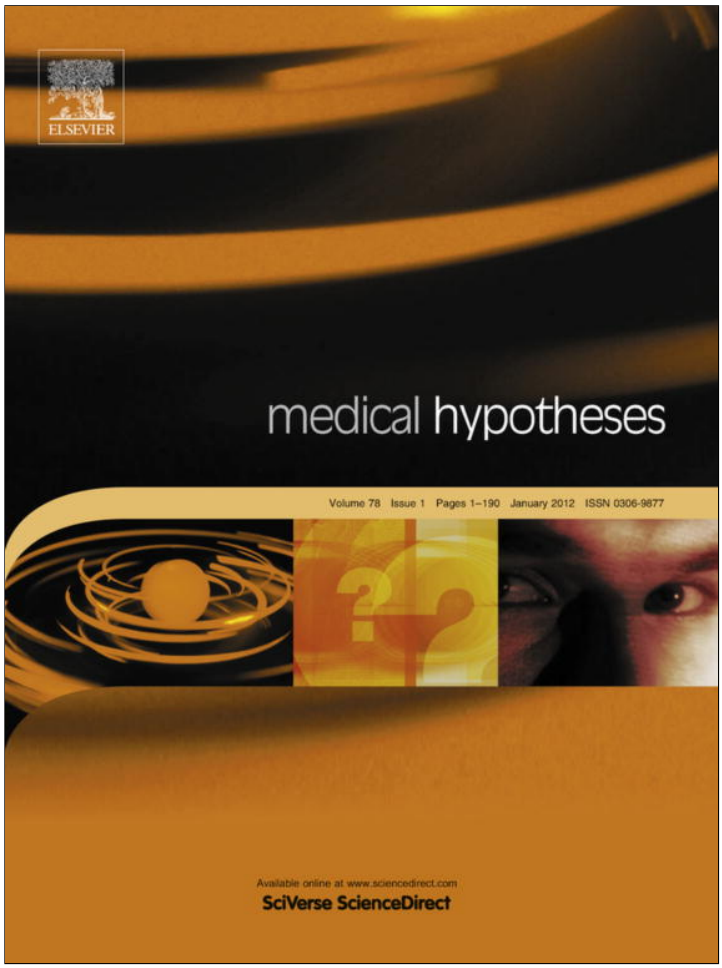

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Dopamine sudden depletion as a model for mixed depression

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ABSTRACT

Up to date research on Bipolar Disorders' phenomenology is in keeping with early descriptions made by E. Kraëpelin regarding the overlap in clinical presentation of both manic and depressive symptoms, namely, mixed states. The latter constitute a highly prevalent and characteristic clinical presentation of Bipolar Disorders' and entail therapeutic difficulties, prognostic implications and increased suicidal risk. Notwithstanding, mixed states', more specifically mixed depression, have been underestimated and bypassed to the point where currently neither diagnostic criteria nor specific therapeutic recommendations are provided. In addition to the lack of agreement on nosography and diagnostic criteria, mixed depression is usually excluded from Bipolar Disorders' neurobiological models. Furthermore, renewed interest in the role of dopamine in Bipolar Disorders' physiopathology has left aside hypothesis that may account for the aforementioned clinical presentation. Interestingly enough, other syndromes arising from sudden dopamine depletion such as neuroleptic dysphoria or withdrawal syndromes from dopaminergic drugs, bear remarkable clinical similarities with mixed depression. These syndromes have been subject of further research and may thus provide a model for mixed states' physiopathology.

Indeed, this article accounts for clinical similarities between mixed depression, neuroleptic induced dysphoria, and other behavioural syndromes arising from sudden dopamine depletion. After reviewing neurochemical basis of such syndromes we present, to the best of our knowledge, the first neurobiological hypothesis for mixed depression. Specifically, such hypothesis regards over activation symptoms as auto regulatory attempts to compensate for sudden dopaminergic depletion. This hypothesis provides with a beginning step for the neglected problem of mixed depression, a non-antithetic link between the dopaminergic hypothesis for both manic and depressive symptoms, a plausible explanation regarding inter individual variability to mixed depression susceptibility, and suggests new approaches for the development of novel treatments in which dopamine dysregulation should be targeted.

Introduction

Mixed states (MS) were first conceptualized by W. Weygandt in the late 1890s [1] but it was not until the sixth edition of Kraëpelin textbook [2] that they deserved more attention and were included in a separated section. The description of MS was in keeping with both Kraëpelin and Weygandt's view of mood disorders [3], highlighting the unity of manic depressive insanity (illness). If symptoms of opposite polarity were present during the same episode, then mania/hypomania and depression could not be distinct disorders [4,5].

The pioneer vision of pre pharmacology psychiatrists has been further validated by recent clinical studies with modern statistics which depict a clinical picture where approximately one third of acute episodes have mixed symptomatology and where boundaries between depression and mania are a quantitative transition rather than a categorical cut off [6,7]. Benazzi, has gone further in clinically and epidemiologically characterizing the concept of MS, particularly mixed depression (MxD) [5]. Currently, the problem of MS in general has been progressively marginalized and bypassed. The DSM IV-TR lacks proper clinical, therapeutic, or pathophysiological definition and there is neither unified diagnostic criteria for MS in general nor for MxD in particular to the extend that the International Society of Bipolar Disorders' (ISBD) Task Force excluded them from its diagnostic guidelines [8]. In the same fashion, specific criteria for MS were not included in the ISBD recent publication on nomenclature, course and outcome of bipolar disorders [9]. Despite reported prevalence of up to 39%, increased suicidal risk and specific therapeutic and prognostic implications [10], most treatment guidelines for BD fail to provide recommendations for MS and research about their treatment is marginal [11]. Finally, according to the fifth edition of the Diagnostic and Statistical

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Manual of Mental Disorders draft, MS would be replaced and relegated to a course specifier.

Accordingly, pathophysiological models proposed for BD have avoided the problem of MxD. Although many intend to account for mania, depression and mood dysregulation, only a few psychological models have attempted to address MxD [12] and none at the level of neurotransmission or neurobiology. While nomenclature and diagnostic discussions allow for pragmatic solutions, any valid pathophysiological model pretending to depict BD phenomenology should not ignore that most episodes do not present themselves as pure mania or depression but rather, more than half of the time, as episodes with joint symptomatology.

Despite the fact that renewed consideration on the role of dopamine (DA) in the psychopathology of BD has resulted in new plausible models for this condition, the tendency of bypassing MxD remains [12]. Interestingly enough, neuroleptic-induced dysphoria (ND) and other syndromes secondary to sudden DA depletion, bear clear symptomatic overlap with MxD and may thus provide a novel approach in understanding its pathophysiology. The present article reviews DA depletion clinical presentation while discussing its similarities with MxD, presents current evidence of dopaminergic depletion models in its pathophysiology, and poses a dopaminergic model for MxD.

Dopaminergic models in bipolar disorders

Phasic release of DA in ventral thalamus – ventral striatum connections and cortical projections serve as signals to novel and behaviourally relevant stimuli which are critical in organizing and begetting goal directed behaviour. In addition, DA release in the striatum is related to pleasure-reward association, fear response regulation, anxiety and euphoric mood states [13]. Imbalance in DA has been also related to impulsive behaviour frequently found in affective episodes [14].

DA plays an important role in cognitive functioning, which in turn is closely involved in BD symptomatology. Multiple lines of evidence support the participation of the dopaminergic system in BD's pathophysiology (for a review see Cousins DA, 2009). Firstly, dopaminergic models explain manic and depressive symptomatology as an up or down regulation of DA, respectively. The main line of evidence supporting DA up-regulation during mania comes from experience with drugs that induce its increase (i.e. amphetamines, L-dopa). Amphetamine administration raises DA level by means of several mechanisms including reversal of the direction of its reuptake through DA transporters (DAT), especially in the striatum, nucleus accumbens and frontal areas [12]. In turn, this leads to behavioural changes that resemble those of mania even in normal subjects at low risk of BD [12,15]: mood elevation and drive, and lessened need for sleep [16]. Therapeutic use of DA precursor L-dopa, and selective dopaminergic agonists such as pramipexol and ropinirol may cause manic syndromes [17]. On the contrary, evidence supports DA deficiency in depressive syndromes. Administration of alphamethyl paratyrosine (AMTP) reduces catecholamine synthesis by inhibiting tyrosine hydroxylase, worsening depression [18] and produces depressive symptoms even in healthy volunteers. Dopamine antagonizing drugs such as haloperidol [19] or beta-blockers [20] may induce depression. Furthermore, almost half of patients with Parkinson's disease suffer from depression [21] which improves with dopaminergic agonists such as pramipexol. Coincidentally, this drug has also positive evidence for the treatment of BD depressive episodes [22]. Accordingly, motor symptoms and motor side effects may be more frequent in BD depression [23,24].

As mentioned above, new evidence supports a general dopaminergic dysregulation in BD. Indeed, recent data confirms early findings regarding a greater risk of acute and tardive extrapyramidal symptoms (EPS) secondary to DA blockers in BD patients compared to that of schizophrenic patients. In a review of second-generation antipsychotics (AP) and EPS, the NNH in BD patients was of 3, while in schizophrenic patients equaled 5 [23]. In a naturalistic study including more than 3400 BD patients, van Rossum et al. [25] reported that 4.1% presented with tardive motor syndromes which positively correlated with AP time of exposure and other DA proxy measures. The authors concluded that these findings indirectly supported the notion of a general DA dysregulation in BD. Interestingly enough, EPS are present in BD even during euthymia. Two independent studies have found not only that motor symptoms in euthymic BD patients are independent from DA blockers exposure and age, but that they positively correlate with impaired executive and overall functioning as well [26–28]. Recently, Berk et al. [29] described the "Dopamine Dysregulation Syndrome": a cyclical dysregulation in DA transmission which, although accounting for manic and depressive symptoms, mood dysregulation and hedonistic activity, does not account for MS in particular.

Be as it may, all these models leave MxD aside, and by anchoring BD episodes to the increase or decline of DA levels they fail to provide hypotheses that account for the frequent co-occurrence of manic and depressive symptoms.

Nevertheless, the DA hypothesis is not a simplistic model. Indeed, quantitative changes in DA turnover at the central nervous systems result in qualitative (behavioural) changes. More importantly, subjective and objective behavioural changes secondary to DA down-regulators provide a scenario where depressive, anxious and manic symptoms may present simultaneously, changing qualitatively according to the time of exposure and the intensity of DA depletion.

Neuroleptic dysphoria and experiences under dopamine depletion resemble the clinical scenario of depressive mixed states

Although no systematic definition has yet been coined, there is expert consensus in considering MxD as a depressive syndrome with racing thoughts, inner restless, dysphoria or anxious feelings. Benazzi has defined depressive mixed states as the combination of a major depressive episode (MDE) and at least three hypomanic symptoms [30–32]. More synthetically, Koukopoulos [33] has defined mixed depression as the presence of MDE and specific symptoms of mental over activity. Notwithstanding the differences between both authors, MxD may be clinically described as the combination of MDE with opposite (excitatory) polarity symptoms. Of these, psychomotor activation/agitation, irritability and mood liability, racing/crowded thoughts, sexual arousal, insomnia, panic attacks, talkativeness, and suicidal crises predominate [31]. Goodwin and Jamison collected a series of subjective descriptions of MxD phenomenology that is in keeping with the general definitions proposed [34] (see in Table 1).

Dating back to the introduction of AP medication for treatment of tuberculosis, a clinical syndrome resembling MxD has been recognized. Until the late 1970s when the modern term was finally coined, it has been successively labeled as akinetic depression, behavioural toxicity, and neuroleptic induced psychic indifference [35–38]. Precipitated by acute exposure to AP medication, ND is a subjective syndrome that, in a depressive or dysphoric milieu, comprises restlessness, anxiety, anger, hostility, dejection and apathy, without any relation to other cognitive or motor side effects [36]. Further descriptions include mood swings, crying, despondence, panic attacks and separation anxiety [39,36,38,40]. ND has been described for virtually all conventional AP regardless

Table 1
Characteristics of two clinical scenarios resulting from dopamine depletion.

Mood	Depression, despair, lachrymose, despondence, irritability, anxiety, lachrymose, dysphoria, mood liability	Depression, anxiety, despairing, despondence, mood liability, apathy, dysphoria, anger, hostility, dejection, crying, separation anxiety, emotional blunting
Activity	Inner restlessness, pressure of activity, akathisia, pressure of activity, agitation, sexual arousal, insomnia, talkativeness, suicidal crises	Restlessness, akathisia, impulsivity
Thought	Racing thoughts, distractibility, thought rumination	Racing thoughts, distractibility, thought rumination, clouded thinking

of dosage and although most clinical descriptions and research has been on schizophrenic patients, it has been further reported in healthy volunteers, Tourette's syndrome and other psychotic spectrum disorders [38]. Not all patients exposed to AP develop ND. Indeed, in those receiving first generation AP, prevalence ranges between 10 and 60% [39,41], while no data is yet available for second generation AP.

Back in the seventies, Belmaker and Wald, noticed a possible relationship between ND, MxD and DA. After self-administration of haloperidol (5 mg intravenously) they reported: *"...Within ten minutes a marked slowing of thinking and movement developed, along with a profound inner restlessness (...)."* Each subject complained of paralysis of volition and lack of physical and psychic energy. "*There was no sleepiness or sedation* (and) *both subjects complained of severe anxiety*." While discussing their experiences they highlighted that: "*...The similarity of the above-described state to that of some cases of agitated depression and post-psychotic depression suggests involvement of dopamine in these affective states...*" [42]. Several case reports by Caine and Polinsky described similar findings: after haloperidol treatment subjects experienced mood changes in a dosage-dependent manner [41]. Contemporarily and secondary to AP treatment, van Putten described dysphoric reactions, which entailed emotional blunting, restlessness and anxiety; and were strong predictors of treatment adherence and overall outcome in schizophrenia [43,44]. Furthermore, the author linked such symptoms with akathysia [45].

More recently, studies combining DA depletors and functional imagining techniques replicated those findings. De Haan et al. reported on the subjective experience of a healthy volunteer exposed to a reversible inhibitor of tyrosine hydroxylase, AMTP, while assessing striatal D2 receptor occupancy by SPECT. Comparably to the experience of Belmaker and Wald, the subject initially underwent an apathy-anergic syndrome ("*...stimuli had less impact; visual and audible stimuli were less sharp (...) environmental stimuli seemed dull...*"); yet, afterwards he presented with inner restlessness, flight of ideas, felt ashamed, frightened, anxious and finally, experienced depressed mood [46].

Voruganti and Awad reported acute behavioural and subjective changes in 13 medication free schizophrenic patients after the infusion of AMPT while controlling DA depletion by SPECT. Soon after the first dose a syndrome including blunted pleasure and responsiveness, clouded thinking, loss of motivation and lowered vigilance unfold. Dysphoria steadily worsened, resulting in social withdrawal and personal distress. Finally, akathisia, akinesia and rigidity followed. At the end of assessment (48 h after AMTP infusion), patients reported increases from baseline of 38% in dysphoria, 29% in anxiety, 16% in depression, 24% in anger-hostility and decrease in friendliness of 28%, 33% in elation, 41% in vigor and 3% in euphoria [47].

Other situations of DA depletion produce clinical scenarios resembling that of MxD. A specific withdrawal syndrome has been described for drugs which increase DA level in mesocorticolimbic areas either for compounds related to substance abuse (i.e. cocaine, amphetamines), or to DA agonists used in Parkinson's disease replacement therapy (i.e. L-dopa, pramipexole). The symptomatology derived from the DA Withdrawal Syndrome (DAWS) resembles that observed in MxD: intense anxiety, panic attacks, dysphoria, agitation, irritability, and impulse control disorders such as pathological gambling, compulsive eating, compulsive buying, and hypersexuality [48]. Furthermore, some aspects of sleep disturbances during cocaine deprivation [49] resemble those found in BD: increased sleep latency; decreased total sleep, slow wave sleep and slow wave activity; and altered REM sleep [50]. In a randomized study controlled by placebo, Morgan et al. observed that the use of modafinil in abstinent cocaine abusers improved nocturnal sleep, resituated sleep architecture and reduced diurnal somnolence [49], thus relating DA with deprivation symptomatology [51].

In summary, MxD, ND and other syndromes arising after sudden DA depletion bear clear clinical resemblances (see Table 1): inner restlessness, anxiety, impulsiveness, and racing thoughts in a depressive/apathetic milieu. What would then be the advantage of further conceptualizing such correspondence? As discussed, while pathophysiological descriptions of MxD are yet almost inexistent, pathophysiology of ND has been largely investigated.

Sudden and partial dopamine depletion along with individual susceptibility may be necessary for mixed depression to arise

As mentioned, ND has been linked to DA depletion early on. Furthermore, evidence suggests that DA decrease has to unfold in a sudden manner and up to certain levels for these clinical settings to arise. Caine and Polinsky reported drastic clinical changes secondary to minimal changes in haloperidol dosage: when receiving 2.5 mg/day, subjects experienced mood swings, crying, sadness, depression, dysphoria, agitation, anxiety and despondence, all of which subsided after lowering dosage to 2 mg/day. These seminal reports stress that, after exposure to DA blockers, dysphoria has a rapid onset, progresses with time, and may be followed by other symptoms, such as EPS [41]. In replication of their earlier study, Voruganti et al. examined the clinical profile and time course of behavioural and subjective consequences of DA depletion. While all studied subjects experienced changes, subjective indices showed a quicker and greater progression compared to those observed in the objective ones. Clinical description noted: "*...steady worsening of dysphoria along with akathysia and mild rigidity,* (that) *resulted in gradual social withdrawal, diminished interest in surroundings and little communication which was followed by the emergence of akathysia and a failure to settle down*". The authors described this technique as helpful in "examining the phenomenology of dysphoria, the temporal relationship between subjective and behavioural consequences of dopamine depletion" [47].

Another simple but dramatic example of such time- dependent unfolding of DA decline may be found in Parkinson's disease treatment. During late stages of (L-dopa) treatment, patients with this condition suffer "on–off" crisis, triggered by sudden and marked DA plasmatic level fluctuations. Of interest, during "off" periods, DA level plunges but the akinetic motor symptoms do not develop first-hand. On the contrary, "off" periods firstly present themselves with acute anxiety, depressive symptoms and inner feelings of restlessness and only later on with akinesia and hypertonia.

Accordingly, Maricle et al. noted that mood and anxiety during "off" periods improves after L-dopa infusion in a dose-time-depending manner, and independently from motor symptoms improvement [52].

In keeping with previous evidence, de Haan et al. reported that subjective response to haloperidol in schizophrenic patients is optimal when D2 receptor occupancy is between 60 and 70%. Above that level, not only does the risk of subjective dysphoric experience rise significantly, but it may develop with lower levels of occupancy than those observed in EPS as well. Furthermore, a similar relationship between D2 receptor occupancy and dysphoric feelings has been described for both first and second generation AP [53], and even in healthy subjects by means of an AMTP-SPECT design [46].

On the other hand, an idiosyncratic susceptibility may be necessary for the unfolding of a dysphoric reaction after DA depletion. Van Putten was the first to point out the relationship between AP plasmatic levels and dysphoric feelings in schizophrenic patients [54] and to notice the importance of inter-individual variability to EPS susceptibility and, as a consequence, to treatment outcome [55]. Modern studies have further confirmed inter-individual susceptibility to ND. Voruganti et al. managed to experimentally induce dysphoria in schizophrenic patients by manipulating DA activity in the striatal–accumbens complex, thereby directly linking dysphoria to D2 receptor binding ratios. All patients had received AP medication at some point in their treatment but were medication free at the time of the study. According to the Drug Attitude Inventory scores, a scale which measures subjective experience while on psychotropic medication, the sample was divided into two groups: those who had previously experienced ND and had higher scores in subjective scales ("dysphoric responders"); and those who had lower scores in subjective measures and had not experienced ND ("non dysphoric responders"). The investigators administered AMPT which interferes with DA synthesis and produces temporary depletion of DA without causing D2 receptor up-regulation. Individual's subjective experiences over a 96 hour-period were registered. Concomitantly, striatal DA receptor D2 binding was measured using SPECT at baseline and after AMPT infusion. Although all patients experienced dysphoria, "non dysphoric responders" developed later and less severe symptoms, while "dysphoric responders" experienced earlier and more severe symptoms, and presented with higher risk of akathisia and EPS. As for subjective responses and DA D2 binding ratios, both variables correlated positively. Furthermore, variance analysis showed that changes in binding ratios distinguish both groups and was significant over time. As a result, authors concluded that vulnerability to ND could be linked to low DA synaptic levels at baseline [56].

Inter individual variability in DA activity has been further confirmed by recent studies, elucidating why not every patient on AP medication develops dysphoria: those with low basal DA activity in the nucleus accumbens may be most vulnerable to such adverse effect [38]. In addition, inter individual variability to EPS in schizophrenic and bipolar subjects correlated with DA degradation enzyme genes (COMT G158A, A-278G) [57].

In the same line of evidence, even the DA Withdrawal Syndrome (DAWS) described by Rabinak may be conditioned by inter individual susceptibility. Indeed, those patients who develop DAWS after long- term use of DA agonists had previously shown signs of impulse control disorders associated with such drugs [48].

Dysphoria secondary to dopamine depletion as a model for mixed depression

The evidence presented describes that after DA decline, a syndrome consisting of anhedonia, dysphoria and sadness, along with psychomotor agitation, anxiety, and impulsiveness arises. This condition may be secondary to sudden DA decline up to intermediate levels. Both time elapsed since the beginning of DA depletion and the intensity of such depletion may determine the manner in

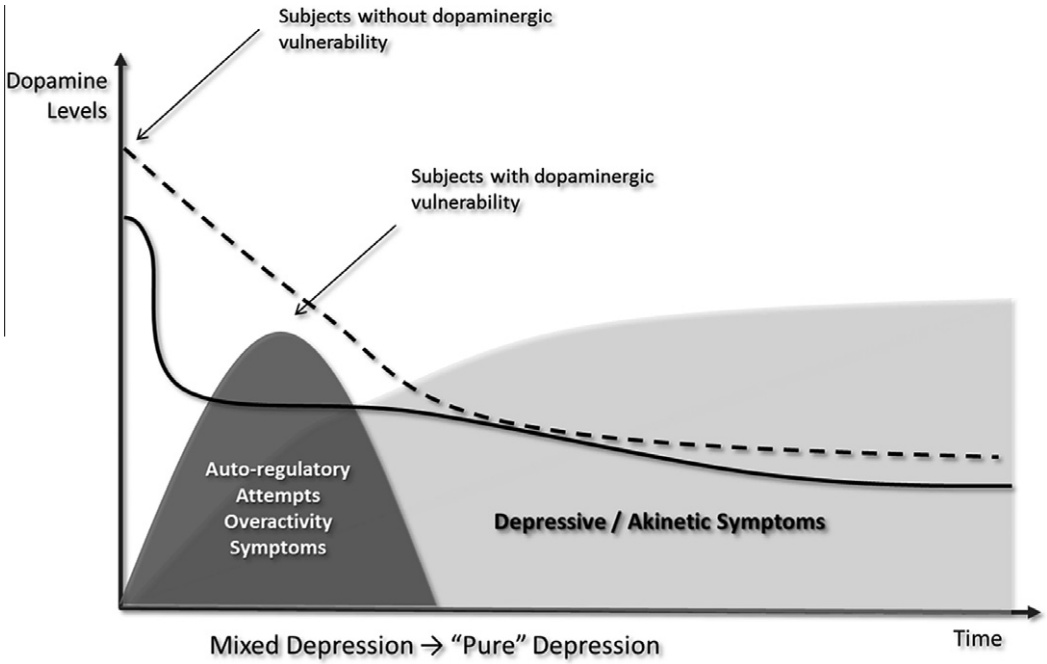

Fig. 1. Interaction between auto-regulatory attempts and depression in subjects with and without dopaminergic vulnerability. In this model, when vulnerable subjects undergo sudden depletion of dopamine levels, in an attempt to compensate for such decrease auto-regulatory mechanisms arise. Early on, such overactivity symptoms overlap with depressive and akinetic symptomatology. Later on, when such auto-regulatory attempts fail, a more "pure" depressive scenario arises. On the contrary, in non-susceptible subjects, dopamine depletion is less abrupt and may be compensated without overactivity mechanisms. Thus, this group undergoes a gradual increase of "pure" depressive symptoms without overlap with overactivity symptoms. This model allows for the explanation of several clinical scenarios.

which this syndrome unfolds. Of note, dysphoric symptoms appear early on, and may persist with further DA decrease or until complete DA depletion. It is not until then that akinetic and depressive symptoms take place. [56,46,47]. As a result, depressive symptoms coincide with psychomotor agitation. If further DA decline takes place, such array of activation symptoms become overshadowed by more complex depressive symptomatology such as psychomotor inhibition, anergia and cognitive impairment, resembling those findings described after DA exhaustion (see Fig. 1). In addition, this model would explain why not all patients present with this kind of mood episodes: as in ND, an interindividual susceptibility together with an specific "tempo" in DA depletion are of need in order for this mixed clinical picture to unfold.

Nevertheless a critical question remains: how can dopaminergic down-regulation induce manic-like symptoms? To answer this question, a parallelism with ADHD may be illustrative. Indeed, ADHD characterizes by over-activation symptomatology associated with DA down-regulation. Its treatment with catecholaminergic agonists such as amphetamines is supported by the idea that hyperactivity is an auto regulatory attempt to compensate for deficits in focal attention. In line of with such hypothesis, Hegerl et al. [58,59] propose a novel pathophysiological model for manic symptoms. Based on EEG patterns of unstable wakefulness and common clinical features with ADHD, the authors posit that hyperactive, impulsive and chronobiological symptoms of mania are autoregulatory attempts to stabilize a deficient vigilance regulation system.

Finally, for this model to be consistent, it should agree with current data on MxD treatment. MxD poses a particular difficult therapeutic challenge: poor response to lithium is reported in 60–70% of cases and, despite some efficacy reported for valproate, olanzapine and quetiapine, data is still scarce and, more importantly, it comes from sub-analysis of studies initially designed to address the efficacy of treatments for mania or depression [60,61]. The fact that olanzapine and quetiapine act as DA blockers while valproate does so as a DA down-regulator may seem to contradict our hypothesis. However, data on their efficacy does not describe the sequence in which they improve symptomatology [61–63]. Indeed, as observed in clinical practice, amelioration of manic symptoms such as agitation, anxiety, racing thoughts and insomnia is followed by, only in some cases, improvement of depressive symptoms. Furthermore, despite all second generation AP being efficacious in treating of mania, only olanzapine and quetiapine are so in treating depression. Consequently, future studies on the proper treatment of MxD should discriminate which depressive symptoms improve and, ideally, describe the sequence of such improvement. On the other hand, electric convulsive therapy (ECT) is an effective, safe and tolerable treatment for MxD even in medication refractory patients. In a systematic review, Valentí et al. report that ECT is even more effective in treating MxD than for bipolar depression [64]. While ECT mechanism of action is still controversial, many agree on its enhancement of monoaminergic neurotransmission, especially of DA [64–68]. A clinical example of ECT enhancement on DA system functioning may be found in patients with Parkinson's disease in whom it ameliorates motor symptoms [67].

Summary and conclusions

In keeping with the existing lack of agreement on nosography and diagnostic criteria for MS, MxD is usually excluded from neurobiological models of BD. We have presented a novel and plausible pathophysiological model based on previous data and clinical experience on DA depletion. This model has the following advantages: (a) it provides a beginning step for the neglected problem of MxD, a critical issue in BD phenomenology; (b) it provides a not antithetic link between dopaminergic hypothesis for manic and depressive symptoms therefore accounting for their frequent concurrent presentation; (c) it provides a plausible explanation on why not all patients develop MxD; (d) it provides a better understanding of current treatments mechanisms of action; and, finally, (e) it provides new approaches for the development of specific treatments in which DA dysregulation in itself should the target.

A better comprehension of the biological basis of mixed phenomenology is in urgent need. Leaving aside MxD in pathophysiological hypothesis seems phenomenological inaccurate, since up to one-third of BD episodes present with concurrent manic and depressive symptoms. The experience obtained from the study of ND should be replicated in the study of MxD pathophysiology.

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