: A meta-analysis and systematic review. J Affect Disord. 2018 (01);241:519–32.

35. Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry. 2017;4(5):409–18.

36. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev. 2017;77:317–26.

37. Arnone D, McKie S, Elliott R, Juhasz G, Thomas EJ, Downey D, et al. State-dependent changes in hippocampal grey matter in depression. Mol Psychiatry. 2013 Dec;18(12):1265–72.

38. Fu CH, Costafreda SG, Sankar A, Adams TM, Rasenick MM, Liu P, et al. Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. BMC Psychiatry. 2015 Dec;15(1):82.

39. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, et

al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. Arch Gen Psychiatry. 2005 Apr;62(4):417–22.

40. Cuijpers P, Hollon SD, van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open. 2013;3(4):e002542.

41. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. J Clin Psychiatry. 2013 Jun;74(6):595–602.

42. Weissman MM, Prusoff BA, Dimascio A, Neu C, Goklaney M, Klerman GL. The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. Am J Psychiatry. 1979 Apr;136(4B):555–8.

43. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006 Aug;74(4):658–70.

44. de Maat S, Dekker J, Schoevers R, van Aalst G, Gijsbers-van Wijk C, Hendriksen M, et al. Short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression: a mega-analysis based on three randomized clinical trials. Depress Anxiety. 2008;25(7):565–74.

45. Barth J, Munder T, Gerger H, Nüesch E, Trelle S, Znoj H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. PLoS Med. 2013;10(5):e1001454.

46. Palpacuer C, Gallet L, Drapier D, Reymann J-M, Falissard B, Naudet F. Specific and non-specific effects of psychotherapeutic interventions for depression: Results from a meta-analysis of 84 studies. J Psychiatr Res. 2017;87:95–104.

47. Fu CHY, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiol Dis. 2013 Apr;52:75–83.

48. Sankar A, Melin A, Lorenzetti V, Horton P, Costafreda SG, Fu CHY. A systematic review and meta-analysis of the neural correlates of psychological therapies in major depression. Psychiatry Res Neuroimaging. 2018 Sep;279:31–9.

49. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive Therapy of Depression. New York, NY: Guildford Press; 1979.

50. Jacobson NS, Dobson KS, Truax PA, Addis ME, Koerner K, Gollan JK, et al. A component analysis of cognitive-behavioral treatment for depression. J Consult Clin Psychol. 1996 Apr;64(2):295–304.

51. Ekers D, Webster L, Van Straten A, Cuijpers P, Richards D, Gilbody S. Behavioural activation for depression; an update of meta-analysis of effectiveness and sub group analysis. PloS One. 2014;9(6):e100100.

52. Cuijpers P, Donker T, Weissman MM, Ravitz P, Cristea IA. Interpersonal psychotherapy for mental health problems: a comprehensive meta-analysis. Am J Psychiatry. 2016 Jul;173(7):680–7.

53. Driessen E, Cuijpers P, de Maat SCM, Abbass AA, de Jonghe F, Dekker JJM. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. Clin Psychol Rev. 2010 Feb;30(1):25–36.

54. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002 Oct;59(10):877–83.

55. Tang TZ, DeRubeis RJ. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. J Consult Clin Psychol. 1999 Dec;67(6):894–904.

56. Tang TZ, DeRubeis RJ, Beberman R, Pham T. Cognitive changes, critical sessions, and sudden gains in cognitive-behavioral therapy for depression. J Consult Clin Psychol. 2005 Feb;73(1):168–72.

57. Lutz W, Ehrlich T, Rubel J, Hallwachs N, Röttger M-A, Jorasz C, et al. The ups and downs of psychotherapy: sudden gains and sudden losses identified with session reports. Psychother Res J Soc Psychother Res. 2013;23(1):14–24.

58. Strunk DR, Brotman MA, DeRubeis RJ, Hollon SD. Therapist competence in cognitive therapy for depression: predicting subsequent symptom change. J Consult Clin Psychol. 2010 Jun;78(3):429–37.

59. Jarrett RB, Vittengl JR, Doyle K, Clark LA. Changes in cognitive content during and following cognitive therapy for recurrent depression: substantial and enduring, but not predictive of change in depressive symptoms. J Consult Clin Psychol. 2007 Jun;75(3):432–46.

60. Furlong M, Oei TPS. Changes to automatic thoughts and dysfunctional attitudes in group CBT for depression. Behav Cogn Psychother. 2002 Jul;30(3):351–60.

61. Vittengl JR, Clark LA, Thase ME, Jarrett RB. Are improvements in cognitive content and depressive symptoms correlates or mediators during acute-phase cognitive therapy for recurrent major depressive disorder? Int J Cogn Ther. 2014 Sep;7(3):251–71.

62. Grencavage LM, Norcross JC. Where are the commonalities among the therapeutic common factors? Prof Psychol Res Pract. 1990;21(5):372–8.

63. Krell HV, Leuchter AF, Morgan M, Cook IA, Abrams M. Subject expectations of treatment effectiveness and outcome of treatment with an experimental antidepressant. J Clin Psychiatry. 2004 Sep;65(9):1174–9.

64. Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. Br J Psychiatry J Ment Sci. 2014 Dec;205(6):443–9.

65. Constantino MJ, Arnkoff DB, Glass CR, Ametrano RM, Smith JZ. Expectations. J Clin Psychol. 2011 Feb;67(2):184–92.

66. Webb CA, Derubeis RJ, Barber JP. Therapist adherence/competence and treatment outcome: A meta-analytic review. J Consult Clin Psychol. 2010 Apr;78(2):200–11.

67. Elliott R, Bohart AC, Watson JC, Murphy D. Therapist empathy and client outcome: An updated meta-analysis. Psychotherapy. 2018;55(4):399–410.

68. Bocchio M, Nabavi S, Capogna M. Synaptic Plasticity, Engrams, and network oscillations in amygdala circuits for storage and retrieval of emotional memories.

Neuron. 2017 May 17;94(4):731–43.

69. Takeuchi T, Duszkiewicz AJ, Morris RGM. The synaptic plasticity and memory hypothesis: encoding, storage and persistence. Philos Trans R Soc Lond B Biol Sci. 2014 Jan 5;369(1633):20130288.

70. Fu CHY, Williams SCR, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry. 2008 Sep 15;64(6):505–12.

71. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry. 2004 Sep;61(9):877-89.

72. Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, et al. Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. Am J Psychiatry. 2012 Aug;169(8):841–50.

73. Che X, Cash R, Chung S, Fitzgerald PB, Fitzgibbon BM. Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2018;92:437–52.

74. Neugebauer V. Amygdala pain mechanisms. Handb Exp Pharmacol. 2015;227:261–84.

75. Amick HR, Gartlehner G, Gaynes BN, Forneris C, Asher GN, Morgan LC, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. BMJ. 2015 Dec 8;h6019.

76. Bowlby J. Attachment and Loss. London, UK: Hogarth Press and the Institute of Psychoanalysis; 1969.

77. Reis S, Grenyer BFS. Fearful attachment, working alliance and treatment response for individuals with major depression. Clin Psychol Psychother. 2004 Nov;11(6):414–24.

78. Swift JK, Greenberg RP, Tompkins KA, Parkin SR. Treatment refusal and premature termination in psychotherapy, pharmacotherapy, and their combination: A meta-analysis

of head-to-head comparisons. Psychotherapy. 2017 Mar;54(1):47–57.

79. Ran G, Zhang Q. The neural correlates of attachment style during emotional processing: an activation likelihood estimation meta-analysis. Attach Hum Dev. 2018 Nov 2;20(6):626–33.

80. Sambo CF, Howard M, Kopelman M, Williams S, Fotopoulou A. Knowing you care: effects of perceived empathy and attachment style on pain perception. Pain. 2010 Dec;151(3):687–93.

81. Kim HJ, Park J-Y, Seo SW, Jung YH, Kim Y, Jang H, et al. Cortical atrophy pattern-based subtyping predicts prognosis of amnestic MCI: an individual-level analysis. Neurobiol Aging. 2019 Feb;74:38–45.

82. Dong A, Toledo JB, Honnorat N, Doshi J, Varol E, Sotiras A, et al. Heterogeneity of neuroanatomical patterns in prodromal Alzheimer's disease: links to cognition, progression and biomarkers. Brain. 2017 Mar;140(3):735-747.

83. Honnorat N, Dong A, Meisenzahl-Lechner E, Koutsouleris N, Davatzikos C. Neuroanatomical heterogeneity of schizophrenia revealed by semi-supervised machine learning methods. Schizophr Res. 2017 Dec; pii: S0920-9964(17)30760-0.