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REVIEW

Bipolar disorder in the International Classification of Diseases-Eleventh version: A review of the changes, their basis, and usefulness

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Abstract

The World Health Organization's 11th revision of the International Classification of Diseases (ICD-11) including the chapter on mental disorders has come into effect this year. This review focuses on the "Bipolar or Related Disorders" section of the ICD-11 draft. It describes the benchmarks for the new version, particularly the foremost principle of clinical utility. The alterations made to the diagnosis of bipolar disorder (BD) are evaluated on their scientific basis and clinical utility. The change in the diagnostic requirements for manic and hypomanic episodes has been much debated. Whether the current criteria have achieved an optimum balance between sensitivity and specificity is still not clear. The ICD-11 definition of depressive episodes is substantially different, but the lack of empirical support for the changes has meant that the reliability and utility of bipolar depression are relatively low. Unlike the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the ICD-11 has retained the category of mixed episodes. Although the concept of mixed episodes in the ICD-11 is not perfect, it appears to be more inclusive than the DSM-5 approach. Additionally, there are some uncertainties about the guidelines for the subtypes of BD and cyclothymic disorder. The initial results on the reliability and clinical utility of BD are promising, but the newly created diagnostic categories also appear to have some limitations. Although further improvement and research are needed, the focus should now be on facing the challenges of implementation, dissemination, and education and training in the use of these guidelines.

Key Words: ICD-11 guidelines; Bipolar disorder; Utility; Reliability

Core Tip: This review evaluates the clinical utility and the scientific basis for the changes made to the section on bipolar disorders in the 11th version of the International Classification of Diseases. The diagnostic requirements for many categories have changed. However, some of these alterations are still controversial based on the existing evidence. The examination of the reliability and utility of the newly created categories has yielded encouraging results, but certain limitations are evident. Thus, there is scope for further improvement, but the greater challenge will be to implement and disseminate the new guidelines and train the potential users of these guidelines.

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INTRODUCTION

Bipolar disorder (BD) is a complex condition with several facets that influence its diagnosis and treatment[1,2]. Some of these aspects include early onset, a lifelong course characterized by frequent relapses and recurrences, inter-episodic morbidity consisting of residual symptoms, cognitive dysfunction, and functional impairment, high rates of psychiatric and medical comorbidity, and high risks for self-harm or violence. There is a predominance of depression, from the onset of the illness and throughout its course including the inter-episodic periods. Therefore, distinguishing BD from unipolar depression is difficult. The full spectrum of BD commonly includes milder and subthreshold disorders that overlap with normal variations of mood, personality, and other non-mood disorders. In contrast, the more severe forms such as psychotic BD are often indistinguishable from schizophrenia. These complexities mean that the accurate diagnosis and initiation of treatment are often delayed by several years.

In the absence of laboratory tests, the diagnostic process in psychiatry relies on signs, symptoms, and the course of psychiatric disorders[3-5]. Psychiatric classifications utilize these features to frame operational definitions that enhance the diagnostic accuracy of the disorders. Apart from naming and providing explicit descriptions of the disorders, psychiatric classifications also determine their place in the organizational structure. This provides a theoretical perspective that aids research regarding their scientific basis. The creation of classificatory systems in psychiatry has a long history and much effort is spent on revising them to keep pace with the recent advancements in the field.

The principal psychiatric classifications are the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association and the International Classification of Diseases (ICD) of the World Health Organization (WHO). The fifth version of the DSM (DSM-5) has been published in 2013[6]. The WHO's 11th revision of the ICD (ICD-11) including the chapter on mental, behavioural, or neurodevelopmental disorders has come into effect from January 2022[7]. The draft versions of the ICD-11 guidelines including the one on mood disorders are available on the Global Clinical Practice Network (GCPN) website[8].

Revising the ICD is a part of the core responsibility of the WHO. Its Department of Mental Health and Substance Abuse was responsible for developing the ICD-11 guidelines for the chapter on mental, behavioural, or neurodevelopmental disorders[9-13]. The benchmarks for the revision of this ICD-11 chapter included attention to several guiding principles and priorities. These are summarized in Table 1.

This review focuses on the "Bipolar or Related disorders" section of the ICD-11, Clinical Descriptions and Diagnostic Requirements (CDDR) on mood disorders. It summarizes the changes that have been made in this section and attempts to evaluate the scientific basis and the usefulness of these changes.

SUMMARY OF THE CHANGES MADE

New nomenclature and revised organizational structure

The name of the section has been changed from mood (affective) disorders in the tenth revision of the ICD (ICD-10)[14] to mood disorders in the ICD-11 version. Consequently, the term "bipolar affective disorder" has become "bipolar disorder". This is appropriate since the word "affective" was redundant, while the label BD is more precise[15]. Additionally, the part on BD is now labelled "Bipolar or Related Disorders" which is similar to the DSM-5.

During their development, efforts were made to forge a comparable organizational structure for both the DSM-5 and the ICD-11 CDDR[16,17]. Reviews regarding the placement of BD concluded that considering the available evidence, the best possible solution would be an independent cluster for BD

Table 1 Benchmarks for the revisions of the new classifications[9-13]

Principles and priorities	ICD-11-CDDR	DSM-5[1]
Guiding principles		
Public health imperative	The guidelines should be useful in alleviating the global mental health burden, especially the burden in the low-and middle-income countries	The manual is meant to be used as a tool for collecting and communicating accurate public health statistics on mental disorders
Clinical imperative	Clinical and public health utility were accorded the greatest priority followed by scientific validity	Clinical utility was accorded the highest priority followed by the scientific evidence
Stakeholders	The guidelines are meant for use in all countries, for all professionals, and for all service users	The manual is meant for all professionals and service users
Multiple uses	The guidelines are meant for clinical, research, teaching, and training purposes, and for collecting data	The manual is meant for clinical, research, teaching, and training purposes, and for collecting data
Settings	The guidelines are meant for all settings including specialist and primary-care settings, with special emphasis on primary-care settings in low-and middle-income countries	The manual should be applicable to all settings including specialist, primary-care, community, and forensic settings
Cross-cultural applicability	The revision should be relevant and acceptable to clinicians from all cultures	Cultural aspects relevant to the diagnosis was a key consideration
Priorities		
Global applicability	Global and universal applicability: The guidelines should be relevant for all countries, all stakeholders, and in all settings	Professionals from 39 countries were involved in developing the scientific basis of the diagnostic criteria
Clinical utility	Clinical and public-health utility was accorded the highest priority during the process of revision	The manual is primarily intended for clinical use and should be feasible for clinical practice
Scientific validity	The scientific basis should be based on best available evidence. Compromises for the sake of utility should be avoided	The revision was guided by a thorough review of the best scientific evidence
Harmonization	Efforts to harmonize the ICD-11 revision with the DSM-5 involved enhancing similarities and minimizing arbitrary differences between the two systems	The APA collaborated with the WHO to develop a common and globally applicable research base for the DSM-5 and the ICD-11 disorders

[1]The priorities of the DSM-5 classification were quite similar to those of the ICD-11.

APA: American Psychiatric Association; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8]; WHO: World Health Organization.

[18,19]. The DSM-5 thus created a separate chapter for BD. The ICD-11 organization was also influenced by these efforts and its structure is largely similar to that of the DSM-5[13,20]. However, the ICD-11 configuration was also determined by surveys of mental health professionals and studies examining their conception of a more clinically useful structure[13,21-24]. The structure of mood disorders in the ICD-11 was changed based on these studies. The "Mood Disorders" section was retained to refer to a "superordinate" grouping of bipolar and depressive disorders. This avoided cutting the cord between BD and depressive disorders, which belong to the same spectrum[25,26]. Following the spectrum approach, the ICD-11 has grouped cyclothymia with BD. The "Mood Disorders" section opens with the definitions of mood episodes. The longitudinal pattern of mood episodes determines the diagnosis of either depression or BD[13]. This simpler and more clinically useful "building blocks" approach to diagnosing mood disorders[27] is in line with the DSM-5.

Manic and hypomanic episodes

The descriptions of manic and hypomanic episodes in the ICD-11 guidelines differ substantially from the ones in the ICD-10 but are analogous to those in the DSM-5[6,28]. This is depicted in Table 2.

There are only minor differences between the two classifications. Nevertheless, the ICD-11 definitions are somewhat broader than the DSM-5 ones. This is the result of a flexible diagnostic approach used by the ICD-11 CDDR, which avoids rigid and often arbitrary cut-offs imposed in the DSM-5[29]. The requirements for a minimum number of accessory symptoms for mania and hypomania and a minimum duration of symptoms for hypomania have been avoided. This circumvents many difficulties associated with these diagnoses[30]. Moreover, it places greater emphasis on exercising clinical judgment and therefore resembles the diagnostic process in everyday practice[31,32]. The differences in the two diagnostic approaches also reflect the differences between the prototype-based methods followed by the ICD-11 guidelines in contrast to the operational diagnostic criteria used by the DSM-5[33-37]. Although prototype-based methods are not infallible, they are often more congruent with the clinician's diagnostic practices and therefore preferred by them. They are less complex and cumbersome than the operational criteria, but equally reliable and useful in diagnosing mood disorders. The ICD-11 guidelines attempted

Table 2 Comparison of diagnostic criteria for manic and hypomanic episodes

	ICD-11-CDDR	DSM-5
Manic episode		
Gate/entry level criteria	Both extreme and persistent mood changes (euphoria, irritability, expansiveness, mood lability) and abnormally increased activity or subjective experience of increased energy	Both abnormal and persistent mood changes (elevated, expansive, or irritable) and abnormal and persistent increase in goal-directed activity or energy[1]
Accessory criteria	Significant changes in several of the following seven areas: talkativeness/pressured speech, flight of ideas/racing thoughts, increased self-esteem/grandiosity, decreased need for sleep, distractibility, impulsive/reckless behaviour, increased sexual or social drive/increased goal directed activity	Significant and noticeable changes in three of the seven accessory symptoms; four if mood is only irritable; accessory criteria almost identical to the ICD-11 definition
Persistence and duration	Symptoms present most of the day, nearly every day for a minimum of one week unless shortened by treatment	Symptoms present most of the day, nearly every day for a minimum of one week unless shortened by hospitalization
Functional impairment	Significant impairment in all the areas of functioning; the patient may require intensive treatment/hospitalization to prevent self-harm or violence; the episode may be accompanied by psychotic symptoms	Significant impairment in all the areas of functioning; the patient may require hospitalization to prevent self-harm or violence; the episode may be accompanied by psychotic symptoms
Exclusions	Mania secondary to medical conditions or substance use; mixed episodes excluded	Mania secondary to medical conditions or substance use; manic episodes with mixed features allowed
Effects of antidepressant treatment	The episode should be considered a manic one if all the criteria are met even after the effects of treatment have diminished	The episode should be considered a manic one if all the criteria are met even after the effects of treatment have diminished
Grading of severity	Severity not graded	Severity graded as mild, moderate, or severe based on the number of symptoms, their intensity, and functional impairment
Psychotic symptoms	No distinction between mood-congruent and incongruent symptoms	Mood-congruent and incongruent symptoms distinguished
Hypomanic episode		
Gate/entry criteria	Both persistent mood changes (elevation, irritability, mood lability) and abnormally increased activity or subjective experience of increased energy that are significantly different from the usual mood state; changes are apparent to others and do not include changes that are appropriate to the circumstances[2]	Both abnormal and persistent mood changes (elevated, expansive, or irritable) and abnormal and persistent increase in activity or energy; changes in mood differ significantly from the usual state and are apparent to others
Accessory criteria	Significant changes in several of the seven accessory symptoms that are identical to the definition of mania; these changes are apparent to others	Significant and noticeable changes in three of the seven accessory symptoms, four if mood is only irritable; accessory criteria are the same as those for mania and almost identical to the ICD-11 definition
Persistence and duration	Symptoms present most of the day, nearly every day for at least several days	Symptoms present most of the day, nearly every day for a minimum of four consecutive days
Functional impairment, hospitalization, and psychotic symptoms	Socio-occupational functioning is not markedly impaired; the patient does not require intensive treatment or hospitalization to prevent self-harm or violence; the episode is not accompanied by psychotic symptoms	Clear change in socio-occupational functioning from the usual state apparent to others, but functioning is not markedly impaired; the patient does not require hospitalization to prevent self-harm or violence; the episode is not accompanied by psychotic symptoms
Exclusions	Hypomania secondary to medical conditions or substance use; mixed episodes are excluded	Hypomania secondary to substance use[3]; hypomanic episodes with mixed features allowed
Effects of antidepressant treatment	The episode should be considered a hypomanic one if all the criteria are met even after effects of treatment have diminished	The episode should be considered a hypomanic one if all the criteria are met even after effects of treatment have diminished; however, full syndromal manifestation of hypomania is necessary

[1]Updated in 2015 to persistent increase in activity or energy ("goal-directed" removed)[28].
[2]In the ICD-11 CDDR, the word "extreme" is not used to describe the mood change in hypomania as in manic episodes, possibly denoting a reduced severity of mood alterations; no such distinction is present in the DSM-5.
[3]Updated in 2015 to include hypomania secondary to medical conditions[28].
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

to enhance the utility of the prototype approach by using a standardized content form that contained systematic and consistent diagnostic information for all disorders[10,13].

The expanded gate criterion is the most important alteration in the definitions of mania and hypomania both in the ICD-11 CDDR and the DSM-5. It was not present in the earlier versions of both these classifications including the ICD-10 guidelines. Changes in both mood and activity or energy are mandatory for the diagnosis now. This change was made to improve the diagnostic accuracy, specificity, and reliability of mania and hypomania[13,38-40]. It was also meant to differentiate the diagnoses from normal mood fluctuations, particularly in the case of hypomania. The intention was to prevent the overdiagnosis of manic or hypomanic episodes as well as BD. Simultaneously, this change aimed to facilitate earlier detection of BD by minimizing the under-reporting of hypomania in those with major depression.

Adding overactivity to mood symptoms is evidence-based and considered to be a well-founded change[30,38,41-43]. The empirical support for including hyperactivity as a core criterion derives from factor-analytic investigations of mania and large-scale community studies of BD. Recent reviews of the factor-analytic studies of mania have indicated that overactivity is the most prevalent symptom of this condition[44,45]. It is more common than mood changes and is associated with several other key symptoms of mania. Although community-based studies have also shown that any of the three criteria, euphoria, irritability, and overactivity, are sufficient for diagnosing mania or hypomania, overactivity is the foremost diagnostic criterion with the maximum sensitivity[46-50]. In contrast, there is less evidence for irritability being an entry-level criterion for mania or hypomania. Irritability is common in many other disorders and is not specifically associated with mania or hypomania. Moreover, it is rarely associated with overactivity[30,40,41]. The ICD-11 draft also includes lability of mood as a symptom of mania and hypomania, but its diagnostic role is not clear. Although there is a high prevalence of mood lability during manic episodes[51], very few factor-analytic studies have found it to be an important constituent of mania[45].

Additionally, the inclusion of antidepressant treatment-induced prolonged manic or hypomanic switches is also reasonable because such switches occur mainly in those predisposed to bipolarity[41,49,52]. In contrast, the exclusion of mood episodes secondary to medical conditions or substance use is considered faulty because it is based on causal attributions[53]. Lastly, the ICD-11 guidelines have added functional impairment to the definition of mania to bring it more in line with the DSM-5. The ICD-10 had avoided using functional impairment as a diagnostic requirement because cultural factors were thought to confound socio-occupational performance. However, the ICD-11 has included impaired functioning as a part of the diagnosis because it helps in distinguishing mood disorders from normal mood changes, determining their severity, and improving their clinical utility[5,9,10].

The change that has generated the maximum debate is the diagnostic requirement of combined mood changes and overactivity for mania and hypomania. Proponents of this change have insisted that the combination provides an optimal balance between diagnostic specificity and sensitivity[42,43]. Moreover, the higher diagnostic threshold reduces the chances of a false positive diagnosis of BD. They argue that an incorrect diagnosis of BD may be more harmful than being falsely diagnosed with major depression. However, the majority of the other researchers feel that this requirement is too restrictive [31,39,41,53,54]. They believe that the dyadic criterion decreases the chances of diagnosing mania and hypomania. Consequently, the prevalence of type I BD (BP-I) or type II BD (BP-II) will decline because many patients will be relegated to the categories of subthreshold BD or major depression. They point out that community studies of BD have demonstrated that either mood change or overactivity is sufficient for the diagnosis. Thus, using either mood change or overactivity as entry-level criteria could increase the sensitivity of the manic and hypomanic diagnoses without affecting the prevalence of BD [29,40,53]. These contrasting propositions have been examined in some studies on the prevalence of BD using the DSM-5 and ICD-11 criteria. These are included in Table 3.

This table shows that prevalence studies using the DSM-5 criteria are far more common. Only one study has considered the ICD-11 guidelines. Angst *et al*[31] (2020) used the ICD-10, DSM-5, and the ICD-11 criteria to re-analyse the prevalence of mania and hypomania according to the Zurich cohort study. They proposed that the rate of hypomania will be doubled with the ICD-11 criteria compared to the ICD-10 and the DSM-5. This was presumably because of the broader definition of hypomania in the ICD-11 and the inclusion of patients with antidepressant-induced prolonged hypomanic switches. The lifetime prevalence of DSM-5 defined BD appears to be unchanged[55-58]. In contrast, several DSM-5-based studies have found about a 20%-60% reduction in the point prevalence of manic and hypomanic episodes or BD[38,59-61]. In these studies, patients diagnosed according to the DSM-5 criteria had more severe manic symptoms[40,59,61] than those diagnosed with DSM-IV criteria[62,63]. Moreover, these studies suggested that the prevalence with DSM-5 criteria was lowest early in the course of BD and increased with time[38,58,59]. This was confirmed by the study of newly diagnosed patients with BD, in which the rate of DSM-5 BD was reduced by 62% at the baseline, but only by 50% on long-term follow-up[61]. This is because newly diagnosed patients are a more heterogenous group and are less likely to meet the stricter DSM-5 definitions than those with more chronic illnesses[40]. Thus, the reduction in the prevalence of BD attenuated with time and there were no differences in the lifetime rates or clinical characteristics of mania, hypomania, and BD diagnosed with DSM-5 or DSM-IV criteria[39,40,61]. These findings imply that although the DSM-5 criteria may prevent overdiagnosis of BD as intended, patients with less severe and recent-onset BD may be missed[40]. Extrapolating from these results, it appears that although the short-term prevalence of BD may be reduced, the long-term prevalence of BD is likely

Table 3 Prevalence of bipolar disorder according to the International Classification of Diseases, 11th version and the Diagnostic and Statistical Manual of Mental Disorder, 5th edition criteria

Ref.	Criteria sets	Patients	Bipolar types	Type of prevalence	Results regarding the prevalence of BD
No change in the prevalence of bipolar disorder					
Fassassi *et al* [55], 2014	DSM-5	Community-based	BP-I, BP-II, Other BD[1]	12-mo and lifetime	Prevalence similar to earlier studies of BD
Calvó-Perxas *et al*[56], 2015	DSM-5	Community-based	BP-I, BP-II, Other BD	Lifetime	Prevalence was within the range of previous reports of BD
Blanco *et al*[57], 2017	DSM-5	Community-based	BP-I	Lifetime	Prevalence was within the range of previous reports of BD
Gordon-Smith *et al*[58], 2017	DSM-IV and DSM-5	Community-based and outpatients	BP-I, BP-II	Lifetime	Up to 94% of the patients with DSM-IV BD also met the DSM-5 criteria
Decrease in the prevalence of bipolar disorder					
Angst *et al*[53], 2013[2]	DSM-5	Analysis based on a previous community study (BRIDGE)	BD	Lifetime	About 22% reduction in prevalence
Machado-Vieira *et al*[38], 2017	DSM-IV and DSM-5	Outpatients	Maniaand hypomania	Point prevalence	The prevalence of mania and hypomania according to the DSM-5 criteria was reduced by about 50%
Fredskild *et al* [59], 2019	DSM-IV TR and DSM-5	Outpatients	Maniaand hypomania	Point prevalence	A reduction of 35% in the prevalence of mania and hypomania with the DSM-5 criteria was noted
Faurholt-Jepsen *et al*[60], 2020	DSM-5	Patients taking part in trials	Mania and hypomania	Smartphone-based activity assessments over 6-9 mo	The prevalence of hypomania according to the DSM-5 criteria was substantially less (0.12%) than patients not meeting these criteria (24%)
Fredskild *et al* [61], 2021	DSM-IVand DSM-5	Outpatients	Mania and hypomania	Assessments at baseline and at 3-year follow-up	The prevalence of mania and hypomania according to the DSM-5 criteria was reduced by 62% at baseline and by 50% on follow-up
Increase in the prevalence of type II bipolar disorder					
Angst *et al*[53], 2013[3]	DSM-5	Analysis based on a previous community study (BRIDGE)	BP-II	Lifetime	Prevalence of BP-II disorder will be twice as much with the DSM-5 than earlier
Angst *et al*[31], 2020[4]	ICD-10, DSM-5, and ICD-11	Analysis based on an earlier community study (Zurich cohort study)	Mania (BP-I) and hypomania (BP-II)	Lifetime	Prevalence of hypomania (BP-II) will be doubled with the ICD-11 criteria compared to the ICD-10 and the DSM-5 criteria; no change in the prevalence of mania (BP-I) is likely

[1]The Other BD group refers to the "Other Specified Bipolar and Related Disorders" category of the DSM-5.
[2]This reduction is proposed to be a consequence of the mandatory requirement for both mood changes and overactivity.
[3]The increase in prevalence is proposed to be a consequence of inclusion of patients with antidepressant-induced prolonged hypomanic switches.
[4]The increase in prevalence is proposed to be a consequence of a somewhat broader definition of hypomania in the ICD-11 and the inclusion of patients with antidepressant-induced prolonged hypomanic switches.
BD: Bipolar disorder; BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; BRIDGE: Bipolar disorders: Improving diagnosis, Guidance, and Education[49]; DSM-IV/DSM-IV TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition/Text revision[62,63]; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11: International Classification of Diseases, 11th version[8].

to remain unchanged despite the use of the new definitions in the ICD-11 CDDR[39,40,61].

The description of hypomanic episodes in the ICD-11 draft brings it closer to the DSM-5 definition in several aspects. Both distinguish mania from hypomania based on the lack of marked functional impairment, no requirement for hospitalization, and the absence of psychotic symptoms in hypomania. However, these distinguishing features of hypomania are not without their problems. For example, the lack of marked impairment in functioning is often difficult to make out with certainty[64-66]. There are no clear criteria to determine the level of impairment and it is often a subjective judgement on the part of the clinician. Moreover, many patients with hypomania report an improvement in their functioning. Similarly, the decision to hospitalize someone with hypomania is often determined by several cultural, socioeconomic, or health-service-related factors than simply by the lesser clinical severity of the episode [31,65,67]. In some instances, those with hypomania are more likely to be hospitalized than those with mania[65]. Lastly, there is some evidence of an association between psychosis and hypomania, particularly from longitudinal community-based studies[68,69]. Then again, other studies have shown that

patients with hypomania/BP-II disorder are much less likely to experience psychotic episodes or be hospitalized because of psychosis than those with BP-I disorder[66].

Finally, the issue that has been the bone of contention for a long time is the requirement for a minimum duration of 4 d for hypomania in the DSM-5. The existing evidence derived mainly from large community studies shows that there is no difference between hypomanic episodes lasting less or more than 4 d in terms of prevalence, clinical features, and associated impairment[29,53,54,65,66]. However, the proposal to include short-lasting hypomanic episodes was not accepted by the DSM-5 because of concerns about the overdiagnosis of BD[29]. Nevertheless, the DSM-5 has included some of these short-lasting presentations in the category of "Other Specified Bipolar and Related Disorders" and its section three as a condition for further study. By defining the minimum duration as "several days", the ICD-11 guidelines seem to have avoided this controversy, but they are likely to have the same limitations as the DSM-5 in the other criteria for hypomania[65]. It is also unclear whether the lack of clear thresholds will hamper the clinical utility of the ICD-11 diagnosis[70].

Depressive episodes and bipolar depression

The ICD-11 CDDR has made many changes to the definition of the ICD-10 depressive episode so that the ICD-11 description corresponds to the DSM-5 definition[13,29,30]. These changes are shown in Table 4.

There are certain minor differences between the ICD-11 and DSM-5 definitions, but the major difference is the inclusion of the "bereavement exclusion" criterion while diagnosing depression in the ICD-11 draft[29,30]. The DSM-5 has been widely criticized for removing the (operationally defined) "bereavement exclusion" criterion and supplanting it with the application of clinical judgement. The ICD-11 has followed the DSM-IV approach in setting a higher threshold in terms of duration and severity while diagnosing depression in the context of bereavement. Nevertheless, the subject of "bereavement exclusion" remains controversial, with some justifying its removal[71,72] and others claiming its retention to be more in agreement with the evidence[73,74].

Another problem is that the definitions of depressive episodes in the ICD-11 and the DSM-5 lack empirical support[29,75,76]. These definitions arbitrarily impose a categorical threshold on what is essentially a dimensional concept. Accordingly, the distinction between major depression and normality, minor depression, and severe melancholic depression is unclear. The functional impairment criterion does not resolve this threshold problem. Therefore, major depression is a heterogenous category both in terms of the diagnostic criteria and the patients meeting these criteria. Moreover, it has been shown that the current definitions do not include the most important symptoms and that simpler definitions of major depression may be more appropriate. All these limitations lead to poor reliability and clinical utility of the current category.

The definitions of unipolar depression and bipolar depression are identical in both the ICD-11 and the DSM-5[29,54]. This is primarily because the existing evidence indicates that there are no characteristic features that could distinguish the two categories[77-79]. However, certain symptoms, course characteristics, and family history are more common in either unipolar or bipolar depression and in those with unipolar depression who convert to BD. These features could be used to distinguish between unipolar or bipolar depression[77]. Although this "probabilistic" approach might have reasonable predictive power[80,81], there are obvious difficulties in incorporating such a scheme in the current classifications. Nevertheless, the lack of distinction between unipolar and bipolar depression is problematic, because one of the reasons that the diagnosis of BD is often missed is the inability to distinguish between the two types of depression[82].

Mixed episodes

Mixed states consist of an admixture of the usual manic and depressive symptoms along with certain characteristic features such as agitation, irritability, and hostility[83-87]. More than a third (30%-70%) of the patients with BD present with mixed mania or mixed depression. Mixed states are associated with a more severe form of BD, higher comorbidity, poorer course and outcome, inadequate treatment response, higher disability, and greater risk of suicide.

The DSM-IV TR definition of mixed episodes was thought to be too restrictive because it required the concurrent presence of full manic and depressive syndromes. Since the most common presentation of mixed episodes is subsyndromal with a few symptoms of the opposite polarity, the DSM-5 replaced mixed episodes with a "mixed features" specifier[83]. This was defined by the presence of a full mood episode of one polarity accompanied by at least three contrapolar symptoms, excluding those common to both kinds of episodes (overlapping symptoms). The DSM-5 also made it possible to use the specifier for major depressive episodes because of the high rates of subthreshold bipolarity in unipolar depression. It was anticipated that this definition would be better at capturing the subsyndromal manifestations of mixed presentations in BD[82,83]. Indeed, studies showed that with the use of the new DSM-5 specifier, mixed presentations were about three times more common than those with the DSM-IV TR[85,87]. However, several problems with the new specifier have gradually become apparent. The DSM-5 decision to leave out overlapping symptoms has often led to the exclusion of symptoms that are considered to be central to the presentation of mixed states. Several reviews on the subject have pointed out that psychomotor agitation is the principal component of these core features, followed by irritability

Table 4 Changes to the diagnostic guidelines for bipolar depression in the International Classification of Diseases, 11th version

	ICD-11-CDDR	DSM-5	ICD-10
Core symptoms	One of the following: Depressed mood or diminished interest or pleasure	One of the following: Depressed mood or loss of interest or pleasure	Two of the following: Depressedmood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability, diminished activity, and marked tiredness
	Reported or observed changes	Reported or observed changes	
	Change from usual functioning	Change from usual functioning	
Accessory symptoms	Eight symptoms including the new symptoms of hopelessness, fatigue, and agitation/retardation	Seven symptoms: Hopelessness is not included, but fatigue and psychomotor changes are included	Seven symptoms: Bleak and pessimistic views of future instead of hopelessness, no psychomotor changes or fatigue that are part of the core symptoms
	Other symptoms (unchanged) are inattentiveness, changes in sleep and appetite, low self-worth or guilt, and suicidal ideation	Other symptoms are the same as in the ICD-11	Other symptoms are the same as in the ICD-11
Persistence and duration	Symptoms occur most of the day, nearly every day during a minimum period of two weeks	Symptoms occur most of the day, nearly every day during a minimum period of two weeks	Minimum duration of two weeks usually required but shorter periods suffice if symptoms are unusually severe and of rapid onset
Diagnostic threshold	Five out of ten symptoms	Five out of nine symptoms	Four out of ten symptoms
Functional impairment	Part of the diagnostic criteria	Part of the diagnostic criteria	Used to rate severity
Exclusions	Depression secondary to medical conditions or substance use and mixed episodes; mixed episodes excluded	Depression secondary to medical conditions or substance use; diagnosis of depressive episodes with mixed features possible	No clear exclusions
Bereavement exclusion	Operationalized definition present	Only an explanatory note that advises the use of clinical judgement in such instances	Not mentioned as a part of the diagnostic guidelines
Severity ratings	Mild, moderate and severe depressive episodes based on symptom-severity and functional impairment; no requirement for a minimum number of symptoms	Grading similar to the ICD-11; no requirement for a minimum number of symptoms	Grading similar to the ICD-11, but a minimum number of symptoms required for grading different levels of severity; clinical judgement also advised
Psychotic symptoms	Moderate depression with psychotic symptoms is a new category	Mood congruent and incongruent symptoms distinguished	Mood congruent and incongruent symptoms distinguished
Description of melancholia	Descriptions similar to the ICD-10, but no requirement for a minimum number of symptoms	Description more elaborate; a minimum of four symptoms required	Descriptions similar to the ICD-11; a minimum of four symptoms required
Additional specifiers	With prominent anxiety, panic attacks, chronicity, seasonal pattern, puerperal onset	Similar to the ICD-11; additionally mixed features, atypical features, and catatonia	No other specifiers

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

or hostility (dysphoric mood), mood lability, and distractibility[86-90]. Although these features are more prominent in mixed manic episodes, they are present in both mania/BD and depression/unipolar disorder. Accordingly, the DSM-5 definition of mania or hypomania with mixed features is consistent with the existing evidence[29]. However, the category of major depression with mixed features has been criticized because it leaves out many of these key symptoms while including relatively rare ones such as euphoria and grandiosity[85,88-90]. Leaving out the characteristic symptoms means that a considerable proportion of those with mixed depression will be missed by the DSM-5 criteria. Moreover, it has been demonstrated that patients with major depression and mixed features often convert to BD and therefore should be included with the bipolar spectrum disorders[84,91,92]. Additionally, the minimum number of contrapolar symptoms required for the specifier is unclear[84,87,93]. Lastly, the specifier is likely to have poor clinical utility because of its poor predictive validity and uncertain treatment implications of the symptoms included[91,94].

Therefore, it was suggested that the ICD-11 should retain the mixed episode category rather than adopt the DSM-5 approach[95,96]. Retaining the category allows for further research examining its usefulness and treatment requirements. It also ensures that information about mixed states is properly captured because the category is coded. The ICD-10 definition of mixed episodes only required the

rapid alternation of prominent manic, hypomanic, and depressive symptoms for 2 wk. Although it was less restrictive and more in tune with the existing concepts, it was neither too detailed nor precise. Additionally, the 2-wk duration was considered to be excessive. Consequently, a departure from the ICD-10 approach was also proposed[95,97]. The need to include the core symptoms of agitation, irritability, lability, and distractibility was endorsed, as was the retention of the rapid alternating pattern of symptoms[95,96]. Nevertheless, the ICD-11 draft has essentially followed the ICD-10 approach by including the concurrent presence or rapid alternations of manic or depressive symptoms for 2 wk or less if treatment is initiated[13,29]. Unlike the ICD-10, it has included all the core contrapolar symptoms mentioned above. However, no threshold has been set for the number of such symptoms required for diagnosis. The episodes should cause significant functional impairment. The diagnosis of a mixed episode will automatically signify a diagnosis of BP-I disorder. Therefore, the ICD-11 does not have a category equivalent to major depression with mixed features in the DSM-5. The exclusion of mixed episodes from the BP-II diagnosis is also debatable because of their high prevalence in this subtype[98,99]. Although the concept of mixed episodes in the ICD-11 is not perfect, it may still turn out to be more inclusive than the DSM-5 approach, but this can only be established by further research.

Bipolar I disorder

A history of at least one manic or mixed episode will be sufficient to make a diagnosis of BP-I disorder in the ICD-11 CDDR, unlike the ICD-10 which required the presence of at least two episodes. The reliance on a single episode of mania to define BP-I disorder is based on the current evidence, which demonstrates that the occurrence of mania predicts the typical course of BDs, and separates it from other mood and psychotic disorders[30]. Consequently, an independent diagnosis of a manic episode is no longer possible as it was in the ICD-10. However, like the ICD-10, the ICD-11 draft consigns the illnesses characterized by recurrent manic or hypomanic episodes without depression to the "Other Specified Bipolar or Related Disorders" category. Recently, Angst *et al*[31,53,100] have presented evidence that contradicts the traditional view of recurrent mania as a rare condition indistinguishable from BD[27]. Rather, epidemiological studies have found recurrent mania to be common[101] and clinical studies indicate that about 15%-20% of the patients with BD have this condition[102]. The rates are considerably higher in Asian studies coupled with the predominantly manic course of BD in these countries[103]. Moreover, recurrent mania can be reliably distinguished from BP-I disorder in terms of its diagnostic stability, lifetime course, familial-genetic features, and treatment response[31,53,100,102,104]. Therefore, reviving the recurrent mania diagnosis has been proposed.

Bipolar II disorder

The most noticeable change in the ICD-11 CDDR distinguishing it from the ICD-10, is the inclusion of the BP-II subtype. Similar to the DSM-5, a diagnosis of BP-II disorder will require a history of at least one hypomanic episode and one depressive episode. The BP-II subtype was officially recognized in the DSM-IV, based on its diagnostic stability and familial-genetic links with BD[105]. Although historically perceived to be a milder form of BD, it is now clear that BP-II disorder is a chronic and highly recurrent condition that is equally, if not more disabling than, the BP-I subtype. A predominance of depressive pathology during the acute episodes, subthreshold depression in the inter-episodic periods, and suicidal behavior are more common in BP-II disorder[29,106]. The initial evidence suggested that BP-II disorder could be distinguished from BP-I disorder based on its epidemiology, familial-genetic aspects, longitudinal course, and higher suicidal risk[98,107,108]. However, subsequent reviews concluded that there were more similarities than differences between the two subtypes[109-111]. More recently, this debate has been revived in a slightly different fashion. The essential controversy seems to be whether to use a dimensional or a categorical model of BD. Those who favor a dimensional model have argued that BP-II disorder has to be subsumed under the broader bipolar spectrum diagnosis[70,99,112-114], whereas others who favor a categorical approach maintain that there is sufficient evidence for an independent BP-II category[115-119]. The actual evidence in terms of validators provides almost equal support for both the dimensional and the categorical approaches. Moreover, the size of the evidence base is small and plagued by numerous methodological problems. Additionally, most of the differences seem to arise from the way that BP-II disorder (and hypomania) is defined and assessed across the different studies [32,42,111,120]. Nevertheless, the final verdict seems to be that it would be premature to abandon the BP-II subtype. Rather, it should be retained to encourage further research that may improve its definition and utility[118,119,121-123]. The controversies surrounding the BP-II diagnosis in the ICD-11 and the DSM-5 classifications are detailed in Table 5.

Cyclothymic disorder

The ICD-11 draft has made substantial changes to the diagnostic requirements for cyclothymic disorder compared to the ICD-10 version, bringing the definition closer to the one in the DSM-5. These changes are shown in Table 6.

Unlike the DSM-5, there is no requirement for mood symptoms to be present more than half the time in the ICD-11 version. Moreover, the diagnosis of hypomania can be made at any time after the onset of the disorder, and that of depressive disorder after the first two years. Thus, the definition is less rigid

Table 5 Controversies about type two bipolar disorder

Controversy	For retaining BP-II disorder	Against retaining BP-II disorder
The definition of hypomania	Current definitions of BP-II disorder in the ICD-11 and the DSM-5 represent an optimal balance between sensitivity and specificity; they will prevent the over-diagnosis and harmful effects of inappropriate treatment of a false positive diagnosis[30,38,42,43]	Current criteria are too restrictive and under-diagnose hypomania and BP-II disorder. The minimum duration required is not evidence-based and should be shorter[32,113,114,120,121]
Prevalence of BP-II disorder	The prevalence of BP-II disorder is as high as BP-I disorder, or even higher than the BP-I subtype[98,108-110]	Data on prevalence are mixed. Prevalence is also influenced by factors such as broader definitions, improved recognition, and increased awareness[111, 114]
Course of BP-II disorder	Compared to BP-I disorder, BP-II disorder has a more chronic course, greater syndromal and subsyndromal depressive symptoms, and higher episode frequency[98,107-109,112]	The seemingly adverse course of BP-II disorder could be a function of confounding factors such as symptom-severity, comorbidity, and the effects of treatment[32,70,99,114]
Diagnostic stability of BP-II disorder	The diagnosis of BP-II disorder remains the same for several years. Only 5%-15% of the patients with BP-II disorder develop BP-I disorder[6,98,105, 109]	The boundaries between BP-II and BP-I disorder, between BP-II disorder and cyclothymia, and between BP-II disorder and personality disorders are unclear [70,99,113,115]
The prevalence of psychotic symptoms	Patients with BP-I disorder are more likely than those with BP-II disorder to have psychotic symptoms[66,111,115]	Psychosis is also associated with hypomania, especially in longitudinal community studies[68,69, 113]
Suicidal behaviour	Suicide rates are higher in BP-II disorder than BP-I disorder[107-109,120, 121]	The higher suicide rates in BP-II disorder could be a function of comorbid personality disorders and comorbid substance use[98]
Family-genetics	BP-II disorder runs in families. Genetic studies help distinguish BP-II disorder from BP-I disorder[98,110,116,118,121]	Genetic studies show that BP-II and BP-I disorders lie on a continuum of genetic risk without any distinction between the two subtypes[106,112,114,120]
Neuroimaging	Some studies suggestquantitative or qualitative differences between the two subtypes[116,123]	There are no differences in neuroimaging between the two subtypes[98,111,112,114,120]
Neurocognition	Patients with BP-II disorder are less impaired on neuropsychological tests than those with BP-I disorder[98]	There is a great degree of overlap in the neurocognitive performance between the two subtypes[114,116]
Treatment response	The treatment requirements of patients with BP-II disorder are different [115,118,119]	There is no difference in treatment response between the two subtypes[98,108,111,114,120]

BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11: International Classification of Diseases, 11th version[8].

than the DSM-5 one.

However, the existing literature suggests that cyclothymic disorder is not only characterized by persistent subsyndromal mood changes, but also by mood lability, irritability, increased emotional sensitivity, and a lifelong pattern of impulsivity and interpersonal difficulties that make up the cyclothymic temperament[124-126]. Moreover, cyclothymic temperament seems to be the central part of the presentation of cyclothymia and has been linked to an increased risk of suicide. Accordingly, the selective emphasis on mood changes and the neglect of personality characteristics in the ICD-11 definition may be misplaced. Moreover, the complex diagnostic requirements may reduce the utility of the disorder[127]. The decision to allow hypomanic episodes creates further difficulties. Mixed states are very common in cyclothymia but they have been excluded from the ICD-11 because they denote a diagnosis of BP-I disorder. Therefore, more comprehensive and precise guidelines may be required to improve the reliability and clinical utility of cyclothymia in the ICD-11 CDDR.

Bipolar spectrum disorders

The ICD-11 has followed a somewhat contradictory approach to introducing a dimensional aspect to the BD category. Although it has tacitly accepted the existence of a bipolar spectrum by including BP-II disorder, mixed episodes, cyclothymia, and antidepressant-induced mania and hypomania as a part of BD, it has stopped short of including other categories from this spectrum. This is contrary to the evidence supporting a wider spectrum of BDs[128-132]. This evidence indicates that bipolar spectrum disorders are possibly more common than BP-I and BP-II disorders[133-136]. Additionally, up to half of those with major depression show signs of subthreshold bipolarity. Spectrum disorders are clinically significant forms of BD, often associated with a poor prognosis and enhanced risk of converting to BP-I or BP-II disorders. The failure to detect spectrum disorders often leads to inappropriate or delayed diagnosis and ineffective or harmful treatment. However, the ICD-11 draft chose not to include these disorders. This was because of the concerns about the uncertain boundaries of spectrum disorders and the risk of overdiagnosis and inappropriate treatment[132-135]. The relative lack of external validators,

Table 6 Changes to the diagnostic guidelines in the International Classification of Diseases, 11th version for cyclothymic disorder

	ICD-11-CDDR	DSM-5	ICD-10
Core features	Chronic mood instability of more than two years consisting of several hypomanic and depressive periods (irritability in children and adolescents)	Several hypomanic or depressive symptoms for more than two years	A persistent instability of mood, involving numerous periods of mild depression and mildelation (No duration mentioned)
	Hypomanic symptoms may meet the criteria for hypomanic episodes	Symptoms do not meet the criteria for hypomanic or major depressive episodes	None of these symptoms meet criteria for mania/BD or depressive episode/recurrent depressive disorder
Symptom-free periods	Symptom-free periods are no longer than two months during the course of the disorder	Hypomanic and depressive symptoms are present at least half of the time during the course of the disorder	Mood state may be normal and stable for months (No minimum duration for symptom-free periods specified)
		Symptom-free periods are no longer than two months during this period	
Children and adolescents	Duration of one year is appropriate	Duration of one year sufficient	No mention of duration in children and adolescents
Manic mixed, and depressive episodes	Criteria for manic and mixed episodes are never met. Depressive episodes cannot be diagnosed during the first two years of cyclothymia. After that, they can be diagnosed if criteria are met	Criteria for manic, hypomanic, or major depressive episodes are never met during the first 2 years. If the person subsequently experiences major depression, mania, or hypomania, the diagnosis is changed to major depressive disorder, BP-I disorder, or other specified or unspecified bipolar and related disorders	Criteria for manic, mixed, and depressive episodes are never met
	Criteria for BP-I or BP-II disorder are never met		Criteria for BD or recurrent depressive disorder are never met
Exclusions	Cyclothymia secondary to medical conditions or substance use	Cyclothymia secondary to medical conditions or substance use	No exclusions
Functional impairment	Symptoms result in significant distress and/or functional impairment	Symptoms result in significant distress and/or functional impairment	Symptoms are so mild that patients often do not seek treatment
Progression to BD	Mentioned	Mentioned	Mentioned
Inclusion of additional personality features	Not included-unlike personality disorders, cyclothymia does not include persistent self and interpersonal dysfunction	Included-the person may be temperamental, moody, unpredictable, inconsistent, or unreliable	Included-in some instances, mood changes are less prominent than cyclical disturbances of activity, self-confidence, and social behaviour

BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

the problems with diagnostic and prognostic validity, and the absence of controlled data on treatment also proved problematic. Incidentally, the DSM-5 has included some of these disorders in the "Other Specified Bipolar and Related Disorders" category. Moreover, a community study utilizing DSM-5 criteria for BD has shown that the spectrum disorders are as frequent and disabling as BP-I and BP-II disorders[55].

Specifiers

Much like the DSM-5, the ICD-11 CDDR uses several specifiers for mood disorders to create more homogeneous subgroups. These specifiers are also intended to increase diagnostic specificity, assist treatment selection, and help prognostication[29]. They include those related to the course, severity, and descriptive symptom patterns. However, unlike the DSM-5, all specifiers can be coded in the ICD-11 draft so that this information is preserved. The primary specifiers include psychotic symptoms, severity in the case of depressive disorders, and course specifiers such as partial or full remission. Additional specifiers for melancholia and chronicity apply to depressive episodes. The rapid cycling specifier is used to describe BP-I and BP-II disorders. Specifiers common to both depression and BD include the presence of prominent anxiety symptoms, panic attacks, seasonal patterns, and the puerperal onset of episodes. Although most of these specifiers have been included in successive DSM classifications and are evidence-based, there are some uncertainties about their definitions and clinical utility[29]. However, the anxiety symptoms specifier is new to both the ICD-11 and the DSM-5. It is based on the evidence for the frequent occurrence of anxiety symptoms and the influence of these symptoms on the

Table 7 Considerations guiding the notion of clinical utility in the International Classification of Diseases, 11th version

Concept	Application to the ICD-11 CDDR
Working definition	Clinical utility of the classification and its categories includes the ability to facilitate communication among clinicians, having characteristics that help clinical practice (diagnostically accurate, easy to use, and feasible), and containing guidance for appropriate treatment choices[141,142]
Why clinical utility?	Validity is not a pragmatic goal; enhanced diagnostic reliability has not led to increased validity[143,144]. Current classifications have several shortcomings and are not useful in real-world settings[11,37,142]
Levels of utility	Clinical utility has two levels including the architectural or organizational level and the category level[24,141], utility should focus on both the levels and emphasize coverage, description of attributes, and ease of use[145]
Application to healthcare settings	The need for utility is the greatest during clinical encounters in routine practice settings. The classification must provide information of value to the clinician in these situations[9-11,13,146]
Public health utility	Consideration must be given to the features of the classification that enhance global applicability and reduce global mental health burden[9,147]
Contextual aspects	Utility is context-specific; it depends on the purpose for which a classification is used, clinical, research, or for public health[9,10,146]
Utility and scientific validity	Clinical utility has to go hand-in hand with the scientific evidence. Moreover, compromising the scientific basis of the classification to meet the needs of clinical utility has to be avoided as far as possible. There is considerable overlap between clinical utility and predictive validity and sometimes it is difficult to distinguish between them[105,145,147]
Greater emphasis on clinical utility in the ICD-11	[1]Clinical utility as the ultimate organizing principle is not a new notion, but the ICD-11 has paid the greatest systematic attention to this aspect[10,147,148]
Improving clinical utility in the ICD-11	Clinical utility has been the guiding principle at all the stages, from the evidence review, to content formation, and to the field trials. The standardized template or content-form was structured to enhance clinical utility. Working Groups were asked to consider the clinical utility of the changes suggested. The protype-based approach contributed to enhanced clinical utility. Cross-cultural usefulness was addressed. The ICD-11 field-trial studies used methodology specifically designed to examine clinical utility in naturalistic settings. The results of these studies have been used to improve the revision further[9-13]

[1]Similarities between the ICD-11 and the DSM-5 in this regard are shown in Table 1.

ICD-11: International Classification of Diseases, 11th version, CDDR-Clinical Descriptions and Diagnostic Requirements ICD-11[8].

course and outcome of BD[137-140].

Clinical utility

The notion of clinical utility and its examination in the ICD-11 were influenced by different aspects of the concept. These included its working definition[141,142], the need for clinical utility[143-145], levels of utility[141,145], and clinical, research, and public health aspects of utility[146-148]. These are shown in Table 7.

Although clinical utility has been a consideration for the DSM-5 and the earlier versions of both classifications, systematic attention to its study was much greater during the preparation of the ICD-11 CDDR[147,148]. Notably, it was the guiding principle at all stages of the development of the ICD-11 draft, from its adoption as the primary principle, framing an operational definition, using it to guide the evidence review and the description of diagnostic categories, and conducting field trials to examine its relevance[9-11,13,141].

The ICD-11 field studies

The clinical utility of the ICD-11 CDDR categories was examined in a series of studies with a varied methodology in naturalistic settings. These studies were coordinated and conducted by the Field Studies Coordination Group and the GCPN[10,11,149,150]. They included internet-based surveys and clinic-based studies conducted at the field trial centres (FTCs). The formative field trials were conducted early during the guideline development and were meant to provide data to help improve the ICD-11 draft. These included surveys of mental health professionals to elicit their opinions and utilization patterns. Studies on the clinicians' organizational map were meant to inform the structure of the ICD-11 CDDR. Evaluative field studies were designed to assess the utility and reliability of the classification and the individual categories. They included internet-based studies using clinical vignettes and clinic-based FTC studies. The results of these studies regarding BD or mood disorders are shown in Table 8.

At the first glance, the results are encouraging. The clinical utility and utilization of the ICD-11 BD and mood disorders were very high[22,151-154]. The overall structure of the ICD-11 version and the structure of the mood disorders section was endorsed by the clinicians[23,24]. The diagnostic accuracy of BP-II disorders in the ICD-11 CDDR was better than that in the ICD-10 guidelines[155,156]. The clinical utility and inter-rater reliability of BP-I disorder, BD, and mood disorders all proved to be high [142,157-160]. While the clinical utility of these ICD-11 categories was similar to that of the ICD-10[161, 162] and the DSM-5 diagnoses[163], their inter-rater reliability was better than that of the corresponding

Table 8 The International Classification of Diseases, 11th version field trials on reliability and clinical utility of bipolar disorder[1]

Ref.	Manuscript type	Results
Formative field trials		
Surveys of mental health professionals: Opinions and utilization patterns		
Reed *et al*[22], 2011	Internet-based survey	The ICD-10 category of BD had considerable clinical utility and was commonly used. The category of single depressive disorder was commonly used and should be retained. Functional impairment should be a diagnostic criterion for mood disorders
Evans *et al* [151], 2013	Internet-based survey of psychologists	The ICD-10 category of BD was not as commonly used. BD was rated to have low clinical utility, especially regarding its ease of use
Avasthi *et al* [152], 2014	Internet-based survey	The ICD-10 category of BD was commonly used and was easy to diagnose (high ease of use)
Robles *et al* [153], 2014	Internet-based survey	The ICD-10 category of BD was considered a problematic diagnosis by about 4% of the participants because of its non-specificity. Only about 1% of the participants felt that BP-II disorder should be included in the current version
Maruta *et al* [154], 2013	Internet-based survey	A majority (69%) of the participants felt that BD should be included in a separate category of mood disorders
Studies on the clinicians' organizational map for classifications		
Roberts *et al* [23], 2012	Internet-based survey	Clinicians' concepts were in keeping with the current evidence and similar across all groups and countries. BP-I, BP-II, and cyclothymic disorders were considered to be adult rather than developmental onset disorders. Clinicians' views about the organizational structure corresponded more to the ICD-11 classification than the ICD-10 or the DSM-5
Reed *et al*[24], 2013	Clinic-based FTC study	Clinicians' concepts were in keeping with the current evidence and similar across all groups and countries. Mood disorders including BP-I, BP-II, cyclothymic, depressive, and dysthymic disorders were grouped together by clinicians. This group was also among the most cohesively organized groups. The results supported the ICD-11 organization of the mood disorders group
Evaluative field trials		
Studies of clinical vignettes		
Gaebel *et al* [155], 2020	Internet-based based field study	Diagnostic accuracy of the ICD-11 BP-II disorder category was significantly higher than a modified ICD-10 BP-II category. However, regarding disorders already existing in the ICD-10, *e.g.*, BD, there were no differences between the ICD-11 and the ICD-10. There were no significant differences in overall clinical utility of BD between the ICD-11 and the ICD-10
Kogan *et al* [156], 2021	Internet-based based field study	Greater diagnostic accuracy was found for the ICD-10 categories of BP-I disorder and a modified category of BP-II disorder on initial analysis. However, there were no significant differences on re-analysis. There were no significant differences between the ICD-11 and the ICD-10 categories of cyclothymic disorder. Clinical utility was somewhat lower for the ICD-11 category of BP-I disorder. Ratings of severity of depression were better with the ICD-10
Clinic-based FTC studies		
Reed *et al* [142], 2018	ICD-11 diagnoses-reliability and utility	The clinical utility of BP-I disorder was higher than schizophrenia, schizoaffective disorder, and depressive disorders on all three parameters including diagnostic accuracy, ease of use, and clarity. Agreement between the raters was also the highest for BP-I disorder (k = 0.85)[2,3]
Reed *et al* [157], 2018	ICD-11 diagnoses-reliability	Agreement between the raters was one of the highest for BP-I disorder (k = 0.84). It was relatively low though adequate for BP-II disorder (k = 0.62)[3,4]
Hackmann *et al*[158], 2019	Qualitative study on patient perceptions of BP-I disorder	The patients commented on several additional features that were missing from the description of BP-I disorder in the ICD-11 CDR. They preferred native language and idioms. A lay language version of the diagnostic descriptions was preferred
Medina-Mora *et al*[159], 2019	ICD-11 diagnoses-reliability and utility	Inter-rater reliability of the mood disorders category was high (percentage agreement-87%). This was higher than schizophrenia and most of the other disorders. Clinical utility was also high
Onofa *et al* [160], 2019	ICD-11 diagnoses-reliability and utility	Inter-rater reliability of BP-I disorder (k = 0.83) was high. Ratings of diagnostic accuracy and ease of use were also high, but the descriptions were felt to be less useful in selecting treatment

[1]Only those trials that have included results about the categories of bipolar or mood disorders are shown.

[2]The results were very similar to those of two ICD-10 FTC studies of clinical utility[161,162]. They were also similar to those of a clinical utility study of the DSM-5[163].

[3]The inter-rater reliability for a single depressive episode ranged from k values of 0.43 to 0.64. This was lower than the corresponding ICD-10 category (k = 0.66-0.73). Inter-rater reliability of recurrent depressive disorder was higher (k = 0.74) and similar to that of the ICD-10 category (k = 0.69-0.70)[161,162].

[4]The results were comparable to the BD category in the ICD-10 FTC studies (k = 0.81-0.82)[161,162]. Inter-rater reliability was also higher than that found in the DSM-5 FTC studies where reliability for BP-I disorder was 0.56 and for BP-II disorder was 0.40[164,165].

BD: Bipolar disorder; BP I: Type I bipolar disorder; BP II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; FTC: field trial centre; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11: International Classification of Diseases, 11th

version, CDDR-Clinical Descriptions and Diagnostic Requirements[8]; *k*: Kappa value.

DSM-5 categories[164,165]. However, there were a few limitations. There was a divergence of opinion between psychiatrists and other mental health professionals in certain studies[151,153]. Although the ICD-11 categories were not inferior to the ICD-10 ones in terms of utility and reliability, there were no substantial differences between the two versions[155,156,161,162]. The reliability of BP-II disorder though adequate was relatively low[157]. Certain aspects of the clinical utility, *e.g.*, making treatment decisions based on the diagnoses, were difficult[160]. Patients' perceptions were not invariably favourable[158]. Finally, methodological limitations such as a selection bias towards those positively predisposed to the ICD-11 and inadequate generalization of the results to routine clinical practice could confound these findings[149]. Therefore, there is much scope for improving the utility and reliability of the ICD-11 guidelines as well as conducting further research on the subject.

CONCLUSION

The ICD-11 guidelines on BD have been more or less finalized following a protracted and complicated process. Many changes have been suggested. Many limitations are also evident, mostly arising from the conflicting nature of the existing evidence. Imperfections are also due to the consensus-based system of creating classifications[166] and the limitations of the current state of knowledge about the aetiology of psychiatric disorders[167-171]. The conservative approach followed may lead to some frustration. However, it has to be accepted that any change can only be incremental and that the scope for paradigmatic shifts is limited at present[30,172]. It is also time to move beyond the endless debates about the necessity of revisions[145,173,174] and focus on the challenges of implementation, dissemination, and education and training of the potential users of these guidelines. A provision for continuous upgrading similar to the DSM-5[175] and a greater focus on treatment-utility are also needed[148]. Although the initial results of clinical utility and reliability of BD seem promising, it will take several years and many studies to evaluate the real impact of the ICD-11 guidelines on the current psychiatric practice. It would be imperative that all stakeholders including the policymakers, professionals, and the people impacted by mental illnesses are engaged in this process[9]. Ultimately, only they will determine if the revision was worth the effort.

FOOTNOTES

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MINIREVIEWS

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Jin-Huan Deng, Han-Wen Zhang, Xiao-Lei Liu, Hua-Zhen Deng, Fan Lin

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

Key Words: Parkinson's disease; Dopaminergic neurons; Magnetic resonance imaging; Substantia nigra; Morphological

Core Tip: Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is primarily caused by the loss of dopaminergic neurons in the substantia nigra. The classical clinical symptoms of PD include movement symptoms such as bradykinesia, resting tremor, rigidity, and postural instability. Recent studies have shown that symptoms of PD extend beyond motricity and include cognitive and neuropsychiatric symptoms. Non-motor symptoms can be identified at all stages, even before the appearance of motor symptoms[1]. In addition to clinical markers, PD biomarkers include neuroimaging, genetic, and biochemical markers[2]. This review focuses primarily on the use of neuroimaging in PD.

The main pathological features of PD are the degeneration of dopaminergic neurons in the substantia nigra and deposition of Lewy bodies, leading to pathophysiological changes in the downstream basal ganglia circuits. The basal ganglia system includes the striatum, globus pallidus, and structures with functional connections to the striatum, including the subthalamic nucleus, substantia nigra, and red nucleus.

Magnetic resonance imaging (MRI) is one of the most useful noninvasive techniques for examining intracranial structures, showing macroscopic alterations of the subcortical structures, and can visualize their volume and surface morphology. Therefore, MRI-based morphological analysis of the subcortical structures has the potential to be a prominent diagnostic neuroimaging marker for PD. This review focuses on the shape analysis of the striatum, thalamus, and hippocampus, which has been mostly discussed in previous studies.

METHODS

A literature search was conducted for relevant studies using four databases: PubMed, Web of Science, Google Scholar, and Scopus. The key search terms in the different combinations were "Parkinson's disease, shape analysis, subcortical structures, striatum, thalamus, and hippocampus." The final search was conducted on October 25, 2022.

The inclusion criteria were the studies that included: (1) A background or introduction on PD; (2) the clinical criteria of PD; (3) an introduction to methods of the subcortical structure segmentation; (4) shape analysis of the subcortical or cortical structures; and (5) data utilization of structural MRI sequences.

We excluded studies based on the following exclusion criteria: (1) Articles published in languages other than English; (2) animal model or theoretical articles; (3) studies with a sample size of < 10 patients; (4) studies whose methodology did not involve volumetric or shape analysis; and (5) review or meta-analysis articles of shape analysis.

RESULTS

Figure 1 shows a flowchart of the study selection. This review included 69 references, of which 2 provided a background/introduction on PD, 5 referred to the segmentation methods, and 62 to the morphology of the subcortical or cortical structures in PD. Subcortical structures mainly included the striatum, thalamus, and hippocampus. Further information on the structures and morphological changes is provided in Table 1.

Table 1 Morphological studies in Parkinson's disease

Subcortical structures	Ref.	Segmentation methods	Analysis type	Results
Striatum				
	Geng *et al*[12], 2006; Pitcher *et al*[10], 2012; Owens-Walton *et al*[11], 2018	Manual	Volume	Reduced volume of bilateral caudate and putamen nuclei
	Sterling *et al*[13], 2013	Semi-automatic	Volume	Reduced volume of bilateral caudate and putamen nuclei
	Geevarghese *et al*[15], 2015; Vasconcellos *et al*[17], 2018; Tanner *et al*[16], 2017; Melzer *et al*[30], 2012	Automatic	Volume	Reduced volume of bilateral caudate nuclei
	Oltra *et al*[35], 2022	Automatic	Volume	Reduced volume of bilateral caudate nuclei (with RBD)
	Lee *et al*[14], 2014; Garg *et al*[20], 2015	Automatic	Volume	Reduced volume of bilateral putamen nuclei
	Garg *et al*[20], 2015	Automatic	Volume	Reduced volume of right putamen nuclei
	Kamps *et al*[33], 2019	Automatic	Volume	Reduced volume of right putamen nuclei (with RBD severity)
	Kluger *et al*[34], 2019	Automatic	Volume	Reduced volume of dorsal striatum (with fatigue)
	Messina *et al*[18], 2011; Menke *et al*[19], 2014; Nemmi *et al*[21], 2015; Khan *et al*[22], 2019; Gong *et al*[32], 2019	Automatic	Volume	No significant difference in bilateral striatum
	Chung *et al*[31], 2017	Automatic	Volume	Locally reduction of right caudate nuclei
	Devignes *et al*[28], 2021	Automatic	Shape	Locally reduction of left caudate nuclei (with cognition)
	Garg *et al*[20], 2015	Automatic	Shape	Locally reduction of right putamen nuclei
	Gong *et al*[32], 2019	Automatic	Shape	Locally reduction of bilateral caudate and right putamen nuclei (with RBD)
	Tanner *et al*[16], 2017	Automatic	Shape	Locally reduction of the lateral and medial caudate nuclei
	Sterling *et al*[13], 2013	Semi-Automatic	Shape	Locally reduction of the head and dorsal body of caudate nuclei
	Nemmi *et al*[21], 2015	Automatic	Shape	Locally reduction of the medial surface of left caudate nuclei (with the right UPDRS)
	Tanner *et al*[16], 2017	Automatic	Shape	Locally reduction of the medial surface of putamen nuclei
	Sterling *et al*[13], 2013	Semi- Automatic	Shape	Locally reduction of the caudal and ventro-lateral putamen nuclei
	Sigirli *et al*[23], 2021	Automatic	Shape	Locally reduction of the middle-posterior of right putamen nuclei
	Lee *et al*[14], 2014	Automatic	Shape	Locally reduction of the posterolateral and ventromedial putamen nuclei
	Nemmi *et al*[21], 2015	Automatic	Shape	Locally reduction of the lateral and medial posterior putamen nuclei (with UPDRS)
	Khan *et al*[22], 2019	Automatic	Shape	Locally reduction of the caudal-motor and rostral-motor sub-regions
Thalamus				
	McKeown *et al*[43], 2008	Manual	Volume	No significant difference
	Garg *et al*[20], 2015	Automatic	Volume	Significant difference
	Vasconcellos *et al*[17], 2018; Mak *et al*[26], 2014; Sivaranjini *et al*[27], 2021; Foo *et al*[45], 2017	Automatic	Volume	Reduced volume of bilateral thalamus
	Niccolini *et al*[46], 2019	Automatic	Volume	Reduced volume of bilateral thalamus (with non-motor symptom)

	Kamps *et al*[33], 2019	Automatic	Volume	Reduced volume of left thalamus (with RBD)
	Chen *et al*[44], 2020	Automatic	Volume	Increased volume (20) of right subnuclei
	Chen *et al*[44], 2020	Automatic	Volume	Increased volume (21), reduced volume (2) of left subnuclei
	Kaya *et al*[40], 2019	Manual	Shape	Locally reduction of the dorsolateral of bilateral STN
	Devignes *et al*[28], 2021	Automatic	Shape	Locally reduction of right thalamus (with cognition)
	Chung *et al*[31], 2017	Automatic	Shape	Locally reduction of bilateral thalamus (with cognition)
	McKeown *et al*[43], 2008	Automatic	Shape	Locally reduction of the dorsal surface of bilateral thalamus
	Garg *et al*[20], 2015	Automatic	Shape	Net-inward and outward deformation of left thalamus
Hippocampus				
	Wang *et al*[55] , 2018	Automatic	Volume	Reduced volume of right hippocampus
	Chen *et al*[56], 2016	Automatic	Density	Reduced density of left hippocampus
	Geevarghese *et al*[15], 2015	Automatic	Volume	Reduced volume of left hippocampus (with cognition)
	Lee *et al*[14], 2014; Tanner *et al*[16], 2017; Radziunas *et al*[53], 2018; Melzer *et al*[30], 2012	Automatic	Volume	Reduced volume of bilateral hippocampus
	Vasconcellos *et al*[17], 2018	Automatic	Volume	Reduced volume of bilateral hippocampus (with disease duration)
	Camlidag *et al*[68], 2014; Xu *et al*[59], 2020	Automatic	Volume	Reduced volume of bilateral hippocampus (with cognition)
	van Mierlo *et al*[64], 2015	Automatic	Volume	Reduced volume of bilateral hippocampus (with depression)
	Rahayel[63], 2019	Automatic	Volume	Reduced volume of bilateral hippocampus (with REM-RBD)
	Wilson *et al*[54], 2019	Automatic	Volume	Reduced volume of bilateral hippocampus (with cognition, motor and disease duration)
	Luo *et al*[60], 2021	Automatic	Volume	Reduced volume of subfields (with cognition)
	Uribe *et al*[61], 2018	Automatic	Volume	Reduced volume of subfields, especially CA1
	Becker *et al*[62], 2021	Automatic	Volume	Reduced volume of CA1 (with cognition)
	Xu *et al*[59], 2020	Automatic	Volume	Reduced volume of subiculum, CA2/3, CA4, ML and right GC-DG
	Park *et al*[57], 2019	Automatic	Volume	Volume asymmetry, especially in CA4-DG and CA2-3
	Tanner *et al*[16], 2017	Automatic	Shape	Locally reduction in the head and CA1 bilaterally
	Devignes *et al*[28], 2021	Automatic	Shape	Locally reduction of right hippocampus (with cognition)

REM: Rapid eye movement; RBD: Sleep behavior disorder; STN: Subthalamic nucleus; CA: Cornu ammonis (subfields of hippocampus); ML: Molecular layer subfields; GC-DG: Granule cell layer of the dentate gyrus.

Parkinson's disease

The Movement Disorders Society (MDS) has proposed the main diagnostic criteria for PD in clinical settings[3]. The recent version of the MDS diagnostic criteria considers three stages in the progression of PD: Preclinical, prodromal, and clinical. Clinical PD can be diagnosed when typical motor symptoms occur. Neurodegeneration may occur in patients with PD before they reach the clinical stage[3]. Previous studies have been mostly conducted based on clinical diagnosis; therefore, this review focuses

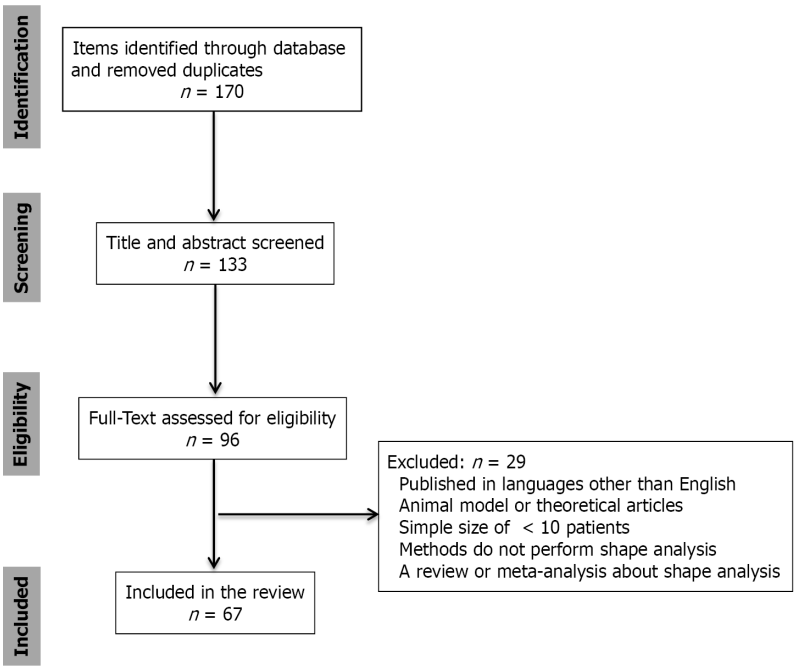

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Figure 1 A flowchart of the study selection.

on PD in the clinical stage. The striatum is one of the most affected structures in the nigrostriatal pathway because of the degeneration of dopaminergic neurons. In addition to the striatum, neurons in the substantia nigra project to other basal nuclei, such as the pallidum, substantia nigra, and thalamic nucleus basalis. A decrease in dopamine levels may cause the structural and morphological changes observed in PD.

MRI allows noninvasive observation of morphological changes in the subcortical structures in patients with PD to find changes in neuroimaging characteristics. Hence, it may help in clinical intervention, especially in the preclinical or prodromal stages of the disease. However, the naked eye cannot identify subtle changes in structures; hence, quantitative analysis using a computer may help determine the presence or absence of morphological changes in these structures. Segmentation of subcortical structures based on the images is the prerequisite to performing an accurate analysis. The following sections describe the common segmentation methods and the results of morphological analyses of the subcortical structures obtained from previous studies.

Methods of segmentation

Both manual and automatic segmentation have been used in recent studies. Manual segmentation, usually the gold-standard approach for automatic segmentation, is a tedious and time-consuming task that depends on the subjectivity of the physician. Therefore, many investigators have used publicly available automated segmentation software for efficiency and objectivity. Automatic segmentation methods include voxel-based morphometry (VBM) and surface-based morphometry (SBM). The tools used for segmentation in most studies include FSL and FreeSurfer, among others. The FIRST software, distributed with the FSL package, is a tool that employs manually labeled image data to offer anatomical training information for 15 different subcortical regions using 336 manually labeled T1-weighted MRI images[4]. FreeSurfer is a suite of tools for extensive automated analysis of key features in the human brain that can be used in most MRI sequences and provides an accurate geometric surface model[5]. By minimizing the difference between the original image and the converted target image, large deformation diffeomorphic metric mapping (LDDMM) creates a differential homogenous transformation that has its own inherent smoothness and simulated displacement size. It is often applied in the object-matching segment of medical imaging data processing[6]. This review focuses on the morphological analysis of subcortical structures in PD using the techniques mentioned above in recent years.

Several scholars have compared the effects of manual and automatic segmentation. For the hippocampus and amygdala, segmentation using VBM and FreeSurfer is performed at a level comparable to manual segmentation[7]. In another study, automated segmentation revealed different degrees of variability in the subcortical structures compared to manual segmentation, with particularly pronounced differences found in the FreeSurfer and FSL pipelines for the pallidum and thalamus[8]. From these studies, it can be seen that the efficiency of automatic segmentation is comparable to that of manual segmentation. Automatic methods save more time and display better segmentation results,

which could be used in the shape analysis of the subcortical structures in patients with PD.

Shape analysis of the striatum

The striatum is a critical component of the brain that controls the motor, reward, and executive functions, and dopamine serves as an important mediator[9]. Decreased dopamine levels have the greatest impact on striatal structures in patients with PD. Several studies have segmented the striatum by manual segmentation of T1-weighted MRI images for its morphology, showing that the volume of the caudate nucleus or putamen was smaller in patients than in normal controls[10,11]. In addition, studies using automatic segmentation showed the same results as those using manual segmentation of the volume of the caudate nucleus and putamen[12-17]. However, some studies have found no significant difference in striatum volume between patients with PD and normal controls[18-21]. Studies that performed further surface morphometric analyses under automated shape analyses showed: (1) A regional contraction of the posterolateral and ventromedial putamen bilaterally in patients with PD[14]; (2) areas of local atrophy in the lateral and medial posterior parts of the bilateral putamen; (3) atrophy locally on the medial surface of the left caudate nucleus[21]; and (4) a reduction in the volume and an inward displacement of the surface of the caudal motor striatum[22]. Studies using other machine learning methods have also found local atrophy in the caudate and putamen nuclei, including the caudal portion of the putamen or the middle-posterior putamen and the head of the caudate[13,23]. A study attempted to distinguish different stages of PD based solely on the shape analysis of the bilateral caudate nucleus and putamen through an automated process, with balanced accuracies in the range of 59%-85%[24].

Dysfunction of the basal ganglia plays a key role in developing motor and non-motor symptoms in PD[25]. When exploring the relationship between volume and symptoms, several studies have shown that greater atrophy of the caudate and putamen in PD is usually associated with more severe motor symptoms and cognitive impairment[11,17,26-28]. Additionally, some correlation analyses did not find a significant correlation between striatal volume and cognitive or motor symptoms[10].

Local morphological analyses provided more details; local atrophy in the left putamen and thalamus correlated with the right Unified Parkinson Disease Rating Scale (UPDRS) motor scale score, which is the most widely used scale for the clinical studies of PD[21,29]. A previous study identified PD with mild cognitive impairment (PD-MCI) with limited atrophy of the right putamen[30]. When PD-MCI converted to dementia, smaller local shape volumes were found in the right caudate nucleus of the patients compared to that of patients with PD-MCI who did not convert[31]. In addition, logistic regression analysis indicated that the local shape volumes in the right caudate nucleus were significant independent predictors of conversion to dementia in patients with PD-MCI. Distinct structural changes in the caudate and/or putamen are associated with performance in the attention or working memory domain, fatigue, the severity of rapid eye movement (REM) sleep behavior disorder (RBD), and excessive daytime sleepiness[26,32-35].

Specifically, volume atrophy of the left caudate nucleus or right putamen was found to be more pronounced in the patient cohort[11,23], which may be due to disease lateralization. Previous studies have shown that the decrease in dopamine capacity in the striatum is more pronounced in the contralateral hemisphere on the side with more severe clinical symptoms of PD[36]. It has been suggested that the onset of motor symptoms may always occur in one limb, and morphological analysis has revealed a greater degree of striatal atrophy on the contralateral side of the limb where motor symptoms occur[16]. Local deformation of the posterior side of the putamen has been reported in several articles. According to the literature, the posterior putamen is directly related to the sensorimotor cortex and is preferentially affected; dopamine depletion is mainly located in this region of the basal ganglia[10,23,37,38]. Therefore, we can also infer that the morphological changes in PD can be detected using MRI. Furthermore, we may be able to assess the severity of some symptoms, such as cognitive function in patients with PD, and provide timely interventions for clinical treatment.

Shape analysis of the thalamus

The thalamus is composed of several nuclei that regulate various motor and sensory functions and is usually divided into seven nuclei: The anterior, lateral, ventral, intralaminar, medial, and posterior nuclear groups and the reticular nucleus. Among the nuclei of the thalamus, the ventral thalamus, also known as the subthalamic nucleus (STN), plays an important role in extrinsic inputs reaching the basal ganglia circuitry[39]. A study calculated the morphological changes in the STN and found statistically significant differences in the shape of bilateral STN between the PD and control groups, with the largest deformation site located in the dorsolateral parts of bilateral STNs[40]. Patriat *et al*[41] showed that the volume of STN was smaller in PD patients compared to healthy controls, which was further validated in the field of 7T MRI. Although thalamic degeneration may represent a site of dopaminergic degeneration in PD, the thalamus is also influenced by hyperactivity in glutamatergic signaling, which may be caused by the loss of dopaminergic neurons in the substantia nigra and striatum[42]. Thus, various morphological changes occur in the thalamus of patients with PD. Furthermore, several studies on structural and functional imaging have identified morphological or functional changes in the thalamus in patients with PD. Using manual segmentation, scholars found no significant difference in the thalamus volume between patients with PD and healthy controls[43]. They used spherical harmonic-based representation

methods and detected significant differences in shape[43]. A previous study subdivided the left and right thalamus into 25 subnuclei using automatic methods. It was detected that 21 of the left and 20 of the right thalamic subnuclei had increased volume, accompanied by atrophy in two left subnuclei[44].

More studies have been conducted to correlate thalamic shape changes with clinical symptoms. Nemmi *et al*[21] found a significant correlation between local atrophy of the right thalamus and the UPDRS using FSL scripts. However, one study found that surface morphological changes in the thalamus were not associated with disease severity in UPDRS using FreeSurfer segmentation with LDDMM alignment[20]. This may be due to differences in segmentation methods and cohort sizes, and the influence of glutamatergic neurons on thalamic morphology requires further investigation.

Moreover, most studies have concluded that altered thalamic morphology is associated with non-motor symptoms. Several studies have found a relationship between reduced thalamic volume and poor cognitive function in patients with PD[17,26-28,45]. A more detailed correlation analysis showed that the local shape volume of the bilateral thalamus was a significant independent predictor of the conversion of MCI to dementia. However, the local shape volume of the thalamus was associated with semantic fluency and attentional composite scores[31]. In addition, some scholars have found that the severity of other non-motor symptoms in patients with PD is associated with more pronounced thalamic atrophy. Furthermore, they found that such non-motor symptoms include sleep, fatigue, gastrointestinal dysfunction, and REM-RBD[32,46].

The thalamus, one of the output nuclei of the basal ganglia, is markedly affected by dopaminergic and glutamatergic neuronal degeneration. For living subjects, imaging is potentially one of the most practical tools to detect changes in the thalamus. Precise shape analysis shows that the thalamus in PD undergoes major or minor changes. Compared to manual measurements, accurate automated measurements reflect more pronounced variation and more detailed results. Because of the varying progression of neuronal degeneration, thalamus shape analysis in patients with PD presents differently. Hence, future studies using the same methods and similar cohort sizes may show better consistency. Moreover, several studies have demonstrated the relevance of shape alterations and symptoms, especially non-motor symptoms, probably because the thalamic subnuclei play an important role in the transmission of dopaminergic neuronal pathways. However, the sequence in which the onset of symptoms and the changes within the thalamus occur is still unclear. In addition, abnormal STN activity may be associated with motor dysfunction in PD; however, further studies are needed to confirm the relationship between STN shape changes and motor symptoms.

Shape analysis of the hippocampus

As a subcortical structure, the hippocampus is an important brain region that carries the body's cognitive functions and is closely related to learning ability, memory, and emotion regulation. Cognitive impairment is frequently seen in PD; thus, the hippocampus may be an imaging marker of cognitive impairment[47]. Scholars have found a reduction in hippocampal gray matter density or thickness through automatic methods in the elderly or patients with cognitive impairment, especially in the CA1, which is one of the four hippocampal subfields called the cornu ammonis[48-52]. Several studies on hippocampal morphology have been conducted in patients with PD and normal controls. Using automatic shape analysis, some studies have shown smaller hippocampal volumes in patients with PD than in controls[16,17,30,53-55]. There were also reduced local volumes of the hippocampus in patients with cognitive impairment compared with those without cognitive impairment, including the subfields CA1-4[28,30,31,54-62]. Studies have shown that the development of REM-RBD and depression may be associated with a smaller hippocampal volume[33,63,64]. This suggests a close relationship between hippocampal atrophy and cognitive function, in which the CA1 may be one of the most notable subfields.

The hippocampus is the main source of cholinergic input to the cerebral cortex, and most studies have shown that the hippocampal volume shrinks in patients with PD. Hippocampal shape analysis has focused on non-motor symptoms in PD, primarily the cognitive function, which matches the function of the hippocampus. The relationship between hippocampal atrophy and cognitive decline has been confirmed in patients with PD in the majority of studies. However, recent studies mostly showed volume results; thus, the surface morphological analysis may be able to link hippocampal subregions to specific symptoms of cognitive impairment further. The relationship between morphological changes and other symptoms, such as REM-RBD and depression, warrants further investigation.

Furthermore, a large number of studies are also using these automated pipelines to analyze cortical structures in PD. Cerebral cortices are key to human activity and may be altered as a result of unusual activity in PD, such as thinning. Most studies have found atrophy in various parts of the cortex in patients with cognitive impairment. In a longitudinal study, Garcia-Diaz *et al*[65] confirmed the thinning of cortical thickness in PD patients with cognitive impairment *vs* those without. Among some symptoms related to the cerebral cortex, Vignando *et al*[66] reported a general reduction in occipital, parietal, temporal, frontal, and limbic cortical thickness in patients experiencing hallucinations. Changes in visuospatial and visual supraperceptual impairment also correlated with cortical thinning in occipital, parietal, and temporal regions in the study by Garcia-Diaz *et al*[65]. As for motor symptoms, through the calculation of surface area in a study of PD gait disorders, Wei *et al*[67] found that the larger the surface areas of the left lateral temporal cortex and right inferior parietal cortex, the worse the gait

performance.

This review focuses on the results of patients on 3T instruments, and participants were scanned using a 1.5T MRI instrument and used manual planar measurements, revealing that the normalized STN and red nuclei volumes were larger in patients with PD than in controls[68]. Similarly, 7TMRI imaging revealed atrophy of the overall prefrontal cortex and hippocampus, as well as a reduction in STN volume, for patients with PD[41,69]. Although current studies on 7TMRI have focused only on volumetric rather than morphological changes, higher resolution instruments can help us to detect finer structural changes and conduct more structural studies.

CONCLUSION

Methods for the shape analysis of subcortical structures based on MRI data are becoming increasingly diverse and refined, allowing even minor changes to be detected. This study has reviewed previous research on the application of these techniques in PD. In contrast to manual measurements, most studies employ computational methods to maintain objectivity. Volume atrophy can be found in most structures, including the subcortical and cortical areas. Surface-based morphometry detects structural changes that can be associated with clinical symptoms. We found that pathophysiological changes in PD are closely associated with changes in the subcortical structures and that different sub-structural alterations are consistent with specific clinical phenotypes. Therefore, the shape analysis of the subcortical structures can be used as an imaging biological indicator of PD, helping to explain associated clinical symptoms.

FOOTNOTES

Author contributions: Authors' contributions: Lin F contributed to the conception of the study; Zhang HW, Liu XL, and Deng HZ contributed significantly to analysis and manuscript preparation; Deng JH and Zhang HW performed the data analyses and wrote the manuscript; Zhang HW and Deng JH contributed equally to this study.

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