Progress in Neuropsychopharmacology & Biological Psychiatry 105 (2021) 110133

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

An alternative approach to future diagnostic standards for major depressive disorder

Yong-Ku Kim[a], Seon-Cheol Park[b,*]

[a] Department of Psychiatry, Korea University Ansan Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[b] Department of Psychiatry, Inje University Haeundae Paik Hospital, Busan, Republic of Korea

ARTICLE INFO

Keywords:
Major depressive disorder
Operational criteria
Heterogeneity
Network analysis
Research domain criteria (RDoC)

ABSTRACT

During the period extending from 1780 to 1880, the conceptualization of melancholia changed from an intellectual to a mood model. The modern view of depression, based on Kraepelinian dualism, has reflected changes in opinion on psychiatric taxonomy of individual melancholia. From the point of view of an "operational revolution," the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) were based on a neoKraepelinian approach rooted in disease essentialism. In the revision process from the DSM-IV to the DSM-5, a combined dimensional and categorial approach was used. In the DSM-5, the diagnostic criteria for major depressive disorder are polythetic and operational in approach reflecting the heterogeneity of major depressive disorder. Although 227 different symptom combinations fulfilling the diagnostic criteria for major depressive disorder can be theoretically calculated, certain symptom combinations are more prevalent than others in real clinical situations. The heterogeneity of these operational criteria for major depressive disorder have been criticized in a manner informed by the Wittgensteinian analogy of the language game. Herein, our network analysis proposes a novel perspective on the psychopathology of major depressive disorder. The novel approach suggested here may lay the foundation for a redefinition of the traditional taxonomy of depression.

1. Introduction

Major depressive disorder is currently diagnosed by taking a polythetic and operational approach (Park and Kim 2018; Park and Kim, 2019a, b; Park 2020). A categorical approach is based on disease essentialism, whereby all cases of major depressive disorder are categorized by shared common neurobiological mechanisms (Roseman and Nasti 2012). The current diagnostic criteria for major depressive disorder have been found to be limited in the clinical setting. Most of all, many subtypes of major depressive disorder have been described due to the inevitable heterogeneity of the diagnostic criteria (Østergaard et al. 2011; Zimmerman et al. 2015). In terms of biological approaches to major depressive disorder subtyping, however, only the amplitude of weight gain or loss has been highlighted (Bejers et al. 2019; Simmons et al. 2016). Although neuroticism, morning cortisol, frontal asymmetry of cortical electrical activity, reward learning, and biases of attention and memory have been proposed as endophenotypes for depression (Goldstein and Klein 2014), evidence for these has been quite inconsistent. Additionally, in initial field trials, the interrater reliability for the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (DSM-5) diagnostic criteria for major depressive disorder have been considered questionable (Freedman et al. 2013). Thus, an alternative approach that overcomes the limitations of current diagnostic criteria for major depressive disorder is in order. In the current work we outline a brief history from melancholia to depression, describe the heterogeneity of the current operational diagnosis of major depressive disorder, and highlight network analysis findings for major depressive disorder, in order to inform the Research Domain Criteria (RDoC) for an alternative model for major depressive disorder.

2. Brief history from melancholia to depression

The concept of melancholia had already been formulated based on faculty psychology and comprehensibility during the century starting from 1780, before a modern view of depression was established in the late 18th century (Kendler 2020; Telles-Correia and Marques 2015; Radden 2003). Faculty psychology defined cognition, affect, and volition as basic capacities of the mind. Kendler (2020) proposed dividing the century from 1780 to 1880 into three phases based on changes in the conceptualization of melancholia. In phase 1, from 1780 to 1830,

* Corresponding author at: Department of Psychiatry, Inje University Haeundae Paik Hospital, 875, Haeun-daero, Haeundae-gu, Busan 48108, Republic of Korea.
E-mail address: cogito-ergo-sum@hanmail.net (S.-C. Park).

https://doi.org/10.1016/j.pnpbp.2020.110133
Received 19 June 2020; Accepted 6 October 2020
Available online 10 October 2020

based on the writings of Cullen (1780), Pinel (1801), and Esquirol (1838), melancholia was mainly considered a disorder of intellect often accompanied by sadness. However, in phase 1, sadness was not regarded as a core characteristic of melancholia. In phase 2, from 1850 to 1860, based on the writings of Guislain (1852) and Bucknill and Tuke (1858), melancholia without delusions was mainly considered a disorder not of intellect but rather of mood, in accordance with the paradigm shift. In phase 3, from 1860 to 1880, in the writings of Griesinger (1861), Sankey (1884), Maudsley (1867), Krafft-Ebing (1903), and Kraepelin (1883), the cause of delusional melancholia was considered to be brain-based psychiatry. Since melancholia was mainly considered a disorder of mood, delusions were presumed not to be an independent disorder, but an emerging feature aligned with abnormal mood. A brief history of the period from 1780 to 1880 reflects a transition from an intellectual model to a mood model of melancholia. It also demonstrates a discrepancy between bottom-up clinical studies and top-down theories of faculty psychology. It has been speculated that a more complex pathway mediates the interrelationship between nosological categories and patient observation (Berrios 1984; Berrios 1987; Kendler 2020).

A modern view of depression may be mainly affected by Kraepelin's conceptualization of involutional melancholia (Kendler and Engstrom 2020). In the 6th edition of his textbook (1899), involutional melancholia was considered an independent involutional disorder, but not a part of manic-depressive insanity. Involutional melancholia was characterized predominantly by anxiety, psychomotor agitation, the typical course of a single depressive episode, and a substantially poor outcome, whereas manic-depressive insanity was characterized predominantly by sadness, psychomotor inhibition, recurrent episodes of depression, mania, and mixed states, and uniform full recovery. However, in the 8th edition of his textbook (1990), an incorporation of involutional melancholia into manic-depressive illness was newly proposed. It was speculated that Kraepelin changed public opinion on the definition of involutional melancholia, since a monograph writing by Dreyfus (1907) had demonstrated the blurred distinction between involutional melancholia and manic-depressive insanity in light of clinical descriptions, differences from other disorders, and follow-up studies.

The conceptual change from melancholia to depression was introduced in the operational diagnostic system (i.e., DSM) as follows (Kang and Kim 2014; Kendler 2013). In the DSM-I (American Psychiatric Association 1952), involutional psychotic reactions were defined separately from manic depressive reactions, since it was speculated that involutional psychotic reactions could result from somatic causes, whereas manic depressive reactions could result from psychogenic or non-organic causes. This distinction between involutional psychotic reactions and manic depressive reactions was partly inconsistent with the Kraepelinian change in opinion on the blurred differentiation between involutional melancholia and manic-depressive insanity. In the DSM-II (American Psychiatric Association 1968), the distinction between involutional psychotic reactions and manic depressive reactions persisted. However, it also presented a debate with regard to whether or not involutional psychotic reactions and manic depressive reactions were distinct. In the DSM-III (American Psychiatric Association 1980), an empirical trend based on the neoKraepelinian approach rather than psychoanalytic theory was emphasized. Thus, a diagnosis of melancholia based on psychiatric nosology and taxonomy was rejected. In addition, involutional psychotic reactions and unipolar depression were incorporated into major depressive disorder. Furthermore, major depressive disorder was newly introduced as an affective disorder. The DSM-III was mainly influenced by an "operational revolution," based on an ideal for a high degree of objectivity and evidence-based psychiatry (Parnas and Bovet 2015; Shorter 2013). Thus, in the DSM-III, a diagnosis of major depressive disorder was operationally defined by symptom criteria, including dysphoric mood, loss of interest or pleasure, poor or increased appetite, insomnia or hyposomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, decreased concentration, and suicidal ideations or attempts (American Psychiatric Association 1980).

3. Major depressive disorder from DSM-IV to DSM-5

The DSM-IV (American Psychiatric Association 1994) also followed the empirical trend based on a neoKraepelinian approach. Since disease essentialism highlighted the concept of cases of a diagnostic category having common biological underpinnings, it was considered to be the main theoretical framework to define diagnostic criteria for DSM-IV. Steven E. Hyman (2011), who had previously been the president of the National Institute of Mental Health (NIMH), seriously criticized the disease essentialism of DSM-IV as follows: "The problem is that the DSM has been launched into under-researched waters, and this has been accepted in an unquestioning way." A DSM-5 task force was created aimed at focusing on the paradigm shift from a categorical classification system to a dimensional classification system in psychiatric diagnoses in order to transcend the limitations of DSM-IV, encourage a research agenda that extended beyond disease essentialism, and adapt an etiologically and pathophysiologically based diagnostic system (Adam 2013). However, a "grand ambition" about a dimensional classification system was furiously resisted by categorical approach-insisting scholars such as Allan Frances, former chair of the DSM-IV task force, in the DSM-5 revision process (Whooley and Horwitz 2013). The purpose of the DSM-5 task force was to subtly move towards "bridging the gap between an etiology-based symptomatology and an identifiable pathophysiological etiology" (Kupfer and Regier 2011). In the DSM-5 (American Psychiatric Association 2013), the diagnostic criteria for major depressive disorder have been changed according to the following.

First, the dichotomization of mood disorders into bipolar disorders and depressive disorders has been newly presented (Uher et al., 2012). It is speculated that the dichotomization into bipolar and depressive disorders may be partly inconsistent with the theoretical framework of the Kraepelinian dualism, which consisted of two main disease entities, dementia praecox (chronic psychosis) and manic depressive insanity (recurrent mood illness with psychosis). Thus, depressive disorders have been conceptualized as a disease entity distinct from bipolar disorders in the realm of affective disorders (Park and Kim, 2019a, b).

Second, the diagnostic threshold of major depressive disorder in DSM-5 has been lowered relative to the threshold in DSM-IV. "Hopelessness" has been newly defined as a subjective descriptor of depressed mood and "bereavement exclusion" has been eliminated from the diagnostic criteria. "Hopelessness," which denotes a cognitive attitude of pessimism, is partly consistent with a "black and pessimistic view of the future" (Uher et al., 2012; Park and Kim, 2019b) in the diagnostic criteria for a depressive episode in the International Classification of Disease, 10th revision (ICD-10) (World Health Organization 1992). An elimination of the "bereavement exclusion" item has been partly supported, since bereavement-related major depressive episodes have not been shown to differ significantly from any other context-related major depressive episodes in terms of their genetic or clinical characteristics (Zisook et al. 2012). In addition, in the longitudinal 2-wave Epidemiologic Catchment Area Study, the general distress symptoms of uncomplicated major depressive disorder have not been significantly distinctive from non-pathological intense sadness. Because the "bereavement exclusion" item was eliminated, the boundary between major depressive disorder and non-pathological sadness has been partly blurred. Furthermore, persistent complex bereavement disorder has been newly included as an example of conditions targeted for further study in the emerging measures and models of the DSM-5. Thus, the elimination of the "bereavement exclusion" item has been criticized as being reflective of the medicalization of normal grief reactions (Bandini, 2015; Moller et al. 2015).

Third, the transdiagnostic specifiers, including "with psychotic

features," "with mixed features," and "with anxious features", have been adapted in DSM-5 to indicate quantitative rather than qualitative overlapping symptoms of major depressive disorder in relation to schizophrenia, bipolar disorder, and anxiety disorder, respectively. In DSM-IV, the specifier "with psychotic features" was coded only in severe major depressive disorder in terms of the "severity-psychosis hypothesis" that highlighted psychotic symptoms seen as factors dependent on the severity of major depressive disorder. However, due to the rejection of the "severity-psychosis hypothesis" per several studies (Østergaard et al. 2012), DSM-5 (American Psychiatric Association 2013) coding for the specifier "with psychotic features" has been allowed not only in severe major depressive disorder but also in dysthymic disorder and mild and moderate major depressive disorder. In addition, since it is speculated that "mood-congruence" has not been proportionally correlated with the prevalence of the specifier "psychotic features" presented in depressive disorders, the preponderance of the specifier "mood-congruent psychotic features" over the specifier "mood-incongruent psychotic features" has been eliminated in the DSM-5 (Park and Choi 2017). Furthermore, "mixed episode" has been replaced by the specifier "mixed features" in the DSM-5. While the conceptualization of "mixed episode" in the DSM-IV was based on a categorical approach, the specifier "with mixed features" has been defined from a dimensional approach. In terms of major depressive disorder, the specifier "mixed features" can be coded by the presence of at least three from among the seven hypomanic symptoms, including elevated mood, inflated self-esteem, pressured speech, racing thoughts, goal-directed activity, involvement in risky activities, and a decreased need for sleep (Park and Kim, 2019b). However, it has been proposed that mixed depression is a distinctive condition in a field of mood disorders. Furthermore, one study has noted that hypomanic expansive symptoms in mixed depression have rarely been reported and thus, an argument about the specifier "with mixed features" has been put forth (Park 2018). Indeed, Koukopoulos and Sani (2014) have insisted that the specifer "with mixed features" should be replaced by agitated depression, which is defined by symptoms such as psychomotor agitation, mood lability, and irritability, among others. It has been shown that, as compared to major depressive disorder, mixed depression is characterized by greater frequencies of suicidal ideation and suicidal attempts, comorbidity with anxiety disorders, use of antipsychotics, and treatment costs.

In summary, in the revision from the DSM-IV to the DSM-5, the potential lowering of the diagnostic threshold for major depressive disorder and the new adaptations of certain trans-diagnostic specifiers, including "with psychotic features," "with mixed features," and "with anxious features", into depressive disorders may contribute to the blurring and/or potential expansion of the diagnostic boundary of major depressive disorder in relation to non-pathological sadness and other psychiatric diagnoses (i.e., schizophrenia, bipolar disorder, anxiety disorder).

4. Heterogeneity of the operational criteria for major depressive disorder

According to the concept of Renyi heterogeneity, the measured heterogeneity of a system stems from the measurement of the system itself. Thus, the heterogeneity inherent in major depressive disorder is dependent on its diagnostic criteria. Before the release of the DSM-5, a simpler definition of major depressive disorder was proposed by Zimmerman et al. (2010), whereby the presence of three or more symptoms inclusive of low mood, loss of interest, guilt or worthlessness, impaired concentration or indecisiveness, and death wishes or suicidal thoughts, along with at least a low mood or loss of interest, would be sufficient for a diagnosis. Thus, a favorable concordance rate between a simpler definition of major depressive disorder and DSM-IV diagnostic criteria for major depressive disorder has been repeatedly reported (Zimmerman et al. 2011). However, a simpler definition of major depressive disorder has not been adopted in the DSM-5 revision process. Most of the operational criteria for major depressive disorder have remained the same from the DSM-IV to DSM-5.

In the DSM-5 (American Psychiatric Association 2013), operational criteria for major depressive disorder consist of (i) depressed mood, (ii) diminished interest or pleasure, (iii) weight loss or weight gain, (iv) insomnia or hypersomnia, (v) psychomotor agitation or retardation, (vi) fatigue or loss of energy, (vii) feelings of worthlessness or excessive guilt, (viii) diminished concentration or indecisiveness, and (ix) death wish or suicidal ideation. An operational diagnosis of major depressive disorder is defined as the presence of five or more symptoms alongside the presence of at least depressed mood or diminished interest or pleasure. Thus, using the binomial coefficient reflecting the number of subsets of k drawing from n distinguishable objects without replacement and disregarding order, the number of different symptom combinations fulfilling the DSM-5 diagnostic criteria for major depressive disorder has been calculated. Two hundred twenty-seven different symptom combinations can be estimated to fulfill the diagnostic criteria for major depressive disorder (Østergaard et al. 2011). However, in real clinical situations, 170 and 119 different symptom combinations have been identified among 1566 patients with major depressive disorder in the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project (Zimmerman et al. 2015) and 853 patients with major depressive disorder in the Clinical Research Center for Depression (CRESCEND) study (Park et al. 2017). Thus, certain symptom combinations may be more prevalent than other symptom combinations in patients with major depressive disorder. Moreover, several criteria (i.e., psychomotor agitation or retardation, impaired concentration or indecisiveness, worthlessness or guilt, insomnia or hypersomnia, weight loss or weight gain, death wish or suicidal ideation) consist of more than one symptom component. Thus, considering each symptom component to be an independent criterion, 14,528 different symptom combinations fulfilling the diagnostic criteria for major depressive disorder can be estimated (Zimmerman et al. 2015). The heterogeneity due to the operational criteria for major depressive disorder is considered substantial. A theory of Ludwig Wittgenstein (1889–1951), who worked mainly in the philosophy of language, points to an analogy to language games in his *Philosophical Investigation* as follows:

Consider, for example, the proceedings that we call games. I mean board-games, card-games, ball-games, Olympic games, and so on. What is common to them all? - Don't say: "There must be something common, or they would not be called games" - but look and see whether there is anything common to all. - For if you look at them, you will not see something that is common to all, but similarities, relationships, and a whole series of them, at that. To repeat: don't think, but look! … the concept game is a concept with blurred edges. - "But is a blurred concept a concept at all?" - Is an indistinct photograph a picture of a person at all? Is it even always an advantage to replace an indistinct picture by a sharp one? Isn't the indistinct one often exactly what we need? (Wittgenstein 2001).

Herein, the heterogeneity of the operational criteria for major depressive disorder can be criticized in terms of the Wittgensteinian analogy of the concept of games. Furthermore, from the perspective of Wittgenstein on conceptual confusion, the cases of major depressive disorder are mainly related by a conceptual thread, but not an essential physical process. In other words, major depressive disorder can be represented not by its common neurobiological underpinnings, but by "family resemblance" (Roseman and Nasti 2012).

5. Network analysis of major depressive disorder

Based on the theoretical construct shift in the underpinnings of depression from a chemical imbalance to dysfunctional circuitry, Insel (2012) has proposed that clinical targets should be more personalized in light of 'next-generation treatments for mental disorders', from their

diagnosis (i.e., mood regulation, anxiety, attention) to their symptoms or endophenotypes (i.e., amotivation, attention bias, executive function, anhedonia, hopelessness, social deficits). A new pragmatic perspective on psychopathology has been proposed by McNally et al. (2015), a symptom-based rather than a category-based approach, as follows: "Symptoms are not outcome factors of an underlying disease; symptoms and the associations between them are the disease itself." Thus, network analysis is well-situated as a novel perspective to approach psychopathologies based on bottom-up processes, but not top-down constructs, consistent with standard biomedical and reductionistic models. Network analysis attributes a given psychiatric condition to a network structure of symptom components, whereas the classical structural equation model explains the covariance of constituent symptoms based on the common influence of a latent variable. In accordance with nominalism rather than essentialism, a certain degree of the interrelated symptoms within the network of depressive symptoms may be explained by a network analysis approach (Contreras et al., 2019; Guyon et al. 2017; Saxe 2017). Network analysis can computationally estimate a property of the network structure and the proportional or disproportional effect of each of the component variables on a network structure. Centrality is considered reflective of the overall connectivity of a symptom in an estimated network structure. Each of the centrality indices are as follows (Opsahl et al. 2010). The node strength centrality is defined as overall connection of a node with other nodes within the network, and is calculated by adding the absolute weights of the edges related to a certain node. The closeness centrality is defined as the indirect connection of a node within the network, and is calculated by adding the inverse value of the shortest path length from a certain node to all other nodes within the network. The betweenness centrality is defined as the significance of a certain node in an average path between two other nodes, and is calculated by the number of times that a certain node lies on the shortest path between two other nodes. Thus, since central symptoms may contribute to the rapid activation of intertwined and interrelated symptoms within an estimated network structure, it is assumed that the relatively greater impact of a component variable on the network system implies its involvement in more central symptoms rather than peripheral symptoms (Borsboom and Cramer, 2013; Fried et al. 2016; Opsahl et al. 2010).

The network analysis of major depressive disorder has pointed to a novel emerging approach to psychopathology, whereby a further network analysis of 3463 outpatients with depressive disorders performed by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study has estimated the lack of significant differences between the centralities of the DSM symptoms (e.g., depressed mood) and non-DSM symptoms (e.g., anxiety) (Fried et al. 2016). These findings have also been supported by a network analysis of 5952 Han Chinese female patients with major depressive disorder considering the centralities of DSM symptoms and non-DSM symptoms (Kendler et al. 2018). In addition, a network structure constructed of the 21 Beck Depression Inventory (BDI) (Beck et al. 1996a; Beck et al. 1996b) symptoms and 21 Beck Anxiety Inventory (BAI) (Steer et al. 1993; Steer et al. 1995) symptoms in 223 patients with major depressive disorder has shown that three depression symptoms (i.e., loss of energy, loss of interest, worthlessness) and seven anxiety symptoms (i.e., faintness or lightheadedness, feeling of choking, feeling scared, fear of the worst happening, nervousness, inability to relax, and feeling shaky) are estimated as the ten most central nodes within the network. In comparing overall depression symptoms and overall anxiety symptoms by node strength centrality, closeness centrality, and betweenness centrality, the two symptom groups were not found to be significantly different. Herein, it is speculated that depression symptoms are not more central than anxiety symptoms in a constructed network of symptoms in patients with major depressive disorder (Park and Kim 2020). Furthermore, guilt or self-blame has been identified as the most central domain within an estimated network of diagnostic criteria for depressive episodes in 643 East Asian patients with depressive disorders as classified by the International Classification of Disease, 10th revision (ICD-10) (World Health Organization 1992), followed by fatigue or low energy and suicidal thoughts or acts. In contrast, sadness has been the most central domain within a network of diagnostic criteria in 551 South or Southeast Asian patients with depressive disorders as classified by the ICD-10, followed by low self-confidence and loss of interest or pleasure. These findings have been partly inconsistent with the typical symptoms defined by the ICD-10 diagnostic criteria for depressive episode. Thus, it is speculated that an estimated network of depressive symptoms can be affected by the ethnic or cultural influences related to the geographical distributions of Asian patients with depressive disorders (Park et al. 2020). In summary, DSM symptoms have not been found to be more central than non-DSM symptoms within the network of depressive symptoms among patients with depressive disorders, and neither have depression symptoms been found to be more central than anxiety symptoms within the network of depression symptoms and anxiety symptoms among patients with major depressive disorder. Furthermore, typical symptoms are not more central than atypical symptoms within the ICD-10 diagnostic criteria for depressive episode among patients with depressive disorders.

In addition, using the STAR*D data during citalopram treatment, network analyses of the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al. 2003) items at baseline, endpoint, and change have been estimated (Madhoo and Levine 2016). The estimated network analysis findings have shown that energy is the most centrally situated at baseline, mood is the most centrally situated at the endpoint, and mood and concentration are the most centrally situated for change. These findings are entirely inconsistent with the unidimensionality of depression based on factor analysis and the use of summed total depression change scores in clinical practice or research. Furthermore, in terms of estimating the potential links between specific depression symptoms and brain structure (Hilland et al. 2020), one preliminary network study has identified the proportional interconnections between crying and fusiform gyrus, crying and cingulate, irritability and fusiform gyrus, irritability and hippocampus, loss of interest and hippocampus, self-criticism and fusiform gyrus, and worthlessness and cingulate. In contrast, inverse interconnections have been identified between changes in appetite and hippocampus, between loss of interest in sex and insula, between sadness and cingulate, between sadness and hippocampus, and between sadness and insula. Thus, the links between depression symptoms and brain regions may shed light on the underlying neural mechanisms of major depressive disorder.

6. Research domain criteria as an alternative model for major depressive disorder

The RDoC to "develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures" has been proposed by strategy 1.4 of the 2008 National Institute of Mental Health Strategic Plan. The RDoC seeks to link the classification of psychopathology to recent advances in genetics and neuroimaging. Thus, genes, molecules, cells, circuits, physiology, behavior, self-reports, and paradigms are included in the units of analysis for each domain in the RDoC (Cuthbert and Insel 2013; Wood and Gibb 2015). The Loss construct within the Negative Valence Systems domain and the diverse Reward constructs within the Positive Valence Systems domain of the RDoC domains are associated with the operational criteria of major depressive disorder. At the level of the Loss construct, the functions of glucocorticoids, sex hormones, oxytocin, vasopressin, and cytokines are highlighted (Dillon et al. 2014). At the genetic level of the Loss construct, serotonin transporter polymorphism, 5-hydroxytryptamine receptor genes, monoamine oxidase A, and catechol-*O*-methyltransferase are targeted, since these known to be related with the control of serotonin and dopamine neurotransmission. However, they have not been identified by genome-wide association

studies, targeted sequencing, microarrays, whole exome/genome analyses, etc. (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013).

In the Loss construct, the increased activity in the default mode network, as well as the disruption of cortico-limbic circuitry (i.e., increased limbic reactivity to affective salient stimuli, decreased activation in the prefrontal cortex, reduced functional connectivity between these groups), are highlighted in major depressive disorder studies (Disner et al. 2011; Hamilton et al. 2012). At the behavioral level of the Loss construct, heterogeneous features are consistent with DSM-5 diagnostic criteria for major depressive disorder. In addition, the self-report level is represented by attributional styles and symptoms of hopelessness (Wood and Gibb 2015). With regard to the Positive Valence Systems domain, the identification and engagement in behaviors leading to achievement and satisfaction gained from rewards have been defined. In the context of the development and progression of major depressive disorder, the identification of a longitudinal association between higher intensity of the Positive Valence Systems domain and attenuation of negative affective symptoms has been highlighted (Olino 2016).

Moreover, additional dimensions to the RDoC matrix, including environmental influences and development, have been proposed as follows. First, influences of the occurrence of negative life events on a person's depression risk have been framed in terms of the vulnerability-stress or diathesis-stress models for major depressive disorder. Despite a lack of replication, the gene and environment interaction models for depression risk, which implicate the genes related to serotonergic or hypothalamic-pituitary-adrenal axis function, have been presented (Heim and Binder, 2012; Karg et al. 2011; Risch et al. 2009). Second, amygdala-prefrontal connectivity, cortisol reactivity to stress, attentional biases and pupillary reactivity to affectively salient stimuli, as well as gene and environment interaction models, have been supported by developmental shifts. In addition, a stronger impact on the development and function of neural and physiological systems may be influenced by environmental factors in periods of heightened sensitivity (Gee et al. 2013; Hankin et al. 2010; Harrison and Gibb 2015; Kellough et al. 2008; Lenroot et al. 2009; Schmitt et al. 2014; Silk et al. 2009).

7. Conclusion

During the period from 1780 to 1880, the concept of melancholia transitioned from an intellectual model to a mood model. A modern view of depression was primarily affected by the Kraepelinian conceptualization of involutional melancholia, which changed it from being an independent involutional disorder to one in which manic-depressive insanity was incorporated. The DSM-3 subsequently incorporated involutional psychotic reactions and unipolar depression into the major depressive disorder criteria in light of an “operational revolution.” In the revision from the DSM-4 to DSM-5, it is speculated that a diagnostic threshold for major depressive disorder may potentially be lowered, since the term “hopeless” has been newly added to the subjective descriptor of depressed mood and the term “bereavement exclusion” has been eliminated from the diagnostic criteria of major depressive disorder. In addition, from a dimensional approach rather than a categorical approach, the transdiagnostic specifiers “with psychotic features,” “with mixed features,” and “with anxious features” have been newly used to describe the transdiagnostic symptoms of major depressive disorder in relation to schizophrenia, bipolar disorder, and anxiety disorder. The polythetic and operational definition of the diagnostic criteria of major depressive disorder inevitably incurs a certain degree of heterogeneity. Per a binomial coefficient calculation, 227 different symptom combinations are possible. However, in real clinical situations, fewer than 227 different combinations occur in real patients. Thus, it is speculated that certain symptom combinations are more prevalent than others. The heterogeneity of major depressive disorder is criticized from the point of view of the Wittgensteinian language game analogy. Network analyses can open the door to a new perspective on the psychopathology of major depressive disorder. Network analyses have yielded remarkable findings. In particular, DSM symptoms are not more centrally situated than non-DSM symptoms in the network of depressive symptomatology. In addition, depression symptoms are not more centrally situated than anxiety symptoms in the network of depression and anxiety symptoms in patients with depressive disorders. Furthermore, in terms of RDoC, operational criteria of major depressive disorder may correspond to the Loss construct within the Negative Valence Systems domain and the various Reward constructs within the Positive Valence Systems domain.

Financial disclosures

None.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2019R1A2C1090146).

References

Adam, D., 2013. On the spectrum. Nature 496, 416–418.
American Psychiatric Association, 1952. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington, DC.
American Psychiatric Association, 1968. Diagnostic and Statistical Manual of Mental Disorders, 2nd edition. American Psychiatric Association, Washington, DC.
American Psychiatric Association, 1980. Diagnostic and Statistical Manual of Mental Disorders, 3rd edition. American Psychiatric Association, Washington, DC.
American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. American Psychiatric Association, Washington, DC.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th edition. American Psychiatric Association, Washington, DC.
Bandini, J., 2015. The medicalization of bereavement: (ab)normal grief in the DSM-5. Death Stud. 39, 347–352.
Beck, A.T., Steer, R.A., Brown, G.K., 1996a. Beck Depression Inventory (2nd Manual). The Psychological Corporation, San Antonio.
Beck, A.T., Steer, R.A., Brown, G.K., Ranieri, W.F., 1996b. Comparison of the Beck depression inventories-LA and-II in psychiatric outpatients. J. Pers. Assess. 67, 588–797.
Beijers, L., Wardenaar, K.L., van Loo, H.M., Schoevers, R.A., 2019. Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. Mol. Psychiatry 24, 888–900.
Berrios, G.E., 1984. Descriptive psychopathology: conceptual and historical aspects. Psychol. Med. 14, 303–313.
Berrios, G.E., 1987. Historical aspects of psychoses: 19th century issues. Br. Med. Bull. 43, 484–498.
Borsboom, D., Cramer, A.O.J., 2013. Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 9, 91–121.
Bucknill, J.C., Tuke, D.H., 1858. A Manual of Psychological Medicine: The History, Nosology, Description, Statistics, Diagnosis, Pathology, and Treatment of Insanity. Blandard and Lea, Philadephia.
Contreras, A., Nieto, I., Valiente, C., Espinosa, R., Vazquez, C., 2019. The study of psychopathology from the network analysis perspective: a systematic review. Psychother. Psychosom. 88, 71–83.
Cullen, G., 1780. Synopsis Nosologie Methodicae, 3rd edition. Edinburg Press, London, UK.
Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 11, 126.
Dillon, D.G., Rosso, I.M., Pechtel, P., Killgore, W.D.S., Rauch, S.L., Pizzagalli, D.A., 2014. Peril and pleasure: an RDoC-inspired examination of threat responses and reward processing in anxiety and depression. Depress. Anxiety 31, 233–249.
Disner, S.G., Beevers, C.G., Haigh, E.A.P., Beck, A.T., 2011. Neural mechanisms of the cognitive model of depression. Nat. Rev. Neurosci. 12, 467–477.
Dreyfus, G.L., 1907. Die Melancholie: Ein Zustandsbild des manisch-depressiven Irreseins. Gustav Fischer, Jena.
Esquirol, E., 1838. Des Maladies Mentales: Considerees Sous Les Rapports: Medical Hygienique Et Medico-Legal. Libraire Mediale et Scientifique de J.B., Tome Premier ed. Bruxelles.
Freedman, R., Lewis, D.A., Michels, R., Pine, D.S., Schultz, S.K., Tamminga, C.A., 2013. Initial field trials of DSM-5: new blooms and old thorns. Am. J. Psychiatry 170, 1–5.
Fried, E.I., Epskamp, S., Nesse, R.M., Tuerlincks, F., Borsboom, D., 2016. What are ‘good’ depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of deprssion in a network analysis. J. Affect. Disord. 189, 314–329.
Gee, D.G., Humphreys, K.L., Flannery, J., Goff, B., Telzer, E.H., Shapiro, M., et al., 2013. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. J. Neurosci. 33, 4584–4593.
Goldstein, B., Klein, D., 2014. A review of selected candidate endophenotypes for depression. Clin. Psychol. Rev. 34, 417–427.
Griesinger, W., 1861. Die Pathologie und Therapie der psychischen Krankheiten fur

Aerzte und Studirende. Verlag von Aldoph Krabbe, Stuttgart, Germany.
Guislain, L., 1852. Lecons orales sur les phrenopathies, ou traite theorique et pratique des maladies mentals. In: Hebbelynck, L. (Ed.), Cour Danne a la Clinique Des Etablissements D'Alienes a Gand. Gand, Paris.
Guyon, H., Falissard, B., Kop, J.L., 2017. Modeling psychological attributes in psychology – an epistemological discussion: network analysis vs. lantent variable. Front. Psychol. 8, 798.
Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., Gotlib, I.H., 2012. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am. J. Psychiatry 169, 693–703.
Hankin, B.L., Badanes, L.S., Abela, J.R.Z., Watamura, S.E., 2010. Hypothalamic–pituitary–adrenal axis dysregulation in dysphoric children and adolescents: cortisol reactivity to psychosocial stress from preschool through middle adolescence. Biol. Psychiatry 68, 484–490.
Harrison, A.J., Gibb, B.E., 2015. Attentional biases in currently depressed children: an eye-tracking study of biases in sustained attention to emotional stimuli. J. Clin. Child. Adolesc. Psychol. 44, 1008–1014.
Heim, C., Binder, E.B., 2012. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp. Neurol. 233, 12–111.
Hilland, E., Landro, N.L., Kraft, B., Tamnes, C.K., Fried, E.I., Maglnoc, L.A., Jonassen, R., 2020. Exploring the links between specific depression symptoms and brain structure: a network study. Psychiatry Clin. Neurosci. 74, 220–221.
Hyman, S.E., 2011. Diagnosing the DSM: diagnostic classification needs fundamental reform. Cerebrum [Epub].(2011 Apr 26).
Insel, T.R., 2012. Next-generation treatments for mental disorders. Sci. Transl. Med. 4 (155ps19).
Kang, U., Kim, H., 2014. A historical consideration of psychiatric diagnostic systems: focusing on the concept of depression. J. Korean Neuropsychiatr. Assoc. 53, 259–292.
Karg, K., Burmeister, M., Shedden, K., Sen, S., 2011. The serotonin transporter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch. Gen. Psychiatry 68, 444–454.
Kellough, J.L., Beevers, C.G., Ellis, A.J., Wells, T.T., 2008. Time course of selective attention in clinically depressed young adults: an eye tracking study. Behav. Res. Ther. 46, 1238–1243.
Kendler, K.S., 2013. A history of the DSM-5 scientific review committee. Psychol. Med. 43, 1793–1800.
Kendler, K.S., 2020. The origin of our modern concept of depression - the history of melancholia from 1780-1880: a review. JAMA Psychiatry [Epub].(2020 Jan 29).
Kendler, K.S., Engstrom, E.J., 2020. Dreyfus and the shift of melancholia in Kraepelin's textbooks from an involutional to a manic-depressive illness. J. Affect. Disord. 279, 42–50.
Kendler, K.S., Aggen, S.H., Flint, J., Borsboom, D., Fried, E.I., 2018. The centrality of DSM and non-DSM depressive symptoms in Han Chinese women with major depression. J. Affect. Disord. 227, 739–744.
Koukopoulos, A., Sani, G., 2014. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr. Scand. 129, 4–16.
Kraepelin, E., 1883. Compendium der Psychiatrie: Zum Gebauche fur Studirende und Aerzte. Verlag von Ambr, Abel, Leipzig.
Krafft-Ebing, Rv, 1903. Lehrbuch Der Psychiatrie Auf Klinische Grundlage Fur Prakische Aerzte Und Studirende, 7th edition. F.A. Davis Co. Publishers, Philadelphia.
Kupfer, D.J., Regier, D.A., 2011. Neuroscience, clinical evidence, and the future of psychiatric classification in DSM-5. Am. J. Psychiatry 168, 672–674.
Lenroot, R.K., Schmitt, J.E., Ordaz, S.J., Wallace, G.L., Neale, M.C., Lerch, J.P., et al., 2009. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum. Brain Mapp. 30, 163–174.
Madhoo, M., Levine, S.Z., 2016. Network analysis of the quick inventory of depressive symptomatology: reanalysis of the STAR*D clinical trial. Eur. Neuropsychopharmacol. 26, 1768–1774.
Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013. A mega-analysis of genome-wide association studies for major depressive disorder. Mol. Psychiatry 18, 497–511.
Maudsley, H., 1867. The Physiology and Pathology of the Mind. D. Aplleton and Co, New York.
McNally, R.J., Robinaugh, D.J., Wu, G.W., Wang, L., Deserno, M.K., Borsboom, D., 2015. Mental disorders as causal systems a network approach to posttraumatic stress disorder. Clin. Psychol. Sci. 3, 836–849.
Moller, H.J., Bandelow, B., Bauer, M., Hampel, H., Herpertz, S.C., Soyka, M., et al., 2015. DSM-5 reviewed from different angles: goal attainment, rationality, use of evidence, consequence - part 1: general aspects and paradigmatic discussion of depressive disorders. Eur. Arch. Psychiatry Clin. Neurosci. 265, 5–18.
Olino, T.M., 2016. Future research directions in the positive valence systems: measurement, development, and implications for youth unipolar depression. J. Clin. Child. Adolesc. Psychol. 45, 681–705.
Opsahl, T., Agneessens, F., Skvoretz, J., 2010. Node centrality in weighted networks: generalizing degrees and shortest paths. Soc. Networks 32, 245–251.
Østergaard, S.D., Jensen, S.O.W., Bech, P., 2011. The heterogeneity of the depressive syndrome: when numbers get serious. Acta Psychiatr. Scand. 124, 495–496.
Østergaard, S.D., Bille, J., Søltoft-Jensen, H., Lauge, N., Bech, P., 2012. The validity of severity-psychosis hypothesis in depression. J. Affect. Disord. 140, 48–56.
Park, Y.-M., 2018. The mixed-features specifier of major depressive disorder in DSM-5: is it practical? Psychiatry Investig. 15, 1009–1010.
Park, S.-C., Kim, Y.-K., 2019b. Diagnostic issues of depressive disorders from Kraepelinian dualism to diagnostic and statistical manual of mental disorders, fifth edition. Psychiatry Investig. 16, 636–644.
Park, S.-C., 2020. Symptom-based selection of antidepressants. J. Korean Med. Assoc. 63 (4), 216–226.
Park, S.-C., Choi, J., 2017. Issues in the classification of psychotic depression. In: Kim, Y.-K. (Ed.), Major Depressive Disorder: Risk Factors. Characteristics and Treatment Options. NOVA Science Publishers, Inc., New York, pp. 49–67.
Park, S.-C., Kim, Y.-K., 2018. Depression in DSM-5: Changes, controversies and future direction. In: Kim, Y.-K. (Ed.), Understanding Depression. Clinical Manifestations, vol. 2. Diagnosis and Treatment. Springer Nature, New York, pp. 3–14.
Park, S.-C., Kim, Y.-K., 2019a. Contemporary issues in depressive disorders. Psychiatry Investig. 16 (9), 633–635.
Park, S.-C., Kim, D., 2020. The centrality of depression and anxiety symptoms in major depressive disorder determined using a network analysis. J. Affect. Disord. 271, 19–26.
Park, S.-C., Kim, J.M., Jun, T.Y., Lee, M.S., Kim, J.B., Yim, H.W., et al., 2017. How many different symptom combinations fulfill the diagnostic criteria for major depressive disorder?: results from the CRESCEND study. Nord. J. Psychiatry 71, 217–222.
Park, S.-C., Jang, E., Xinag, X.-T., Kanba, S., Kato, T.A., Chong, M.-Y., et al., 2020. Network analysis of the depressive symptom profiles in Asian patients with depressive disorders: findings from the research on Asian psychotropic prescription patterns for antidepressants (REAP-AD). Psychiatry Clin. Neurosci. 74, 344–353.
Parnas, J., Bovet, P., 2015. Psychiatry made easy: Operation(al)ism and some of its consequence. In: Kendler, K.S., Parnas, J. (Eds.), Philosophical Issues in Psychiatry III: The Nature and Sources of Historical Changes. Oxford University Press, Oxford, UK, pp. 190–212.
Pinel, P.H., 1801. Traite Medico-Philosophique sur L'Allenation Mentale ou La Manie. In: Chez Richard. Ravier, Paris, Calle et.
Radden, J., 2003. Is this dame melancholy? Evaluating todays' depression and past melancholia. Philos. Psychiatry Psychol. 10, 37–52.
Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., et al., 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. J. Am. Med. Assoc. 301, 2462–2471.
Roseman, S., Nasti, J., 2012. Psychiatric diagnoses are not mental processes: Wittgenstein on conceptual confusion. Aust. N. Z. Psychiatry 46, 1046–1052.
Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., et al., 2003. The 16-item quick inventory of depressive symptomatology (qids), clinician rating (qids-c), and self-report (qids-sr): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54, 573–583.
Sankey, W.H.O., 1884. Lectures on Mental Disease, 2nd edition. H.K. Lewis, London.
Saxe, G.N., 2017. Network analysis: computational methods to understand the complexity of psychiatric disorders. J. Am. Child. Adolesc. Psychiatry 56, 669–677.
Schmitt, J.E., Neale, M.C., Fassassi, B., Perez, J., Lenroot, R.K., Wells, E.M., et al., 2014. The dynamic role of genetics on cortical patterning during childhood and adolescence. Proc. Natl. Acad. Sci. 111, 6774–6779.
Shorter, E., 2013. The history of DSM. In: Paris, J., Philips, J. (Eds.), Making the DSM-5. Springer, New York, pp. 3–20.
Silk, J.S., Siegle, G.J., Whalen, D.J., Ostapenko, L.J., Ladouceur, C.D., Dahl, R.E., 2009. Pubertal changes in emotional information processing: pupillary, behavioral, and subjective evidence during emotional word identification. Dev. Psychopathol. 21, 7–26.
Simmons, W.K., Burrows, K., Avery, J.A., Kerr, K.L., Bodurka, J., Savage, C.R., 2016. Depression-related increases and decreases in appetite: dissociable patterns of aberrant activity in reward and interoceptive neurocircuitry. Am. J. Psychiatry 173, 418–428.
Steer, R.A., Ranieri, W.F., Beck, A.T., Clark, D.A., 1993. Further evidence for the validity of the beck anxiety inventory with psychiatric outpatients. J. Anxiety Disord. 7, 195–205.
Steer, R.A., Kumar, G., Ranieri, W.F., Beck, A.T., 1995. Use of the beck anxiety inventory with adolescent psychiatric outpatients. Psychol. Rep. 76, 459–465.
Telles-Correia, D., Marques, J.G., 2015. Melancholia before the twentieth century: fear and sorrow or partial insanity? Front. Psychol. 6, 81.
Uher, R., Perlis, R.H., Henisberg, N., Zobel, A., Rietschel, M., Mors, O., et al., 2012. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. Psychol. Med. 42, 967–980.
Whooley, O., Horowitz, A.V., 2013. The paradox of professional success: Grand ambition, furious resistance, and the derailment of the DSM-5 revision process. In: Paris, J., Philips, J. (Eds.), Making the DSM-5. Springer, New York, pp. 75–93.
Wittgenstein, L., 2001. Philosophical Investigations. (German Text, with a Revised English Translation, Trans GEM Anscombe), 3rd edition. Blackwell, Oxford.
Wood, M.L., Gibb, B.E., 2015. Integrating NIMH research domain criteria (RDoC) into depression research. Curr. Opin. Psychol. 4, 6–12.
World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioral Disorders, Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.
Zimmerman, M., Galione, J.N., Chelminski, I., Young, D., Dalrymple, K., Witt, C.F., 2010. Validity of a simpler definition of major depressive disorder. Depress. Anxiety 27, 977–981.
Zimmerman, M., Emmert-Aronson, B.O., Brown, T.A., 2011. Concordance between a simpler definition of major depressive disorder and diagnostic and statistical manual of mental disorder, Fourth Edition: An independent replication in an outpatient sample. Compr. Psychiatry 52, 261–264.
Zimmerman, M., Ellison, W., Young, D., Chelminski, I., Dalrymple, K., 2015. How many different ways do patients meet the diagnostic criteria for major depressive disorder? ComprPsychiatry 56, 29–34.
Zisook, S., Corruble, E., Duan, N., Iglewicz, A., Karam, E.G., Lanouette, N., et al., 2012. The bereavement exclusion and DSM-5. Depress. Anxiety 29, 425–443.