

Impulsivity, aggressivity and mood disorders: a narrative review

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SUMMARY

Aggressiveness and Impulsivity represent clinically significant elements in the context of coexisting mental disorders and have been extensively studied in the context of mood disorders. Considering their significant impact on prognostic trajectories, accruing evidence suggests the need to consider these elements in the development of specific treatment strategies tailored to the specific requirements at the individual patient level and in the specific context where care is delivered. In the present narrative review, we propose to the reader a selection of study articles deemed relevant to the discussion of this complex subject, with a critical analysis of the available evidence regarding empiric evidence for the association of aggressiveness and impulsivity with a focus on bipolar disorder and major depressive disorder. A brief overview of reports deemed relevant to the discussion for some of the possible biological basis for this phenomena is also outlined, offering a selection of studies based on the study authors' judgement.

Key words: aggressiveness, impulsivity, mood disorders, bipolar disorder, major depressive disorder

Introduction

Impulsivity and aggressivity are clinically relevant aspects of psychiatric disorders and of mood disorders in particular. Indeed, their presence may shape the clinical presentation, increasing the severity of symptoms, inducing relevant behavioral changes and worsening the outcome of the disorders. This review is based upon a comprehensive search of PubMed and Scopus databases for all types of articles, excluding case reports. Relevant evidences from literature are synthesized and presented in a narrative form. Before addressing the issues through a analysis of the most relevant literature, we will provide an overview on the different, and not always overlapping, meanings that have been attributed to these two terms and the various articulations of both the concepts of impulsivity and aggressivity.

Definition of impulsivity

Impulsivity is commonly conceived as a series of specific behaviours related to each other¹⁻³. A core aspect of most of the definitions of impulsivity is the presence of an action without planning or reflection. In other terms, impulsivity is commonly associated with a failure of behavioural filtering processes outside of consciousness⁴, with a compromised ability to reflect on impending acts or a reduced capacity to use knowledge and intelligence to direct behaviour⁵. Differently from the premeditated one, impulsive behaviour is characterized by an inappropriately short threshold for response and a lack of reflection and modulation in the absence of a potential gain so that the consequence may be a sort of dissociation be-

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tween an action and its intent⁶. According to Barratt⁷, impulsivity is composed of three subtraits: cognitive impulsivity, which is involved in making quick decisions; motor impulsivity involves acting without thinking; and non-planning impulsivity is related to the lack of “futuring” or forethought.

Definition of aggressivity

Aggressivity is commonly conceived as a behavior manifesting as verbal and/or physical acts towards other human beings, animals or objects with the aim of causing harm⁸. Instrumental or proactive aggressivity is the intentionally harming of an individual in order to achieve a desired goal, while impulsive aggressivity is generally conceived as any hostile or reactive aggression that has no identifiable goal. These terms may be considered as respectively equivalent to instrumental and hostile aggressivity⁸. Indeed, instrumental aggressivity is conceived as a premeditated means of obtaining some goal other than harming the victim, being proactive rather than reactive, while hostile aggressivity, sometimes called affective or reactive aggression as well as impulsive aggression, is typically thoughtless, unplanned, driven by anger and having as ultimate motive harming the target, occurring as an unplanned reaction to some perceived provocation⁸⁻¹⁰. Thus, anger, as subjective experience, has a central role in impulsive aggressivity, being in turn related to irritability, defined as a “persistent anger, a tendency to respond to events with angry outbursts or blaming others, or an exaggerated sense of frustration over minor matters”¹¹. Some authors have also suggested a distinction between tonic irritability i.e., irritable mood) and phasic irritability, operationalized as “attacks of anger all of sudden” where one would “lose control and break item of some value/hit or attempt hitting a person/threat of harm to a person”¹². Finally, the term violence is referred to as an extreme form of aggressive behaviour with the purpose of physically harming others, irrespective of the consequences⁸.

Impulsivity and aggressivity in unipolar depressive disorders

Impulsivity

Impulsivity is a very common feature of unipolar depressive disorders, although it seems to be more frequently associated with bipolar disorders (BD)¹³. Indeed, a series of studies, mainly regarding patients affected by major depressive disorder (MDD), show a significant association between depression and impulsivity. A study regarding 127 depressed inpatients assessed impulsivity with three different scales at admission and af-

ter four weeks of treatment, the Impulsivity Rating Scale (IRS), the Impulse Control Scale (ICS) and the Barratt Impulsivity Scale (BIS), showing that three dimensions of state-dependent impulsivity (behavioural loss of control, non-planning and cognitive) were all emerging in this group of severely depressed patients. Even though all subscores were not significantly different, higher scores of impulsivity were shown at admission, and lower scores were shown at follow-up. The study also revealed that recent suicide attempts in severe depression were related to loss of control and cognitive but not to nonplanning impulsivity¹⁴. A meta-analytic study regarding nine studies, including 688 cases and 464 controls, all based upon a standardized assessment of trait impulsivity in remitted patients affected by MDD and compared with a healthy control group, demonstrated a significantly higher weighted means scores at the Barrat Impulsivity Scale (BIS) among MDD patients, with a strong association between impulsivity and depression persisting even when remission was obtained. These results are of a particular interest, considering that in this meta-analysis studies with samples constituted by patients affected by bipolar depression, substance use, obsessive-compulsive disorder and other psychiatric co-morbidities were excluded¹⁵.

Higher impulsivity has been shown even in adolescent samples affected by depression. A study employing a matched case-control design and including 25 adolescents with MDD and 75 controls shows that adolescents with MDD were more impulsive compared to controls according to the BIS-11 in its three domains: motor attentional and non planning. Moreover, impulsivity was not correlated with clinical features of MDD, such as suicide attempts, psychiatric comorbidities and antidepressant medication¹⁶. A comparative study assessing impulsivity using the Barratt Impulsiveness Scale (BIS-11) across four different groups of children and adolescents, namely 52 patients with BD, 31 with MDD, 20 unaffected offspring of bipolar parents (UO) and 45 healthy controls (HC), has shown higher BIS-11 total scores among BD patients when compared to HC ($p < 0.01$) and UO ($p < 0.01$) with MDD patients showing higher BIS-11 scores when compared to HC ($p < 0.01$), without any statistically significant differences between MDD patients and UO, as well as between MDD and BD patients. These findings suggested that trait impulsivity is relevant among children and adolescents with mood disorders in general, as well as in unaffected individuals at high genetic risk for BD¹⁷.

In elderly patients, a single study has applied a regression model predicting age using resting-state functional connectivity in 710 healthy adults aged 18-89. This model, trained on normal ageing subjects, was then applied to a sample of actively depressed MDD subjects

($n = 109$). The main findings of this study were that the difference between predicted brain age and chronological age was 2.11 years greater ($p = 0.015$) in MDD patients compared to controls. Moreover, an older MDD brain age was significantly associated with increased impulsivity and increased depressive severity in males. These results indicate that MDD is associated with accelerated brain ageing and that accelerated ageing is selectively associated with greater impulsivity and depression severity, at least among males¹⁸.

The fact that impulsivity remains elevated even during euthymic phases, both in MDD¹⁵ and in BD¹⁹, suggests that it is a trait-like personality characteristic which predisposes to relapses²⁰, but also to new onset depression, as emerging from a study which examined the association between impulsivity and incidence of depression using prospective data from two surveys (2-year time lag) on a large cohort of hospital employees ($N = 4,505$)²¹. Indeed, the study showed that impulsivity was predictive of the onset of depression ($OR = 1.95$, $CI\ 95\% = 1.28-2.97$) even after adjustment for age, sex, education, and a variety of other baseline characteristics²¹.

As generally recognized, impulsivity is considered as a dimension of particular relevance in BD, not only as a state-related but also as a trait component representing a core feature of the illness¹³. Few studies have, however, addressed the question of whether impulsivity is significantly more frequent and/or of higher intensity among bipolar patients with respect to those affected by MDD or other unipolar disorders. The above-cited comparative study among child and adolescent samples¹⁷ showed no statistically significant differences in BIS-11 total scores, both between MDD patients and unaffected offspring of BD patients and between MDD and BD patients. However, in interpreting the results of this study, the composition of the clinical samples of BD and MDD patients should be taken into account. Indeed, both samples included a certain number of patients in different phases of the illness (mania/hypomania, depression and euthymia for BD and depression or euthymia for MDD), with the consequence that the different composition of the samples may have affected the results. Even though scores at impulsivity scales are generally increased both in BD and MDD we also know that MDD impulsivity levels in acute phases are higher than those found after an effective treatment¹⁴. Moreover, there seems to be a differential relationship between impulsivity with depression and mania in BD²², with total and attentional impulsivity scores at BIS-11 correlating both with depression and mania scores, but motor impulsivity correlating only with mania scores and non-planning impulsivity only with depression.

Finally, a large comparative study involving 685 patients

with an MD episode, 455 affected by lifetime unipolar depression, 151 by BD type 1 disorder and 79 by BD type 2 disorder²³, showed, among the many aspects indagated, that BP-I and BP-II depressed patients had higher lifetime impulsivity, compared to unipolar patients. In interpreting these results, we should take into account that all the samples (both BD and UP) of this study were evaluated during an acute depressive episode so that the evidence could not be extended to euthymic patients. In sum, no definite conclusion about the higher frequency and/or intensity of impulsivity in BD may be drawn, taking into account the contrasting evidence available.

Aggressivity and related features

A series of studies showed a significant relationship between aggressivity and MDD. According to a recent review regarding psychiatric inpatients²⁴, depression is reported as a risk factor for aggressive behaviour, mostly but not exclusively in the form of auto aggression/suicidality,

Another relevant review²⁵ reports the evidence regarding the association between different mental disorders and violence, drawn by studies with high-quality designs and replicated findings, showing that relative risks are typically increased for all violent outcomes in most diagnosed psychiatric disorders compared with people without psychiatric disorders, with increased odds in the range of 2-4, even after adjustment for various sources of confounding. Absolute rates of violent crime over a 5-10-year period are typically below 5% in people with mental disorders, including depression, with the exception of personality disorders, schizophrenia, and substance abuse disorders. As regards depression, the authors complain about the scarce amount of research about depression and violence with respect to depression and suicide, also complaining about the limitation of previous work on Depression constituted by the prevalent inclusion of selected groups such as the inpatients, who could have a higher odds to be admitted to hospital due to violence.

Several large outpatients' studies confirm a higher risk for violent acts among depressed patients. A study on 47158 Swedish outpatients with depression²⁶ reported a three times increased risk of violent offending after diagnosis, compared with the general population (adjusted $OR\ 3.0$, $95\%\ CI\ 2.8-3.3$); the odds increase was still significant in depressed patients even after adjustment for familial confounding and in those without substance abuse comorbidity or a previous violent conviction (all $p < 0.0001$).

Another large study examines the relationship between violent behaviour occurring before and since age 15 and specific lifetime DSM-IV Substance Use, Mood, Anxiety, Personality Disorders and Pathological Gam-

bling in a large, nationally representative survey of the U.S. population, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) ²⁷. This study showed a prevalence of violent behaviour among those affected by MDD before age 15 of 2.16%, which raises to 8.31 after 15 years. However, the odds of violence linked to MDD were significantly higher only after 15 years (OR 1.73 range 1.47-2.05). Moreover, the prevalence of violence among “pure” (not comorbid) MDD patients was only 0.74% before the age of 15, with respect to 2.55% among comorbid cases ($p < 0.001$), while after the age of 15 the rates were respectively 2.17% for “pure” MDD cases and 14.36% for comorbid case ($p < 0.001$). Thus, violence risk for those affected by MDD becomes significantly higher both before and after 15 years in case of comorbidity, with substance use and/or personality disorders.

The prevalence and correlates of “aggressive outbursts” among adults with primary MDD ($N = 2,539$) was studied within the Collaborative Psychiatric Epidemiological Surveys ($N = 20,013$) ²⁸. Using generalized linear models, the study shows a prevalence estimate of any aggressive outbursts of 58.7%. The association of MDD with aggressive outbursts was independent of other psychiatric diagnoses. Aggressive outbursts were associated with greater severity and earlier age of onset for MDD. Moreover, positive associations emerged between the frequency of aggressive outbursts and some depressive symptoms, such as weight/appetite change, fatigue, recurrent thoughts of death. In addition, aggressive outbursts significantly increased the odds of a more severe functional impairment, suicidal ideation, suicide plan, and suicide attempts. As the authors comment, aggressive outbursts seem to be much more common than previously recognized among adults with MDD ²⁸.

The Authors of the previous study also reported interesting data about tonic irritability (i.e., irritable mood) and phasic irritability (i.e., aggressive outbursts) with respect to multiple dimensions of depression ²⁹. The study included participants ($N = 5,692$) from the National Comorbidity Survey - Replication (NCSR) part two, showing that both types of irritability were significantly associated with a greater risk for MDD diagnosis. More specifically, the weighted prevalence estimates for tonic and phasic irritability were 33.8% and 47.8%, respectively, in the overall sample, compared to 65.3% and 63.8% among adults with unipolar MDD. The prevalence of having both tonic and phasic irritability was 32.22% in the overall sample and 45.16% among adults with unipolar MDD. Both types of irritability were also significantly associated with a higher risk of having at least one depressive symptom, an early MDE onset, and an MDE chronicity. Both types of irritability were associated

with greater odds of specific depressive symptoms and were differentially related to distinct depressive symptom constellations. Moreover, phasic irritability was related only to severe depression. Lastly, both phasic and tonic irritability were associated with suicidal ideation, while only phasic irritability was associated with a suicide plan and attempt. Data from this study showed that phasic and tonic irritability are differentially related to almost all aspects of depression in adults. More specifically, tonic irritability (irritable mood) shows overall stronger associations with various depressive features, whereas phasic irritability (aggressive outburst) marked higher depressive severity.

Beyond community studies, the relationship between aggressivity and MDD has been evaluated in several clinical studies. A study reporting self-reported data from 282 psychiatric patients (ICD-10 diagnoses) affected by Alcohol Dependency, Schizophrenia or MDD, compared to healthy groups, revealed, as expected, that all three patient groups scored higher in the aggression questionnaires than the normal control group. Specifically, patients with MDD exhibited significantly higher externally directed aggression, reactive aggression, and irritability compared to controls ³⁰.

The presence of anger as a frequently observed feature of depression has been repeatedly reported by several authors. In the early seventieth of the last century Paykel proposed a classification of depression based upon clinical depiction which included the “Hostile depression” ³¹. Fava et al. ³² described in a subgroup of depressives who had not reported losses, an association between hostility and depression, whereas no such association was found in depressives who had reported losses. Subsequently, the same author ³³ described a series of cases in which patients presented with sudden “spells” of anger with physical features resembling panic attacks but lacking fear and anxiety. These spells or “attacks” of anger, generally experienced as uncharacteristic and inappropriate to the situations in which they occurred, responded to antidepressant treatment. The same group ³⁴ demonstrated, submitting 127 medication-free outpatients with MDD to a specific scale, that at baseline, 44% of the depressed outpatients reported anger attacks, showing also significantly higher scores on measures of anxiety, somatization, and state and trait hostility than did the subjects who did not exhibit such attacks. After treatment, there were significant reductions in these measures, and the anger attacks disappeared in the majority (71%) of the patients. Fava et al ³⁵ also developed an Anger Attacks Questionnaire designed to identify the presence of these attacks. Using this instrument, they found a prevalence of anger attacks in depressed patients of approximately 30% to 40%, reporting that attacks have disappeared in 53% to

71% of depressed patients treated with fluoxetine, sertraline, or imipramine.

More recently, a large clinical study regarding 3,800 individuals in charge of an outpatient service within a Hospital Department of Psychiatry in USA ³⁶ has evaluated severity of subjective anger and overt aggression within the past week for each patient, with odds ratios determined for each type of disorder. Multiple regression analyses were conducted to determine which diagnoses independently contributed to increased levels of anger and aggression. Almost 50% of the sample reported moderate-to-severe levels of current subjective anger, and more than 20% endorsed moderate-to-severe levels of current overt aggression, with a frequency of anger similar to the frequencies of depressed mood and psychic anxiety. The study also revealed that anger and aggression were higher in patients with major depressive disorder (Tab. I). According to the authors, these data confirmed the need for clinicians to be concerned with symptoms of anger and aggression even though the chief complaint is not immediately related to these disturbances.

An important contribution about aggression and depressive states has been given by a prospective, naturalistic investigation of patients with unipolar MDD, studied systematically at intake and during up to 31 years of follow-up, in the context of the National Institute of Mental Health Collaborative Depression Study ³⁷. Patients with unipolar MDE at intake (n = 536) were divided into those with and those without current comorbid overtly expressed irritability/anger. Overt irritability/anger was present in 292 of 536 participants with a unipolar MDE at study intake (54.5%) and was associated with a series of features such as higher depressive severity, longer duration of the index MDE, lower impulse control, more chronic and severe long-term course of illness, higher rates of lifetime comorbid substance

abuse, anxiety disorder, and antisocial personality disorders. Moreover, these patients showed a greater psychosocial impairment before intake and during follow-up, reduced life satisfaction, and a higher rate of bipolar II disorder in relatives. No association was found with increased suicidal ideation or behaviour. These results were not explained by comorbidity or other manic spectrum symptoms.

In the context of the Netherlands Study of Depression and Anxiety (NESDA), it has been examined to what extent depressive and anxiety disorders, relevant clinical correlates and sociodemographics determined the level of trait anger and the prevalence of recent anger attacks ³⁸. The study used the Spielberger Trait Anger Subscale and the Anger Attacks Questionnaire in patients with depressive (n = 204), anxiety (n = 288), comorbid (n = 222), and remitted disorders (n = 1,107), as well as in healthy controls (n = 470) based on DSM-IV criteria. Trait anger prevalence was 4% among controls, 19% for remitted patients, 29% for depressed, 31% for anxious and 43% for comorbid anxious-depressed patients. Anger attacks prevalence was 1.3 % among controls, 4.7% for remitted patients, 4.9% for depressed, 11.5% for anxious and 22.1% among comorbid anxious-depressed patients.

The association of self-reported symptoms of irritability with overt behaviour of anger attacks was tested in 293 patients who completed the Massachusetts General Hospital Anger Attacks questionnaire (n = 293) in the context of the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care Study ³⁹. Patients with current anger attacks (n = 109), compared to those without anger attacks at baseline (n = 184), had similar levels of depression but higher levels of irritability [effect size (d) = 0.80] and anxiety (d = 0.32). With acute-phase treatment, participants with anger attacks experienced a greater reduction in

TABLE I. Subjective anger and overt expression of anger among patients affected by Depressive Disorder.

| Patient Group (N) | Subjective Anger | Odds Ratio (95% CI) | Overt Anger | Odds Ratio (95% CI) |
|----------------------------------|------------------|---------------------|-------------|---------------------|
| Major depressive disorder (1598) | 28.8% | 2.9 (2.5 to 3.4) | 27.2% | 1.8 (1.6 to 2.1) |
| Dysthymia (302) | 19.2% | 1.0 (0.7 to 1.3) | 18.5% | 0.8 (0.6 to 1.1) |
| Bipolar I, depressed (53) | 34.0% | 2.2 (1.2 to 3.9) | 34.0% | 1.9 (1.1 to 3.4) |
| Bipolar II, depressed (95) | 28.4% | 1.7 (1.1 to 2.7) | 31.6% | 1.7 (1.1 to 2.7) |
| Any depressive disorder (1889) | 27.7% | 3.2 (2.7 to 3.8) | 26.6% | 1.9 (1.6 to 2.2) |

Modified from Genovese T, et al. 2017³⁶.

irritability ($p < 0.001$) but not in depression ($p = 0.813$) or anxiety ($p = 0.771$) as compared to those without anger attacks. Moreover, irritability levels at week 8 were higher in those with anger attacks ($d = 0.32$) than those without anger attacks. Similar results were found in participants with aggressive behaviours. The findings of this study support the hypothesis that the presence of anger attacks in outpatients with MDD may identify a sub-group of patients with persistently elevated irritability.

A German study⁴⁰ aiming to investigate the relationship between depression and aggression included 681 depressive and non-depressive subjects of the general population as well as 132 depressive patients who completed the Beck Depression Inventory-Revised (BDI-II) and the Short Questionnaire for Gathering Factors of Aggressiveness (K-FAF). Depressive patients and depressive subjects of the general population not only reported the highest levels of self-aggressiveness but also reached the highest scores on the scales of reactive and proactive aggression, indicating a high level of externalizing aggressiveness.

An Italian study designed to assess the relevance of anger, irritability, aggressiveness, hostility, and psychomotor activation in major depressive disorder evaluated 222 newly admitted consecutive outpatients with MDD without comorbid axis I or II DSM-IV disorder who had received no treatment with antidepressants in the preceding two months⁴¹. Patients were assessed with the SVARAD, a validated scale for the rapid assessment of the main psychopathological dimensions. Principal component analysis was performed on SVARAD items, obtaining a three-factor solution accounting for 47.4% of the total variance. The factors were interpreted as 'anger/irritability', 'depression', and 'anxiety', respectively. In particular, the anger/irritability dimension was clinically relevant in 23% of patients, with anger/aggressiveness as especially frequent (21.6%), whereas psychomotor activation was infrequent (0.9%). These findings reveal again the importance of deserving clinical attention to psychopathological dimensions other than depressed mood and anxiety, such as anger/irritability and hostility/aggression.

The unofficial and more general concept of depression with anger attacks or "Irritable-Hostile depression", mostly considered a particular form of unipolar (UP) disorder was further examined in a study including 348 bipolar disorder type II (BP-II) and 254 MDD outpatients, off psychoactive agents, including substances of abuse and without comorbidity with borderline personality disorder; Depressive mixed state (DMX) was defined in this study as a major depressive episode (MDE) plus three or more concurrent intra-depressive hypomanic symptoms, whether it occurred in BP-II or MDD⁴². This

study revealed that MDE with irritability was present in 59.7% of BP-II and in 37.4% of MDD ($p = 0.00001$). Logistic regression revealed a significant independent association between MDE irritability and DMX. Odds ratios of irritability for DMX were highest in the MDD group ($= 12.2$); for predicting DMX, irritability had the best psychometric profile of sensitivity of 66.3% and a specificity of 86.1% for this group as well. In synthesis, irritability is particularly evident in DMX, both in Bipolar and Unipolar Disorders. Although DMX is more frequently observed in BP, higher odds of irritability are more evident in unipolar MDE with mixed features.

Another study evaluated major depressive episodes in MDE patients with (MDE-A, $n = 399$) and without aggressiveness (MDE-N, $n = 2,412$) in the context of both BD and MDD⁴³. MDE-A group resulted more frequently associated with BD ($p < 0.001$), while aggressiveness was negatively correlated with unipolar depression ($p < 0.001$), with the variable most significantly associated with aggressiveness being the presence of DSM-5 mixed features ($p < 0.001$, OR = 3.815). Thus, aggressiveness also emerges as a feature mostly linked to Mixed Depressive Episodes, but only in the context of a BD.

In sum, a convergent series of data from community and clinical studies reveals that aggressiveness, in its various expressions, is a quite common but generally undervalued dimension in MDD. Irritability, one of the basic expressions of aggressivity, is probably more frequently linked to MDD episodes with mixed features.

Impulsivity and aggressivity in bipolar disorder

Impulsivity

BD, much like MDD, represents a heterogeneous and complex mental illness associated with a significant disease burden and a reduced lifespan^{44,45}. Impulsivity represents a prominent element in BD, with its measures appearing to fluctuate depending on the BD illness's severity and/or activity level. The evidence supporting the persistence of inter-episodic, persistent impulsivity is mixed, with some reports either finding no difference between euthymic BD patients as compared with controls and other lines of evidence suggesting persistent higher impulsivity measures between mood episodes and even among unaffected family members of BD-probands⁴⁶. Self-reported impulsivity has been described as an inheritable trait with an inheritance level estimated around 45-50% and proposed as a possible intermediate disease-associated endophenotype⁴⁷. The interpretation of the relevant literature appears particularly complex considering the abundant amount of available outcome measures, inconsisten-

cies in their use across different studies, and the tendency to report on a single measure type and refer to the results vaguely as impulsivity as a whole, but without acknowledging the inherent heterogeneity of the impulsivity construct (e.g. employing self-rated assessments as a stand-alone measure with no concomitant motor- or reflection-impulsivity assessment)⁴⁸. If possible, further compounding the issue in the overall assessment of the available evidence of impulsivity assessments applied to BD, is the possible influence of mood states⁴⁹ and co-morbid anxiety⁵⁰ on single outcome measures⁴⁹, especially when used in isolation^{46,47}. A sizeable body of literature investigated the presence of cognitive impairments in BD, suggesting the presence of a variable degree of impairment in several key cognitive domains. However, at this stage, no convincing evidence exists for a progressive cognitive dysfunction among people living with BD (pBD)⁵¹. Impairment in executive functions has been frequently reported, with verbal fluency, working memory, response inhibition, processing speed, verbal learning and attention among the areas reported to be most affected⁵¹. Disentangling the reciprocal interaction between impulsivity and neurocognition in the pBD subgroup with co-occurring cognitive impairment may represent a daunting task, especially considering the possible impact of cognitive impairment itself in shaping BD severity⁵⁰. An additional layer of complexity may be represented by the possible co-morbidity between BD and conditions known to be associated with impulsivity on their own. Among the others, Attention deficit hyperactivity disorder (ADHD)⁵² and Borderline Personality Disorder (BPD)^{53,54} have been reported to present significant levels of co-morbidity with BD in the relevant literature, with approximately 20% of BD patients having co-morbid ADHD, 10% of BD type I (BD I) and 20% of BD type II (BD II) also receiving a diagnosis of BPD⁵⁵. Among the possible distinguishing factors for BD in the differential diagnosis, classic BD features an episodic course, whilst ADHD and BPD tend to present more persistent symptoms, albeit the persistence of inter-episodic symptoms may be substantial in certain subgroups of pBD. Certain facets of impulsivity appear persistently elevated among pBD as compared with controls, but only on self-report measures and with no clear signs of behavioural measures of impulsivity⁵⁶. All these elements, taken together, further underscore the practical difficulties in differentiating the said conditions, prompting certain authors to ponder whether this ADHD-BD cluster may represent a unique condition with a distinct phenotype within the BD spectrum rather than co-morbidity between distinct conditions⁵². In a similar fashion, BPD and BD co-morbidity present a high level of impulsiveness, possibly moulding the overall prognosis⁵⁷ and leading to an apparent increased risk for

negative outcomes such as suicide attempts⁵⁴. A 2021 paper reported on the results of interviewing 517 outpatients and investigated BD/BPD co-morbidity impact compared with BD or BPD alone, poignantly concluding that BD/BPD co-morbidity was associated with more suicidality, more childhood traumas, more hospitalizations, higher unemployment, were more likely to receive disability allowances and presented higher comorbidity levels with anxiety disorders, substance use, other personality disorders, somatoform disorders along with a higher levels of psychopathology in first-degree relative psychopathology⁵⁷. Notably, in this sample the rate for any impulse disorder was also higher among BD/BPD as compared with any disorder in isolation⁵⁷. An additional report comprising data collected from a one-year follow-up study comprising 120 BD subjects, concluded that BIS-11-defined impulsivity appeared to be significantly associated with BD severity, specifically with BIS-11 attention-subscale⁵⁸. These findings appear in line with previous reports, suggesting that indeed higher attentional deficits may be associated with a higher risk of developing hypomania or manic episodes. Ng et al.⁵⁹, reported that in a sample of 14-19 years-old subjects comprising 163 individuals with high reward sensitivity and 114 individuals with moderate reward sensitivity according to the Behavioral Inhibition System/ Behavioral Activation Scale (BIS/BAS), higher impulsivity measures both on self-reports (i.e., BAS-11) and on behavior tasks (i.e. Balloon Analog Risk Task - BART) appeared significantly associated with a higher risk of subsequent mania or hypomania during an average of 2.68 years follow-up. Further underscoring the possible role of impulsivity assessment as a trans-diagnostic dimension underlying phenotypes with higher clinical burden of disease in BD, an additional paper on adult pBD⁶⁰ reported that higher levels of self-rated ADHD-symptoms severity in childhood scored retrospectively according to the Wender Utah Rating Scale (WURS) were associated with higher BD severity in adulthood, both in terms of co-morbidity and earlier age of onset. Interestingly, in the latter study, the variance in the age of onset was reported to be associated with the WURS-defined factors of impulsivity and temper rather than misdiagnosed ADHD or juvenile mania⁶⁰.

Aggressivity

Aggressivity has been extensively studied in a variety of different contexts, considering the overall interest devoted to this phenomenon from a political, societal and neurobiological point of view⁶¹. As reported in previous sections of the present manuscript, different types of aggressive behaviours have indeed been described, and in specific instances, these may serve specific purposes rather than merely represent the by-product of self-control failures⁶². A more nuanced discussion regard-

ing the role of mental illness as a responsivity factor for criminal behaviour is beyond the scope of the present manuscript and has been discussed elsewhere^{63,64}. The complex interconnection between impulsivity and aggression has been extensively studied in the context of BD, albeit it might not necessarily encompass the diverse nature of aggressiveness even among patient populations. The frequent lack of external validation of self-reported measures of aggressivity, the lack of differentiation between self- and hetero-aggressiveness, and the heterogeneity in both aggression and impulsivity measures employed in the relevant literature may add a further layer of complexity in interpreting the available data⁶⁵. A growing body of evidence suggests that, albeit often connected, impulsivity and aggressiveness represent distinct constructs⁶⁵. Several paradigms have been developed to try and explain the impulsivity-aggressiveness association in pBD⁶⁵. Drachman et al.⁶⁵ reported higher levels of aggression and impulsivity in the BD subgroup in a sample comprising 38 BD subjects and 29 healthy controls, as expected. Significantly, the study reported on the possible existence of distinct brain-based domains underlying both aggressivity and impulsiveness. In line with the relevant literature, the vast majority of aggressive behaviors were reportedly self-directed, as was the case for this report⁶⁵. Molz et al.⁶⁶ reported in a longitudinal sample comprising 104 BD and 96 healthy controls followed up to 4.5 years higher levels of impulsivity traits and aggression as defined according to the Aggression Questionnaire and Impulsive Nonconformity Scale, respectively. Arguably, pertinent to the discussion of aggressive behaviors in BD is the possible co-morbidity with Intermittent explosive disorder (IED). IED is defined as the repeated occurrence of aggressive behaviors against persons or property as a response to often minor environmental stimuli and has been reported to frequently co-occur with BD, MDD, and post-traumatic stress disorder (PTSD, among others⁶⁷⁻⁶⁹. As was the case for other co-morbid conditions previously mentioned, IED- BD co-morbidity is associated with high levels of suicidality and, in general, a higher burden of psychopathology than any condition considered singularly. Interestingly, the level of co-morbidity and the inherent difficulties in distinguishing IED from BD disorder has led some authors to consider a lifetime history of BD as an automatic exclusion criterion for IED⁶⁹. The inherent difficulties in identifying aggressive behaviors related to high impulsivity traits in isolated BD vs BD-IED may render the distinction a daunting task and arguably a sophism with no clear benefits, as high impulsivity may occur in both conditions and represent a significant symptomatic overlap. Ng et al.⁷⁰ reported that in a sample of 120 young BD subjects followed for an average of 3.5 years,

higher self-reported physical and verbal aggression levels were associated with a longer time to depressive episodes as compared with the remaining BD sample. In summary, the evidence described here points to shared phenotypes that translate in the empiric observation for transdiagnostic behavioral patterns that may be better accounted for in a dimensional context rather than being adapted into theoretically distinct categories. In this context, the subgroup of pBD featuring impulsivity and aggressive behaviors may rightfully represent distinct subgroups, possibly requiring specific care paradigms and with distinct prognostic trajectories^{71,72}.

Biological correlates for aggressiveness

A discrete amount of literature investigated the possible role of serotonin (5-HT) and other tryptophan (TRP) metabolites in impulsivity and aggressiveness. Early findings focused on its role in self-aggressive behaviours, but accumulating evidence suggests that this may be a feature of hetero-aggression as well, albeit the evidence is mixed on this regard^{61,73,74}. A hypothesis for low-serotonin levels associated with aggressive behaviours largely derived from early reports suggesting a very large effect size for an inverse association of aggressive scores and 5-HIAA ($r = -0.78$), which has since been questioned based on the results of a recent meta-analysis suggesting a more modest association ($r = -0.12$)⁷⁵. A past report⁷³ comprising serum measures for 361 male inmates found that compared to non-aggressive inmates, lower TRP and kynurenin levels, along with higher levels of 5-HT and 5-HT/TRP ratio, were more common among aggressive inmates. The interpretation of research describing peripherally-assessed TRP metabolite levels in the absence of concomitant central correlate (e.g., CSF samples) may be particularly complex and has been extensively reviewed elsewhere, underscoring several limitations in the relevant literature, such as the disease activity levels, the type of examined blood sample (i.e., serum vs plasma) and discrete heterogeneity in the employed techniques for the analysis⁷⁶. The implications for the literature investigating TRP metabolite's role in impulsivity and aggression in mood disorders are also profound and deserve accurate consideration. More recently, the concomitant analysis of neuroimaging data and serotonin receptor genotyping represent promising complementary analyses and have resulted in a renewed interest in the TRP metabolite role in impulsivity and aggression as a possible modulatory factor⁷⁵. Doyle et al.⁷⁷ reported on the suggestive linkage on chromosomal regions 1p21.1, 6p21.3, and 8q21.13 with attentional and aggressive phenotype of youth with BD. A study describing the results of Genome-Wide Association Study (GWAS) on 123,509-133,517 subjects of Caucasian origin from the 23andMe re-

search sample⁷⁸, found a significant association between BIS and UPPS-P impulsive Personality Scale for the CADM-2 gene. Interestingly, the study authors replicated these findings also in the phenome-wide study (PheWAS) comprising hundreds of thousands of participants of differing ancestry, also finding an association for risky behaviors, cognition and BMI. A mouse translational model also appears to corroborate some of the findings for the human model, including impulsivity, BMI and cognition⁷⁸. Despite initial promises for the association of cholesterol with impulsivity and aggression, in a study reporting on a mixed sample of schizophrenia and BD subjects numbering 1001 subjects, there was no association between Barratt Impulsive Scale-defined impulsivity, Positive and Negative Syndrome scale-defined Excitement with cholesterol levels⁷⁹. In line with empirical observation for a significant BPD-BD co-morbidity, a GWAS study reported a significant shared genetic overlap for genetic risk for BD, along with MDD and schizophrenia⁸⁰. A further report in adolescent BD suggests under the frustrating non-reward task, an inverse level of activity in the left subgenual anterior cingulate gyrus right amygdala, the left Broadmann area 10 and right thalamus in association with aggression defined according to the Brief Rating of Aggression by Children and Adolescents (BRACHA)⁸¹. In the same report, a significant association for BRACHA-defined aggression was also found for four tested TNF-genes⁸¹.

Conclusions

Accruing evidence points to the existence of impulsivity and aggressiveness in BD as distinct albeit related constructs. The possible applications of the recent advancements in translational research for treatment and prognostic prediction in mood disorders appear particularly promising. The implications for clinical practice would be to consider aggressive impulsiveness dimensionally and possibly as an element capable of shaping the clinical phenotype and, as such, relevant for developing tailored clinical treatment paradigms at the singular patient level.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Author's contribution

BC and FP performed the initial draft of the present manuscript and overviewed the development of the review; MM performed an overview of the literature with specific attention to the biological basis for impulsivity and aggressiveness; PP analysed the relevant literature with a focus on bipolar disorder.

Ethical consideration

Not applicable.

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