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Widespread Morphometric Abnormalities in Major Depression: Neuroplasticity and Potential for Biomarker Development

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INTRODUCTION

Major depression is a common mental health disorder, affecting about 350 million persons worldwide with a lifetime prevalence of around 15% of the population,¹ and is predicted to be the leading contributor to the global burden of disease.² The disorder is characterized by a prolonged low mood or an inability to experience usual feelings of enjoyment along with changes in neurovegetative symptoms, such as fatigue and disturbances in appetite, sleep, and psychomotor functioning, as well as cognitive impairments, feelings of guilt, and, for some, suicidal ideation with intent. The disorder is characterized by impairments in mood, behavior, and cognition, which are associated with neurobiological abnormalities. However, the diagnosis is currently based solely on clinical features.^{3,4} This is problematic because the diagnosis is made only from self-report symptoms and observable behaviors. Many phenotypic combinations are possible, which are not linked to a specific pathophysiology. Based on current classification systems, major depression is a heterogeneous syndrome that is not linked to etiology.

Furthermore, treatment selection is based on trial and error. The most common first-line treatments are antidepressant medications and psychological therapies. It typically takes weeks before clinical improvement is evident, and yet the remission rate is only about 30% after a full 3-month treatment trial.⁵ The course of the disorder typically consists of recurrent episodes, although it may be chronic with persistent symptoms for some patients despite a

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series of treatment trials.⁶ There is significant heterogeneity in the clinical outcomes and longitudinal course of the disorder, but it is not possible to predict the likelihood of response for a given treatment at the level of the individual. Currently, there are no biological markers that can help to identify depression or to predict clinical outcome.

Notwithstanding limitations in diagnosis and treatment selection, neural alterations have been observed consistently in neuroimaging studies. Neuroimaging markers offer a promising biological measure, which can aid in identifying depression and predict clinical outcome because no other measure to date has demonstrated the same level of accuracy at the level of the individual. Heritability estimates for major depression are low, around 37%, in contrast with bipolar disorder and schizophrenia, which have consistently high heritability estimates of up to 90%.⁷ Although environmental risk factors are known to have a strong contribution, the mechanism of how genetic risk variants lead to the development of an acute depressive episode is unclear,⁸ and no genetic predictors of clinical response been identified at the level of the individual.^{9,10}

WIDESPREAD MORPHOMETRIC ABNORMALITIES REFLECT CYTOARCHITECTURE ALTERATIONS

The term limbic lobe is derived from Latin, *limbus* for border, to refer to the brain structures located at the inferior rim of the neocortex and superior to the brainstem. Papez¹¹ proposed a circuit as the basis for emotion processing, composed of the hippocampus (subiculum), fornix, mamillary bodies, anterior nucleus of the thalamus, cingulate gyrus, parahippocampal gyrus, and entorhinal cortex, which has since also become recognized for its role in memory formation, in particular episodic memory.¹² MacLean¹³ proposed the limbic system to be a functionally integrated set of regions that underlie emotion processing and motivation. Although the regions that comprise the limbic system continue to be debated, they generally include the orbitofrontal, cingulate and insular cortices, hippocampal formation, and amygdala, as well as thalamus, hypothalamus and basal ganglia.¹⁴

Genetic and environmental factors that lead to major depressive disorder (MDD) are expressed in neural structure and function. A range of sometimes contradictory findings have been reported, owing in part to heterogeneity in sample characteristics, such as medication status, the presence of comorbid disorders, and the form of depression, including treatment-resistant depression, in addition to heterogeneity in methodologies in data acquisition, processing, and analysis. Meta-analyses seek to quantitatively incorporate the collective findings to identify the strongest effects. Widespread volumetric reductions in gray matter have been demonstrated in meta-analyses in MDD. Affected regions include corticolimbic circuits involved in emotion regulation as well as more broadly in cortical and subcortical regions,^{15–19} which can be observed in the first depressive episode^{15,20,21} and reflect neuronal and glial reductions.^{22–24}

Recent meta-analyses have sought to address potential biases and to combine datasets to take into account subtle effects that may not have achieved statistical significance in small samples. Atkinson and colleagues¹⁶ performed a meta-analysis that included studies of recurrent MDD that was not treatment resistant and pooled both voxel-based morphometry

and region of interest-based analyses together with reports of no significant differences in gray matter volume or density in MDD (n = 1341) and healthy (n = 1364) participants. Wise and colleagues¹⁹ conducted a meta-analysis that combined between-group voxel-based morphometry data in MDD (n = 1736) and healthy (n = 2365) participants from individual studies, and Schmaal and colleagues^{15,18} integrated measures of cortical thickness and surface area estimates from individual MDD (n = 1902 adults) and healthy (n = 7658) participants across sites. Gray matter volume is a product of the surface area and cortical thickness, which have distinct genetic and developmental origins.²⁵ Measures of regional gray matter, including gray matter density, complement measures of its components, although surface area has a substantially greater contribution than cortical thickness.²⁶

Gray matter volumetric reductions have been observed in the prefrontal cortex encompassing the bilateral anterior cingulate cortices (Brodmann areas [BAs] 24 and 32), medial regions including superior medial frontal (BA 32) to medial orbitofrontal cortices (BA 11), superior frontal gyri, as well as lateral regions in the middle frontal (BA 46) and inferior frontal cortices (BA 47), which are involved in executive function and emotion regulation.^{15,16,19} Cortical volumetric decreases extend into the bilateral insula, involved in interoceptive awareness, as well as in postcentral, temporal, and inferior parietal cortices, and the cerebellum. Subcortical regions include the thalamus, caudate, and putamen, although with mixed findings.^{16,19} Most regions have demonstrated decrease in surface area as well as cortical thickness, whereas some regions, including the inferior parietal cortices and supramarginal gyri, primarily show decreases in cortical thickness.¹⁵

Structural and functional alterations in the anterior cingulate cortex and amygdala have been widely observed in MDD. Reduced anterior cingulate volumes have been observed in medication naïve MDD in the first episode and when medication free later in the illness course, which avoids potential effects of medication,^{27,28} and decreased amygdala volumes have been reported, although with inconsistent findings.²⁹ The amygdala sends projections toward the subgenual anterior cingulate and in turn receives projections from dorsal cingulate cortex.³⁰ Voluntary emotional regulation is linked to suppression of amygdala activity though activation in pregenual and dorsal anterior cingulate as well as in middle frontal and orbitofrontal cortices.³¹ Effective emotional regulation depends on the interplay between the anterior cingulate, prefrontal regions, and the amygdala, which is disrupted in MDD.³²

One of the most consistent findings has been decreased hippocampal volumes bilaterally, with estimates in the range of 1% to 4%.^{16–20} Hippocampal atrophy was initially identified in recurrent MDD, associated with total lifetime duration of depression^{33,34} and multiple depressive episodes.³⁵ However, hippocampal atrophy has also observed in the first episode of depression,²⁰ in individuals with high familial risk of developing depression,³⁶ and in adolescents with early onset depression³⁷ in whom attenuated growth is linked to the onset of the first depressive episode.³⁸

Decreased hippocampal volumes, however, are not specific to MDD because they are a feature in a many psychiatric disorders, including bipolar disorder, schizophrenia, obsessive–compulsive disorder, and borderline personality disorder.^{39–44} Quantifying the

distinct subfields that comprise hippocampal morphology can delineate the regional deformations that are characteristic as well as shared with other disorders. Deformations have been reported in the subiculum⁴⁵ and in the cornu ammonis (CA) subfields CA1 extending into CA2/3^{45,46} as well as CA4,⁴⁶ and multiple depressive episodes are associated with a significant declines in subfield regional volumes.⁴² Bipolar disorder may be associated with more prominent decreases in subfield volumes,⁴³ although with mixed findings,⁴⁰ whereas more extensive decreases seem to be present in schizophrenia and old age depression.^{39,41,44,47}

In comparison with bipolar disorder, MDD is associated with common as well as distinct patterns of morphometric alterations.¹⁹ Both disorders show decreased gray matter volume in the dorsomedial and ventromedial prefrontal cortices, which included the anterior cingulate, and bilateral insula, suggesting a common neuropathology to affective disorders. Greater decreases in the right middle frontal cortex, left hippocampus, along with parietal, temporal, and cerebellar regions were found in MDD relative to bipolar disorder, indicating a specificity to MDD that could aid in the development of biomarkers.⁴⁸

ENDOGENOUS STRESS RESPONSE SYSTEMS, MONOAMINERGIC SYSTEMS, AND NEUROPLASTICITY

Neural circuitries involved in emotion regulation, such as reward processing, attention and memory, overlap with the neural circuitries that control the homeostatic stress response systems, which are disrupted in MDD. The hypothalamic–pituitary–adrenocortical (HPA) axis is an endogenous feedback circuit activated by perturbations in homeostasis. In addition to the HPA axis, there are many interacting endogenous stress response systems, including the autonomic nervous system, which generates immediate responses, for example, increased heart rate and blood pressure, through sympathetic and parasympathetic innervations, and the inflammatory cytokine systems. MDD is associated with elevated proinflammatory cytokine levels, in particular during an acute depressive episode as well as being a risk factor in itself in the development of MDD and a moderating factor in the association of childhood maltreatment with MDD.^{49,50}

HPA axis hyperactivity is a well-replicated finding in MDD. HPA disturbances characterised by adrenal hypersecretion of glucocorticoids, namely, cortisol in humans, has been linked to hippocampal atrophy with evidence of neuronal loss, dendritic atrophy, and inhibition of neurogenesis in the hippocampus in animal models.⁵¹ The hippocampus is a plastic brain structure with a pivotal role in memory and learning that is, responsive to adrenocortical, thyroid and gonadal hormones together with excitatory amino acid neurotransmitters through N-methyl-D-aspartate receptors.⁵¹

The MR imaging observable regional abnormalities reflect cytoarchitectonic alterations within a local neuroendocrine milieu that has systemic effects. Adrenocorticosteroid receptors in the prefrontal regions regulate glucocorticoid secretion in the HPA axis stress response circuit.⁵² In animal studies, lesions in the dorsal division of the medial prefrontal cortex enhanced HPA glucocorticoid responses to psychogenic stressors, whereas lesions in the ventromedial division attenuated stress responses,⁵³ with comparable opposing effects

on heart rate, in which the dorsal division decreased tachycardiac responses and the ventral division facilitated the effect.⁵⁴ The medial prefrontal cortex has distinct effects on the autonomic nervous system stress response systems as focal damage involving the anterior cingulate cortex in humans has been associated with impaired cardiovascular responses during cognitive effort despite preserved performance.⁵⁵

Monoaminergic neurotransmitters, such as serotonin, dopamine, and noradrenaline, project into the medial prefrontal cortex with direct neural effects as well as modulator effects on psychogenic stress-induced HPA neuroendocrine responses. These effects are associated with distinct in vivo neurocognitive signals in MDD. Postmortem tissue studies indicate that alterations in innervation of medial prefrontal cortex could underlie reduced monoamine availability.^{56–59} Changes in regional cerebral volumes after antidepressant treatment reflect cytoarchitectonic neuroplasticity effects, and early changes have been predictive of clinical outcome. Neuroplastic changes in serotonin (5-hydroxytryptamine) neurons in the ventromedial prefrontal cortex and dentate gyrus in the hippocampus have been associated with antidepressant effects in animal models.⁶⁰

In humans, increased hippocampal volume observed after selective serotonin reuptake inhibitor (SSRI) antidepressant treatment could reflect cellular neuroplasticity.⁶¹ Moreover, an early increase in hippocampal volume and in rostral anterior cingulate thickness after 1 week of treatment was predictive of improved clinical response to antidepressant treatment with serotonin and noradrenaline reuptake inhibitor antidepressant drugs, suggesting that neuroplastic cellular changes may occur early and are predictive of subsequent clinical efficacy.^{62,63} Furthermore, decreased hippocampal gray matter in MDD in a current depressive episode, relative to healthy participants and MDD in remission, subsequently showed increased gray matter after SSRI antidepressant treatment,⁶¹ perhaps representing a human in vivo correlate of cellular neurogenesis with SSRI pharmacologic treatment in animal models.⁶⁴

MR imaging observable changes in hippocampal structure, as well as in other cortical and subcortical regions, reflect the complex inter-relationships of neurotoxic and neuroplastic cellular effects. Persistent depressive symptoms have been associated with a progressive decrease in hippocampal volume,⁶⁵ and recurrent depressive episodes in MDD are associated with decreased hippocampal volumes and more extensive subregional deficits,⁶⁶ supporting neuroprogressive models of stress-related neural atrophy. Increases in hippocampal volume after antidepressant treatment in humans though reflect the potential for neuroplasticity.⁶¹ Moreover, evidence of hippocampal atrophy preceding and present at disease onset also reflect complex neurodevelopmental mechanisms in the potential interactions of genetic vulnerability with environmental risk factors, such as childhood maltreatment and low socioeconomic status, during key periods in the trajectory of cortical and subcortical development leading to the onset of MDD.^{20,67,68}

Advances in functional neuroimaging methods have provided enhanced resolution and capabilities to delineate the functional neural correlates in MDD. Initial studies examined performance-related effects associated with stimuli-induced responses to a specific task. A fundamental neuropsychological impairment in MDD is a mood-congruent processing bias

toward negative valences in which ambiguous or positively valenced stimuli are perceived as negative, which is evident in a number of domain, including memory, attention, and perception.^{69,70} Groenewold and colleagues⁷¹ meta-analysis demonstrated that negative and positive stimuli are associated with opposing effects in limbic and visual processing regions, while there may be valence-specific effects in the prefrontal cortex. Negative stimuli were associated with increased activity in amygdala, anterior cingulate, parahippocampal and hippocampal regions, striatum and cerebellum, and reduced decreased in the left superior and middle frontal regions. Positive emotions were associated with opposing effects in the same regions along with increased activity in the orbitofrontal cortex. The findings consistent with models of emotion processing in MDD, which have proposed limbocortical dysregulation,⁷² as well as a ventral system for production of emotion states, which includes the amygdala, insula, ventral anterior cingulate, orbitofrontal and ventrolateral prefrontal regions, and dorsal system underlying effortful regulation of emotion responses that includes the hippocampus, dorsal anterior cingulate, and middle frontal regions.⁷³ Meta-analysis further suggests that there are specific regions in the prefrontal cortex that distinguish positive and negative emotional valences.

Discerning the specific emotions that comprise a particular valence, for example, sadness, fear, disgust, or anger within the category of negative valence, offers the potential to determine whether there are distinct functional neurocircuitries in the clinical subtypes that comprise MDD and to distinguish MDD from comorbid disorders and the effects of concurrent symptoms, such as anxiety disorders and anxiety symptoms, which are common in MDD. A highly replicated finding in longitudinal pharmacologic treatment studies is that activity in the amygdala and ventral regions in the anterior cingulate cortex in response to sad facial expression is increased during an acute depressive episode and normalizes after antidepressant treatment.^{74,75} This pattern in the amygdala response is specific to sad facial expressions.⁷⁶

Similarly, in a prospective, longitudinal treatment study with cognitive-behavioral therapy, we found that increased amygdala activity to sad facial expressions in MDD during an acute depressive episode normalized after a course of treatment in comparison with healthy participants who underwent the same set of MR imaging scans.⁷⁷ Our meta-analysis of longitudinal treatment effects after psychotherapy found a significant group by time effect in the left rostral anterior cingulate in response to emotional stimuli, in which MDD participants showed increased activity following treatment while healthy participants showed a decrease in activity at the follow-up scan.⁷⁸ Ventral-rostral regions in the anterior cingulate have a regulatory function on emotion processing, as well as in reward processing and decision making, through interconnections with core emotion processing regions, in particular the amygdala.⁷⁹ MDD is associated with a bias toward negative affective valences, which is also evident in a decreased ability to disengage from negative stimuli.⁸⁰ Healthy emotion regulation is associated with suppression of amygdala activity through interconnections with the rostral and dorsal anterior cingulate and middle frontal cortices, but the connectivity between the anterior cingulate and amygdala is impaired in MDD.^{31,32} The observed increase in rostral anterior cingulate activity is suggestive of improvements in emotion regulation after a course of treatment with psychotherapy.

The number of longitudinal psychotherapy treatment studies in MDD, however, has been less than one-third of the number of longitudinal pharmacologic treatment studies.⁸¹ Although combining MDD with other psychiatric disorders, including panic disorder, post-traumatic stress disorder, social anxiety disorder, and obsessive-compulsive disorder, and incorporating different forms of cognitive and emotion-based functional tasks, generates a larger sample size, a meta-analysis⁸² of the combined disorders and combined cognitive and emotion-based tasks may confound the functional neural effects; for example, cognitive and emotional tasks are associated with differing and potentially opposing neural effects, such as on amygdala responsivity.⁸³

NEUROIMAGING-BASED BIOMARKERS

Yet, MDD in its current form is a heterogeneous disorder that is not linked to etiology. Current diagnostic criteria are based solely on clinical features and many phenotypic combinations are possible. The widespread extent of structural volumetric reductions reflects the emotional, social, and cognitive impairments that are common in MDD. To identify an acute depressive episode in MDD and to predict clinical outcome are key clinical challenges.

Multivariate pattern analysis is able to integrate the spatially distributed, subtle alterations into models. From learning to categorize these models, it would be possible to then identify comparable models in novel brain imaging data. We demonstrated the ability to identify MDD at the level of the individual with proof-of-concept data using structural MR imaging and task-based functional MR imaging that included gray matter as well as white matter in the medial and superior frontal regions, superior parietal and inferior occipital gyri, and in the cerebellum, which was distinct from the pattern that was predictive of clinical outcome.^{84–86} In the largest multisite sample to date, multiple classification subtype models were identified, which included a common pattern of altered connectivity that encompassed the ventromedial prefrontal, orbitofrontal and posterior cingulate cortices, insula, and subcortical regions, along with distinct patterns of functional connectivity and clinical symptom profiles in 4 subtypes with different profiles of clinical symptoms.⁸⁷ Distinct patterns of classification have also been demonstrated in bipolar disorder and MDD in which decreased gray matter volumes in the anterior cingulate provided a greater contribution in MDD as supported by morphometric data.^{19,88,89}

Increased anterior cingulate activity during an acute depressive episode before the initiation of treatment, has been consistently associated with a higher likelihood of a better clinical outcome. Our meta-analysis of neural predictors of clinical response found that the regional activity extended from the dorsal to rostral anterior cingulate into the medial prefrontal and orbitofrontal regions, whereas activity in the insula and striatum was predictive of a lower likelihood of clinical benefit from treatment.⁸¹ Applying multivariate pattern analysis, the regional cerebral pattern that predicted clinical outcome before the initiation of treatment included greater gray matter density in the rostral anterior cingulate and posterior cingulate cortices, which increased the probability of a full clinical response and increased gray matter density in the orbitofrontal cortex increased the probability of persistent residual symptoms after pharmacologic treatment.^{84–86}

The quality of the data and methodology in model development are essential inputs. Although the highest rates of classification have been achieved in treatment-resistant forms of MDD, the neural correlates are usually confounded by the potential effects of medication and a chronic course of illness. Developing models in MDD in an acute depressive episode that is medication-free could more accurately reflect the neural features that have not been confounded by effects of medication. We would not expect perfect concordance in the classification results with current diagnostic criteria, which do not reflect specific biological pathophysiologies. We expect that the development of biomarkers would be an iterative process in which the neuroimaging-based biomarkers are applied to specify potential pathophysiology.⁴⁸

We propose that it is essential to address heterogeneity in the symptom profiles that make up the clinical disorder, the clinical outcomes for a given treatment (which reflects a combination of the inherent likelihood of response and the mechanisms of treatment), and the longitudinal course for individual patients. High dimensional clustering methods applied to dissect imaging heterogeneity are confounded by variations related to demographics and other factors that are not related to disease pathophysiology.⁸⁸ Recent literature has proposed 2 semisupervised learning methods in an attempt to address these confounds: CHIMERA⁹⁰ and HYDRA.⁹¹ Both of these methods can be viewed as semisupervised clustering methods—they rely on well-defined groups of patients and controls; however, they let the data reveal patient subtypes based on the way in which they differ from healthy controls. Put simply, these methods do not cluster patients directly, which might be confounded by covariates such as age and sex, but they aim to cluster the differences between patients and healthy controls, which is more likely to yield disease subphenotypes.

CHIMERA is primarily generative, in which it assumes a statistical distribution of imaging features of the patient cohort that is, heterogeneous which is derived from the statistical distribution of healthy controls through a number of transformations that reflect the effects of underlying pathophysiologies that are also heterogeneous. Covariates are taken into account explicitly. CHIMERA is a probabilistic clustering approach that models pathologic processes through a combination of multiple regularized transformations from the healthy population to the MDD patient population. The populations are considered as point distributions that are matched by a variant of the coherent point drift algorithm, such that, for example, a 40-year-old woman with MDD would have been a 40-year-old healthy woman had she been spared the disorder. CHIMERA directly models these effects by seeking to identify the multiple imaging patterns that relate to disease effects to characterize disease heterogeneity.

HYDRA takes a similar approach, but from the discriminative angle. HYDRA applies 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, and the subtypes are captured by multiple linear hyperplanes, forming a convex polytope that separates 2 populations in which each face of the polytope defines a disease subtype. Both CHIMERA and HYDRA methods use cross-validation and split sample analyses to determine the optimal number of subtypes, and have been recently shown to elucidate heterogeneity in mild cognitive impairment and Alzheimer disease, and to associate

neuroanatomical subtypes with clinical progression.⁹² These methods have also revealed, for the first time, significant heterogeneity in neuroanatomical signatures of schizophrenia,⁹³ as well as in adolescents with internalizing symptoms.⁹⁴

Data-driven, inductive modeling strategies would model the neuroanatomical patterns that make up MDD as a collection of directions of deviation from normal neuroanatomical patterns. Classification results in schizophrenia, mild cognitive impairment, and Alzheimer's disease demonstrate the potential of these methods to capture neuroanatomic heterogeneity from MR imaging data.^{92,93} The approaches model the pathologic processes associated with MDD through a combination of multiple regularized transformations from the healthy control population to the patient population. The methods seek to identify multiple neuroanatomic patterns that relate to disease effects and to characterize disease heterogeneity. A deductive approach, such as reported clinical symptoms, would apply prior knowledge to identify the linear and nonlinear combinations of neuroanatomic features that correlate with clinical clusters, which could be a complementary process. A synergistic combination could bring together the data-driven inductive and symptom-based deductive approaches such that the clinical measures will be used in CHIMERA and HYDRA to inform the clustering.

SUMMARY

MDD is associated with widespread morphometric abnormalities extending from frontolimbic regions which reflect cytoarchitectural alterations believed to result from complex inter-relationships of neurotoxic and neuroplastic cellular effects. Neural circuitries involved in emotion regulation overlap with the neural circuitries that control the homeostatic stress response systems, which are disrupted in MDD. Functional and structural effects have been observed after treatment with antidepressant medication as well as psychotherapy. Yet, current diagnostic criteria for MDD are based solely on clinical signs and symptoms, and many phenotypic combinations are possible. MDD in its current form is a heterogeneous disorder that is not linked to etiology. Identifying the neurobiological subtypes that comprise MDD and predicting clinical outcome are key clinical challenges. Applying multivariate pattern analysis offers the potential to identify the neurobiological subtypes that comprise MDD and predictors of clinical outcome at the level of the individual. It is essential to characterize disease heterogeneity in which a synergistic combination could incorporate data-driven inductive and symptom-based deductive approaches in an iterative process. In future, psychoradiology, a subdivision of neuroradiology, may also play an important role for enhancing our understanding of disease mechanisms and aiding clinical management in patients with depression.^{95–98}

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KEY POINTS

- Widespread morphometric abnormalities in depression reflect cytoarchitecture alterations in corticolimbic regions, including anterior cingulate, orbitofrontal, and middle frontal regions to lateral temporal and inferior parietal cortices, hippocampus, and cerebellum.
- Neural circuitries involved in emotion regulation, such as reward processing, attention and memory, overlap with the neural circuitries that control the homeostatic stress response systems, which are disrupted in major depression.
- MR imaging observable changes in hippocampal structure, and in other cortical and subcortical regions, reflect the complex inter-relationships of neurotoxic and neuroplastic cellular effects.
- Multivariate pattern analysis offers the potential to develop biomarkers to identify the biological subtypes that comprise major depression and predict clinical outcome.
- We would not expect perfect concordance in classification results with current diagnostic criteria because they do not reflect specific biological pathophysiologies.