Children and adolescents with disturbed moods, affective instability, behavioral disturbances, attention problems, aggression, and agitation are frequently diagnosed as having pediatric bipolar disorder (PBD), often referred to as early-onset bipolar disorder (BD). Current research centers around a debate on the covariance and respective co-occurrence of early-onset BD with attention-deficit/hyperactivity disorder (ADHD), and the question as to whether these two disorders share common underlying neurobiological processes which produce the same phenomenology and characteristic clinical symptom patterns as outlined above. This debate is highly controversial, because PBD symptoms have frequently been shown to overlap with symptom characteristics related to ADHD (Figures 1 and 2), thus making the task of differentiating the diagnosis of both these disorders extremely difficult. This diagnostic challenge is further complicated by the fact that not only have PBD and ADHD been frequently found to be comorbid, but that they co-occur with other disruptive behavior disorders (DBD) such as oppositional defiant disorder (ODD) or conduct disorder (CD) characterized by aggression and uninhibited behavior, a symptom complex also associated with bipolarity—particularly adult bipolarity.

From a developmental viewpoint, the relationship between primary clinical manifestation and later symptom development could be seen as decisive for a better understanding of early-onset BD and ADHD and their diagnostic differentials and possible psychopathophysiological entity. Child and adolescent psychiatrists in charge of treatment are doubtless faced with formidable challenges to their diagnostic and clinical abilities. As preliminary evidence shows that these two disorders could possibly be inter-related on the grounds of common organic developmental factors and corresponding clinical
characteristics, it can be argued that both conditions may represent two differing facets of an underlying common psychopathophysiological entity. This hypothesis will now be examined, taking into consideration epidemiological, clinical, imaging, neurochemical, and genetic data.

**Epidemiology**

Recent research has suggested that the diagnosis of PBD is scarce outside the USA (clinical samples range from 0% to 7.2% prevalence), whereas in the USA prevalence rates range from 5.9 to 19.6%.\(^3\)\(^,\)\(^4\) Potential explanations for these discrepancies and for the higher prevalence rate of PBD in the USA should take into consideration that the preference for diagnosing clinical manifestations as PBD may have impeded attempts to compare data from European countries with data from the USA. Clinical manifestations which may have been classified as PBD by US researchers or clinicians might have received a different diagnostic characterization in European samples (such as severe ADHD, personality disorders, depressive disorders, or conduct disorders).\(^1\)\(^,\)\(^5\)\(^,\)\(^6\) Moreover, it may be relevant that research in the USA has received considerable funding, thus enabling a large number of studies, whereas in Europe funding for research on PBD is relatively limited. The differing diagnostic classification systems International Classification of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV may also have made studies on PBD prevalence rates in clinical populations around the globe more difficult.\(^1\)

Some researchers also see higher prescription rates for stimulants and antidepressants as a potential reason for higher diagnostic rates for PBD (particularly for drug-induced mania) in the USA. The differences between prevalence rates of PBD in the USA and those in European countries could support the hypothesis that drug-induced mania in children could be due to treatment with antidepressants and stimulants for depressive or ADHD-related symptoms, respectively.\(^7\) In a retro-

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**Selected abbreviations and acronyms**

- ADHD: attention deficit-hyperactivity disorder
- BD: bipolar disorder
- CBCL: Child Behavior Checklist
- PBD: pediatric bipolar disorder
- PFC: prefrontal cortex
- RTD: rapid tryptophan depletion

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**Figure 1.** DSM-IV symptoms of attention deficit-hyperactivity disorder also observable in bipolar mania.

Adapted from ref 23: Wingo AP, Ghaemi SN. A systematic review of rates in diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. J Clin Psychiatry. 2007;68:1776-1784.

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**Figure 2.** DSM-IV symptoms of bipolar mania also observable in attention deficit-hyperactivity disorder.

Adapted from ref 23: Wingo AP, Ghaemi SN. A systematic review of rates in diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. J Clin Psychiatry. 2007;68:1776-1784.

Copyright © Physicians Postgraduate Press 2007; ref 68: Kent L, Craddock N. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord. 2003;73:211-221. Copyright © Elsevier 2003
spective analysis, rates of treatment-emergent mania were approximately twice as high when children who met the modified DSM-IV diagnostic criteria for PBD received antidepressants (44%) compared with those who received stimulants (18%). When stimulants and their potential effects on treatment-emergent manic symptoms were analyzed, adolescents with a history of treatment exposure prior to the onset of PBD had an earlier age of onset than children without prior stimulant exposure. Furthermore, DelBello and coworkers, who carried out this study, showed that PBD-diagnosed adolescents who had been receiving at least two different stimulant medications were younger at onset compared with patients who had received monotherapy stimulant treatment. This suggests a possible cumulative effect of stimulant-emergent manic states as a contextual risk factor for later-onset BD. This finding is supported by other researchers, whose studies indicate that prior treatment with antidepressants and/or stimulants was associated with earlier bipolar diagnosis and who compare these results to those of children who were never exposed to these medications. However, in view of the limited sample sizes and methodological limitations of these studies, these findings must be regarded as far from definite. Furthermore, the diagnosis of juvenile mania is often complicated by the clinical overlap of PBD symptoms and ADHD symptoms. However, there is also evidence not supporting this hypothesis. In view of the limited number of studies available, particularly on developmental aspects, it is essential to tackle the diagnostic challenges posed. If a patient with initial ADHD symptoms and later hypomanic PBD-related characteristics was not seen by his or her child and adolescent psychiatrist during this hypomanic episode, the patient could be classified as an “ADHD only” or “pure ADHD” patient, because the comorbidity of PBD or the shift from ADHD to PBD symptoms would not be observed. Such cases could not only lead to distorted diagnostic prevalence rates for PBD in clinical samples, but also to a camouflage of the ADHD/PBD comorbidity relationship. Further diagnostic factors such as biased symptom reporting by parents and carers, which dilute the observed effects, complicate matters further. In spite of the methodological hurdles hindering the feasibility of studies investigating the ADHD/PBD relationship, future longitudinal research is vital to clarify the complex diagnostic relationship between PBD and ADHD. This would involve studies examining the early diagnostic assessment of children with PBD and/or ADHD symptoms and later follow-up assessments along with detailed documentation of the pharmacological treatment received and other interventions employed. The same concept can be transferred to adult patients with ADHD and/or BD to examine whether treatment-emergent bipolarity (mania in particular) in ADHD patients may also produce higher diagnostic rates of BD. A comparison of such longitudinal results on adults with data obtained from children and adolescents could also help to determine whether a specific group of children and adolescents with PBD and ADHD symptoms may be at a specific risk of developing bipolar symptoms in adolescence and later adulthood, and whether this risk could be related to early exposure to stimulants and/or antidepressants. Such research could contribute to developing concepts on how to identify those children and juveniles at risk, and to develop strategies for prevention and treatment.

**Clinical aspects**

In considering potential explanations for the co-occurrence of PBD with ADHD, it was proposed that the presence of PBD symptoms could lead to an artificial increase in diagnostic rates for PBD in ADHD samples, and that ADHD could be an early and prodromal manifestation of PBD. This proposition was then linked with the findings on treatment-emergent mania—mania triggered by pharmacological treatment with stimulants and/or antidepressants. Following this, it was proposed that ADHD and its associated factors, such as treatment with stimulants, may induce PBD symptoms, and that PBD and ADHD could have an underlying common etiology as regards genetic and neurobiological risk factors. In a recent review analysis, Singh et al have provided evidence that individuals at risk of developing ADHD symptoms may represent early prodromal states of PBD, and that PBD with comorbid ADHD may constitute a particular phenotype of early-onset disturbed mood and impaired affective regulation referred to as early PBD. However, these findings are far from definite, and the extent of comorbidity and the severity of symptom overlap between ADHD and PBD is not yet clear. Moreover, there are also nonoverlapping symptoms, as depicted in Figure 3. Clarification on these issues is handicapped by the lack of longitudinal data on developmental processes in juveniles.
nile PBD, which can in part be put down to problems of feasibility in investigations, one of which constitutes patient recruitment for follow-up measures. In research, the Child Behavior Checklist (CBCL) has frequently been implemented as a tool for the diagnosis of PBD. Biederman and colleagues introduced a particular profile within the CBCL characterized by elevated scale-values of “Anxiousness/Depressiveness,” “Attention Problems,” and “Aggression” scores discriminating children with a diagnosis of PBD from those with ADHD and those without ADHD or PBD.16,17 A CBCL-PBD score can be produced from the sum of all three aforementioned CBCL subscales, with a score of >225 predicting PBD with a specificity of 97%.18-20

It is noteworthy that longitudinal data investigating the contextual framework of the CBCL-PBD profile produce only limited evidence of the stability and outcome of this pattern at the current stage. A recent study investigating the diagnostic and functional trajectories of individuals with the CBCL-PBD phenotype from early childhood through to young adulthood showed that individuals matching the outlined CBCL-PBD phenotype displayed increased rates of suicidal thoughts and behaviors and psychosocial impairments, and an increased risk of comorbid anxiety, bipolar disorder, ADHD in young adulthood, and cluster B personality disorders.22 However, diagnostic accuracy was low for each of the outlined disorders, suggesting that the CBCL-PBD phenotype has a stronger predictive value for the classification of impairments and comorbid symptoms but is weaker in predicting a particular diagnosis.23 This finding is particularly instructive, as observed symptom patterns represented in the CBCL do not represent distinct clinical diagnoses (ie, as outlined in DSM-IV). To a certain extent this CBCL-PBD profile preponderance of aggregated and overt symptoms related to a variety of disorders may be due to the contextual diversity of symptoms which explain differing amounts of variance to their respective disorders. This again underlines the need for ongoing longitudinal research on the CBCL-PBD profile and other operationally defined diagnostic and psychometric measures.

However, it is noteworthy that symptoms shown in the CBCL-PBD profile—such as problems with attention and aggressive behavior—are ambiguous. Moreover, in the realm of affective symptoms only the depressive states in mood swings get some representation in the CBCL-PBD score, which in turn raises the possibility of potential manic mood swings being underrepresented within the CBCL-PBD profile and not being covered by elevated scores of attention problems. The comorbidity of ADHD and BD in adults has also been the subject of recent research. The overlap of ADHD

Figure 3. DSM-IV symptoms of attention deficit-hyperactivity disorder and bipolar mania not showing an overlap.

Adapted from ref 23: Wingo AP, Ghaemi SN. A systematic review of rates in diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. J Clin Psychiatry. 2007;68:1776-1784. Copyright © Physicians Postgraduate Press 2007; ref 68: Kent L, Craddock N. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord. 2003;73:211-221. Copyright © Elsevier 2003
symptoms with those of bipolar mania such as increased activity, restlessness, and increased and rapid talking may also interfere with the process of obtaining a differential diagnosis between these two disorders. However, because of this the diagnosis of manic states in children and juveniles is frequently difficult, so that at this stage the transfer of findings related to the ADHD/BD comorbidity in adults and their application to juveniles is highly problematic. Despite this diagnostic, developmental, and phenomenological dilemma, some major differences between ADHD and BD in adults mentioned by Wingo and Ghaemi should be taken into consideration on the grounds that ADHD symptoms tend to be chronic characteristics, whilst bipolar mania refers to episodic states. This specific finding deserves careful consideration, once again emphasizing the need for ongoing longitudinal studies in populations of children and adolescents at risk for severe mood dysregulation. Moreover, in contrast to mania in adult patients with BD, productivity in patients with ADHD may not be improved, as indexed by problems in daily working life. Sleep disturbances would also be more likely to be observed in bipolar patients. Here again, in similarity to children and juveniles, it has been argued that treatment of ADHD with comorbid BD is challenging, in that treatment-emergent mania and the exacerbation of bipolar symptoms can occur while receiving treatment with stimulants. A recent review article comprising four studies examining phenomenological aspects of ADHD and BD in adults detected two significant levels of overlap between these two disorders. One level was based on the overlap in DSM-IV symptoms for ADHD (ie, excessive talking before questions have been completed, etc). A second level identified an overlap between ADHD symptoms and bipolar mania, indexed by excessive talking in bipolar mania and to a lesser extent in ADHD, distractibility in BD as opposed to difficulties in sustaining attention in ADHD, and increased activity and physical restlessness in BD as opposed to hypermotoric behavior in ADHD (for a summary see Wingo and Ghaemi). Two studies examining the course of illness found an earlier age of onset in adults with ADHD and comorbid BD compared with subjects with a single diagnosis of adult BD. In consequence, studies investigating the overlap in clinical symptom patterns of PBD and ADHD should focus on potential developmental changes demanding large longitudinal investigations from childhood through adolescence to later adulthood.

**Neuroimaging**

For an investigation of the underlying neural components and processes of affective regulation, the prefrontal cortex (PFC) and the amygdala are of particular interest and relevance for PBD. With the neurotransmitter serotonin (5-HT) in frontal brain areas being involved in the inhibition of amygdala activation, the serotonergic system holds a significant position in the regulation of mood and behavior. However, as cognitive disturbances in PBD have been shown to arise regardless of illness stage or medication status, the differentiation between affective and cognitive circuitries in PBD is a matter of considerable scientific relevance in which the reciprocal connections of the PFC and the amygdala are of particular interest. A recent review analysis has supported this view, indicating that PBD could be associated with abnormalities in a circuit comprising the ventral PFC, the striatum, and the amygdala.

A functional magnetic resonance imaging (fMRI) study took the interplay between the neural circuitries underlying affective and cognitive dysfunctioning in patients with PBD into account by employing a pediatric word-matching paradigm with neutral, positive, or negative valence. The results suggested that patients with PBD showed greater activation of the bilateral pregenual anterior cingulate cortex and the left amygdala for a negative affect condition. A diminished activation was detected in the right rostral ventrolateral PFC. This suggested that disinhibition of emotional reactivity in the limbic system and reduced PFC functioning—indexed by reduced activity of the ventrolateral PFC accompanied by increased activation of the amygdala under negative stimuli—play a decisive role in PBD. However, this study involved patients with a comorbid diagnosis of ADHD, which prompts questioning on the diagnostic specificity of these findings. Furthermore, it was found that reduced functioning of the PFC in adults with BD was accompanied by increased amygdala reactivity. An examination of unsuccessful motor inhibition and neural circuitry in patients with PBD showed that unmedicated children with PBD exhibited lower bilateral striatal and right ventral PFC activation compared with controls. This study did not permit an evaluation of the role of comorbid ADHD, as a considerable number of patients with PBD also had a diagnosis of ADHD.

Functional imaging studies in patients with PBD and comorbid ADHD which have neither controls with “pure ADHD” nor with “pure PBD/early-onset BD” or
healthy subjects disregard a possible altered functioning of prefrontal areas in ADHD, for which there is a considerable body of evidence.\textsuperscript{34-42} Inhibition-mediating prefrontal regions appear to be reduced in ADHD, which in turn may be related to affective processing.\textsuperscript{43} A further study exploring the comorbidity of PBD and ADHD has suggested that adolescents with PBD and comorbid ADHD have a diminished activation of prefrontal regions compared with adolescents with pure PBD.\textsuperscript{44} However, the lack of studies involving large numbers of patients with pure early-onset BD without ADHD as a comorbid diagnosis makes further studies indispensable.

Recent research on the role of the neurotransmitter 5-HT showed that diminished 5-HT functioning in children and adolescents with ADHD made low impulsive patients behave aggressively when they were exposed to a competitive paradigm provoking reactive aggression. This finding could be related to those already mentioned regarding hypofrontality in ADHD/PBD and reduced 5-HT availability. These studies should definitely be pursued further.\textsuperscript{45} Data existing to date do not answer questions pertaining to the possible extent of the effect the abovementioned impairments of a potentially common underlying circuitry may have on the diagnostic impact of PBD and ADHD, respectively. Despite the fact that pure PBD appears to be quite a rare diagnosis, future research should focus on accurate diagnostic differentiation between PBD, ADHD, PBD, and comorbid ADHD with respect to age of onset, stage of illness, medication status and history of psychotropic treatment, gender issues, and above all, healthy controls.

**Neurochemistry**

Recent research has suggested that the susceptibility to reaction time changes when the availability of the neurotransmitter 5-HT is reduced distinguishes adolescent ADHD patients with the CBCL-PBD profile from patients with ADHD without such a phenotype.\textsuperscript{46} The sample in this particular study was small, but the rapid tryptophan depletion (RTD) method employed in this investigation can be judged as highly specific in terms of reduction of 5-HT brain synthesis. Moreover, the outlined symptoms covered by the CBCL-PBD phenotype are unspecific and are likely to be found in a whole range of psychiatric disorders. Recent research on the role of the neurotransmitter 5-HT, eg, pharmacological studies comprising selective serotonin reuptake inhibitor (SSRI) treatment, has suggested that depressive symptoms are characterized by a hyposerotonergic state, whereas manic symptoms may be related to increased central nervous system availability of 5-HT.\textsuperscript{47} This applies to drug-induced manic states and treatment-emergent mania, especially when on treatment with antidepressants. From a neurochemical viewpoint, reduced central nervous availability of 5-HT may have a beneficial therapeutic effect in acute manic states. The involvement of the serotonergic neurotransmitter system in mood disorders and bipolar mania suggests that the RTD procedure could be employed as an add-on therapeutic challenge procedure.\textsuperscript{48} The RTD procedure was used recently with remitted manic patients and indicated potential beneficial therapeutic effects of RTD.\textsuperscript{49,50} Nevertheless, the clinical use of RTD has been limited by its frequent side effects, such as vomiting and nausea. A modification of the RTD procedure by Moja and colleagues called Moja-De has recently been developed with a view to establishing acceptable tolerability rates in children and adolescents with ADHD.\textsuperscript{45-56} Unfortunately, no clinical data are currently available for the use of the RTD Moja-De procedure as an add-on therapeutic challenge procedure in children suffering from PBD and acute manic states, hypothesizing pediatric bipolar mania in the sense of a potential hyperserotonergic state. Further confirmation must be awaited.

**Genetics**

Evidence regarding the influence of age of onset may have on bipolar symptoms suggests that the earlier the onset of BD, the stronger the familial risk for relatives, with three peaks of onset at 16.9, 26.9, and 46.2 years, respectively.\textsuperscript{57-62} The lack of adoption and twin studies for PBD has meant that the heritability of PBD has not been determined. Faraone et al\textsuperscript{59} were not able to confirm that transmission was mainly due to environmental influences. This is in accordance with the hypothesis of a non-Mendelian major-gene inheritance accompanied by a polygenic component.\textsuperscript{58,63,64} A review analysis by Faraone et al bearing on the comorbidity of PBD with ADHD indicated that the prevalence of BD was approximately twice as high in relatives of patients with ADHD, as compared with the relatives of control children.\textsuperscript{64} Interestingly, the diagnostic frequency of ADHD was about three times as high with children of bipolar parents compared to the offspring of controls, suggesting that ADHD can be associated with an...
increased risk for bipolarity of family members, but also that BD increases the risk of ADHD in the family. The prevalence rate of roughly 22% for the diagnosis of ADHD among relatives of patients with ADHD and comorbid BD is about seven times as high as that for the relatives of controls (3%), whereas relatives of patients with ADHD alone had diagnostic rates for pure ADHD approximately five times as high as relatives of controls. The prevalence rates of BD were found to be much higher in relatives of patients with ADHD and comorbid BD. In contrast to the rates on ADHD prevalence, no significantly enhanced risk for bipolarity was found regarding relatives of patients with ADHD without bipolar symptoms. Finally, the prevalence of BD without comorbid ADHD was not found to be higher in relatives of patients with ADHD or ADHD and comorbid BD. As Faraone et al point out, these findings are far from being unquestionable; this can be put down to low prevalence rates of pure BD as a single diagnosis without comorbid ADHD. This in turn tends to support the hypothesis that BD and ADHD possibly share underlying psychopathological mechanisms. Faraone and colleagues recommend two pathways towards addressing the issue of familiality in BD and ADHD. The first possibility might be that certain risk alleles for BD and ADHD can be independently transmitted, thus influencing the high comorbidity of BD and ADHD. Secondly, BD and ADHD may share a common underlying psychopathological entity which can be transmitted as a complex differing from BD and ADHD, but still sharing some of the ADHD and BD symptoms. Faraone et al have undertaken a study on ADHD and comorbid BD prevalence in relatives of ADHD patients with and without BD including controls and their relatives. The indication was that relatives of controls tended to have no diagnosis of ADHD and comorbid BD, whereas the ADHD/BD prevalence in relatives of patients with the same diagnoses was 12% and the prevalence of ADHD/BD in relatives of patients with ADHD was 2%. According to Faraone et al, these findings provide preliminary evidence that ADHD and BD could cosegregate through generations as a symptom complex, thus sharing a potential underlying psychopathophysiological mechanism.

**Summary**

Epidemiological data suggest a high comorbidity of ADHD with BD symptoms, whilst each disorder seems to increase the risk of the other, a factor supporting the hypothesis that these two disorders are interrelated in terms of common underlying psychopathological properties. However, in early-onset BD the role of comorbid ADHD remains unclear with regard to developmental aspects such as a possible shift in symptoms from PBD to ADHD and vice versa. These are questions which demand further longitudinal research. Future studies should definitely focus on the longitudinal follow-up of patients with pure early-onset BD, ADHD, ADHD, and comorbid BD, and healthy controls (in combination with genetic techniques) to investigate a possible common underlying etiology of both disorders. The lack of available clinical data currently emphasizes the need for ongoing research and, most importantly, longitudinal data. To date it is not entirely clear whether children with BD will develop bipolar symptoms in adulthood, and classificatory divergences between the ICD-10 and the DSM-IV should be taken into account when addressing this question. Imaging data suggest changes in prefrontal areas both in BD and ADHD; the neurochemical underpinnings of the hypofrontality outlined regarding both disorders and associated cognitive and affective circuits need to be subject of further investigations, particularly those involving patients with pure BD/PBD. The neurochemical results on changes in 5-HT functioning related to RTD are also only preliminary, with future studies employing larger sample sizes being required, in combination with imaging and genetic studies. Adoption and twin studies could help to assess the heritability of early-onset BD, which is uncertain to date. Consequently, we have only preliminary evidence that common underlying psychopathophysiological processes in ADHD and early-onset BD possibly influence such clinical phenomena as attention problems accompanied by affective dysregulation, mood problems, and possibly coexisting aggression. Future research should further disentangle the mutual relationship between ADHD and early-onset BD, and identify it as a syndromal complex with a possible common psychopathophysiological entity. 

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El trastorno por déficit de atención con hiperactividad y el trastorno bipolar de inicio precoz: ¿dos caras de una misma entidad?

El trastorno bipolar de inicio precoz (TB) y el trastorno por déficit de atención con hiperactividad (TDAH) han sido recientemente motivo de un controvertido debate, debido a las teorías basadas en los procesos fisiopatológicos subyacentes y por el traslapo clínico de los síntomas. Los datos epidemiológicos, los aspectos clínicos, los estudios de neuroimágenes, neuroquímicos y genéticos sugieren que podría haber una posible relación entre los factores biológicos y las características clínicas en el desarrollo de los síntomas. Sin embargo, actualmente no se cuenta con datos longitudinales que sustenten la hipótesis de un cambio diagnóstico desde los síntomas de BP a TDAH y viceversa. Estos estudios serían esenciales para facilitar nuevas investigaciones que permitan evaluar si es posible que estos dos trastornos representen dos aspectos diferentes de una misma entidad psicofisiopatológica común subyacente.

Trouble hyperactivity-deficit of attention and trouble bipolare d’installation precoce: deux facettes d’une même entité?

Les troubles bipolaires (TB) de début précoce et les troubles hyperactivité-déficit de l’attention (THADA) ont récemment fait l’objet d’un débat très controversé au sujet des hypothèses de leurs mécanismes physiopathologiques et d’un possible chevauchement clinique de leurs symptômes. Les données épidémiologiques, les aspects cliniques, les études de neuro-imagerie, neurochimiques et génétiques suggèrent une éventuelle relation entre des facteurs biologiques et des caractéristiques cliniques dans le développement des symptômes. Cependant, il n’existe pas actuellement de données longitudinales en faveur de l’hypothèse d’un glissement diagnostique des symptômes de TB vers les symptômes de THADA et vice versa. Ces données seraient pourtant nécessaires avant la réalisation d’autres études sur la représentation possible par ces deux troubles de deux aspects différents d’une entité psycho-pathologique commune.

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