

Research Article

Panic-agoraphobic Spectrum Symptoms are Associated with Impulsivity in Bipolar Disorder

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Background: Bipolar-panic comorbidity seems to configure a specific subgroup of patients from a clinical and genetic point of view. Impulsivity is a core feature of Bipolar Disorder (BD) being a prominent component of mania and mixed mania. The aim of this study is to investigate the relationship between impulsivity and panic disorder comorbidity or panic spectrum symptoms in patients with BD (BDI and II) and MDD (major depressive disorder).

Method: 247 BDI, BDII and MDD euthymic patients are assessed with Structured Clinical Interview Patients Version (SCID-P) for current and lifetime Axis I comorbidity, Structured Clinical Interview for Mood Spectrum, Self-Related (MOOD-SR) and the Structured Clinical Interview for Panic-Agoraphobic Spectrum, Self-Related (PAS-SR). With the intention to investigate impulsivity in our study sample, we rationally defined an "Impulsivity dimension" derived from the MOODS-SR shaped on the Barratt Impulsiveness Scale items (BIS-11).

Results: There was no between-groups difference in impulsivity scores in relationship to the presence/absence of panic disorder comorbidity as assessed with SCID-I. However, patients with subthreshold panic spectrum symptoms showed higher impulsiveness scores. Indeed, a backward stepwise logistic regression in bipolar patients with PAS explained score statistically much higher for impulsivity (pas +6.09 vs pas - 3.88 p<.001) and the difference is statistically significant stratifying for BD. A stepwise linear regression, corrected by age and gender, displayed significantly statistical correlation with impulsivity score and PAS total score (beta=0.418). A backward stepwise logistic regression explained an association between impulsivity scores and PAS (defined by cutoff 35) (OR=1.210).

Conclusion: In patients with BD, impulsivity showed to be related to subthreshold panic symptoms further supporting the need to identify a specific endophenotype among bipolar disorder patients. Further neurobiologies studies are needed to elucidate the implications of and reasons for this association.

Keywords: Bipolar disorder; Panic disorder; Impulsivity; Anxiety

Introduction

Although impulsivity is directly mentioned among the DSM-IV diagnostic criteria for several disorders and is implied in the criteria for others, until recently, little work has been done to clarify the role of impulsivity in psychiatric illnesses [1].

Impulsivity has been variously defined by different authors as a swift action without forethought or conscious judgment [2] as a behavior without adequate thought [3] or as the tendency to act with less forethought than do most individuals of equal ability and knowledge [4]. In our opinion, the best definition has been suggested by Moeller et al [1]. Who put the attention on the predisposition to have rapid and unplanned reactions to internal and external stimuli without regard to the negative consequences of these actions to the impulsive individual or others.

Impulsivity represents a core feature of Bipolar Disorder (BD) [1,5-7] being a prominent component of mania and mixed mania [8-10]. Still, impulsivity seems also to contribute to BD complications, such as suicide [11-14] and substance abuse [1,15-17].

It has been traditionally stated that impulsivity displays a negative relationship with anxiety [18,19]. This was mainly based on the assumption that anxiety alerts the individual to potential danger, and operates to inhibit behavior under conditions of heightened threat [20]. In reality, epidemiological data revealed high rates of co morbidity between anxiety disorders and impulse control disorders [21-23]. Of note, BD patients with a co morbid anxiety disorder seem to display significant higher levels of impulsivity when compared to patients without an anxiety disorder [22,24,25]. Moreover, the level of depression is significant in the intensity of impulsivity and anxiety, and the presence of anxiety, either as a co morbid disorder or as current anxiety symptoms, is associated with higher impulsivity in subjects with either BD or MDD [23]. It is, therefore, evident that the interplay between impulsivity and anxiety co morbidity in patients with BD need to be carefully noted and further investigated in the light of implemented treatment strategies and for a better clinical definition. In fact, it has been estimated that up to 52% of patients with BD can be diagnosed as having a co-occurring anxiety disorder at some point in their lives and up to 30.5% as having a current anxiety

disorder [26]. In particular, epidemiological data demonstrated that panic disorder occurs frequently in BD and in some studies such a co morbidity seems to represent the rule rather than the exception [27,28]. Panic disorder co morbidity is BD is associated with poor response to treatment, earlier onset of BD, elevated rates of comorbid psychopathology, greater levels of depression, more suicidal ideation and increased familial risk of affective disorder [29,30]. These data altogether suggest that bipolar panic comorbidity constitutes a unique entity from a clinical, neurobiological and genetic point of view [31,32]. Moreover, euthymic BD patients with particular addictive and anxiety comorbid disorders have large number of depressive episodes, rapid cycling, mood instability, and high risk of suicidal behavior [14]. Thus, the aim of our study is to investigate the relationship between impulsivity, panic disorder comorbidity, either threshold and sub threshold panic symptoms in patients with BD. Subject were assessed by Panic Agoraphobic Spectrum Self-Report (PAS-SR) in order to investigate typical and atypical lifetime symptoms, temperament characteristics and sub threshold symptoms correlated to panic disorder. Moreover we use a cutoff for PAS-SR (35), to split the sample, like a valid clinical indicator [30].

Materials And Methods

Participants

Data were drawn from a multicenter Italian study aimed to evaluate clinical, biological and psychosocial features of BD-II and to compare them with patients with BD-I and Major Depressive Disorder (MDD). To be enrolled, patients ha to fulfill the following criteria: (1) DSM-IV criteria for BD-I, BD-II, or UD, confirmed by the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-I) [33]; (2) be in a euthymic state for least 2 months, confirmed by HAM-D [34] total score <8 and YMRS [35] <6; (3) age between 18 and 60 years; (4) be willing to provide a written consent to undergo the experimental procedures; (5) absence of brain and/or severe physical illnesses. The protocol was reviewed and approved by the local ethic committee of the five Italian centers.

Measures and instruments

All patients were assessed with the SCID-I [33] for current and lifetime Axis I comorbidity, the Structured Clinical Interview for Mood Spectrum (MOODS-SR) [36] and the Structured Clinical Interview for Panic-Agoraphobic Spectrum (SCI-PAS-SR) [37,38]. In an early phase of the study, inter-rater reliability of Axis-I diagnoses was ascertained, showing a good reliability with a Cohen kappa coefficient of 0.89.

Structured clinical interview for mood spectrum (MOOD-SR): The MOODS-SR questionnaire, developed in English and Italian, is focused on the presence of manic and depressive symptoms, traits and lifestyles that may characterize the ‘temperamental’ affective dysregulation that make up both fully syndromal and sub-threshold mood disturbances. The latter include symptoms that are either isolated or clustered in time and temperamental traits that are present throughout individual’s lifetime. The MOODS-SR consists of 161 items coded as present or absent for one or more periods of at least 3-5 days in the lifetime. It proved to have sound psychometric properties with a good internal consistency (0.79-0.92) and high test-retest reliability ($r = 0.93-0.94$) [36].

Structured clinical interview for panic-agoraphobic spectrum (PAS-SR): The PAS-SR was developed in the framework of the Spectrum Project [39] in order to identify a number of atypical symptoms that patients with panic disorder may manifest and are not included in the criteria set, and that patients with other diagnoses sometimes may show without meeting criteria for panic disorder [29,38,40,41]. The PAS-SR consists of 114 items coded as present or absent and proved to have sound psychometric properties with a good internal consistency and test-retest reliability ($r = 0.65-0.89$) [38,39].

Moreover the panic-agoraphobic spectrum symptom threshold was defined to lie somewhere below the threshold for diagnosable panic disorder. A reliable estimate of the optimal threshold for panic-agoraphobic symptoms was obtained by maximizing the sensitivity while keeping at an acceptable level, and the optimal was obtained at the score 35 [30,42]. This cut-off is used like a valid clinical indicator [30,42].

Impulsivity dimension: We had the intention to investigate impulsivity in our study sample, than we rationally defined an “impulsivity dimension” based on Barratt Impulsiveness Scale (BIS-11). The “impulsivity dimension” derived from MOOD-SR items shaped on the BIS-11 and we took our stand on the Barratt et colleagues impulsivity thinking to build this dimension. In fact, we choosed 12 items of MOOD-SR very similar to some BIS-11 items (see below MOOD-SR and BIS-11 comparative table), and we essentially valued motor-impulsiveness and non-planning impulsiveness items factor structure [43] with this rationally design (Table 1). In literature other authors [44] had rationally constructed by reviewing DSM-III-R personality disorder criteria, affective instability score and identifying items that explicitly referenced a predisposition toward affective lability or instability, and did the same for measuring neuroticism using only the 48-item from NEO Personality Inventory.

Moreover, another reason that we alleged and used this impulsivity dimension, is that BIS-11 and MOOD-SR were lifetime scale, that valued symptoms, behavior and sintomatological features, with a difference in the scoring where MOOD-SR was dicotomic and BIS was nominal (categorical).

Statistical analysis

The frequency of categorical variables was compared using the Chi-Square test. The independent-sample *t*-test was used to compare continuous demographic and clinical variables as well as impulsivity scores. Associations were investigated using Pearson’s bivariate correlation procedures. A backward stepwise logistic regression analysis was applied to identify relevant dimensions related to impulsivity. A stepwise linear regression was used to analyze the association of impulsivity with gender and age distribution. All statistical analyses were 2-sided with an alpha error set at 0.05 and were conducted using SPSS, version 18.

Results

Characteristics of the sample

The study sample includes a total of 247 patients with an axis I diagnosis, issued in 93 (37.7%) bipolar I disorder (BDI), 77 (31.2%) bipolar II disorder (BDII) and 77 (31.2%) Major Depressive Disorder (MDD). The sample is subdivided in 154 (62.3%) female and 93 (37.7%) male. Gender distribution differed between groups: male 44 (47.3%)

Table 1: Comparative Table.

BARRATT IMPULSIVENESS SCALE 11	
2	I do things without thinking
3	I make-up my mind quickly
6	I have "racing" thoughts
16	I change jobs
18	I get easily bored when solving thought problems
21	I am a steady thinker
22	I change residences
24	I change hobbies
25	I can only think about one problem at time
MOOD-SR-lifetime	
5	...you felt very bored?
35	...you found it very pleasurable and easy to buy things, even things you didn't need?
36	...you gave lost of presents, even when you really couldn't afford then?
44	...you were full of plants or got involved in many projects, jumping from one activity to another?
45	...you had difficulty saying "no" to business or social opportunities, even when you knew you did not have time for them?
46	...you frequently change: job, place of residence, friends, favorite sports or hobbies?
52	...you had trouble controlling your temper, for example you felt that you really needed to even the score or you found yourself shouting at people or starting arguments or fights even over minor matters?
72	...you felt that your ideas came and went unusually easily, as if your thoughts were racing?
125	...you were (or other people judged you to be) irresponsible?
126	...you made very important decisions (such as selling or buying a house or car, or changing jobs) extremely rapidly?
127	...you did things such as: spending too much money, driving recklessly or speeding, making foolish business decision?
128	...you tended ignore everyday rules and social etiquette or engaged in illegal activities?

and female 49 (52.7%) in BDI; female 46 (59.7%) and male 31 (40.3%) in BDII; female 59 (76.6%) and male 18 (23.4%) in MDD. The age (mean and standard deviation) is in BDI (43,11± 12,62), in BDII (49,17±10,99) and in MDD (51,46±12,13) respectively. The marital status, education and work status statistics followed data displayed in literature (Demographic Characteristics are explained in Table 2).

Impulsivity and panic disorder axis I diagnosis: Comorbidity for panic disorder was arrange around BDI (11.8%), BDII 15 (19.5%) and MDD 23 (29.9%). There are not significant differences in relationship with impulsivity correlated with panic disorder. In particular Bipolar (BD) and Unipolar (UD) patients with or without panic disorder present negative correlation with impulsivity (BD with PD $p = .089$; BD without PD $p = .082$; UD with PD $p = .190$; UD without PD $p = .182$). The same if we observe the sample subdivided by diagnosis in BDI (BDI with PD $p = .387$; BDI without PD $p = .320$), BDII (BDII with PD $p = .158$; BDII without PD $p = .172$) and MDD (MDD with PD $p = .190$; MDD without PD $p = .182$) (Table 3).

Impulsivity and PAS-SR (cutoff 35): There are a positive correlation between BD, impulsivity and positive PAS. In particular BD patients with or without PAS cutoff positive, irrespective UD patients, present a significant statistical correlation with impulsivity. Finally, in the statistical analysis, in the sample of BD and UD patients with or without PAS cutoff 35 we included presence or absence of PD. We observe that impulsivity was linked only to PAS with a positive correlation with BD patients, irrespective UD patients (Table 5).

Impulsivity and PAS-SR: Irrespective of axis I diagnosis, we

found a significantly statistical correlation between impulsivity dimension and PAS-SR domains. By diagnosis we found in the different bipolar I disorder, bipolar II disorder and MDD groups a significantly different correlation with PAS dimension (Table 4). A backward stepwise logistic regression in bipolar patients with PAS explain score statistically much higher for impulsivity (pas +6.09 vs pas - 3.88 $p < .001$) and the difference is statistically significant stratifying for BD. A stepwise linear regression, corrected by age and gender, displayed significantly statistical correlation with impulsivity

Table 2: Demographic characteristics of the sample (n = 247).

	BD n = 170		MDD n = 77
	BD-I n = 93	BD-II n = 77	
Age, mean (SD)	43,11± 12,62	49,17±10,99	51,46±12,13
Gender			
Male	44	31	18
Female	49	46	59
Marital status (%)			
Married	32	33	41
Separated/divorced	15	12	11
Never married	43	31	21
Widowed	3	1	4
Education (%)			
Less than 8 th grade	7	10	21
9 th to 11 th grade	26	14	17
High school diploma	38	28	22
University degree	17	22	15
Work status (%)			
Employed	53	46	39
Unemployed	27	21	23
Retired	13	10	15

Table 3: BDI, BDII and MDD correlation with impulsivity and Panic Disorder.

	<i>Impulsivity</i>					
	With PD			Without PD		
	media	st.dev.	P	Media	st.dev.	p
BD I	6.3636	4.71747	.387	5.0244	4.10051	.320
BD II	6.8667	3.64234	.158	5.3065	3.99421	.172
MDD	3.9130	2.93742	.190	2.9444	2.87091	.182
**p<0.01 *p<0.05						

Table 4: Impulsivity dimension and PAS-SR domains.

PAS dimension	BD I	BD II	MDD
<i>Separation sensitivity</i>	.336**	.296**	.264*
<i>Typical and atypical panic-like symptoms</i>	.458**	.279*	.251*
<i>Stress sensitivity</i>	.375**	.188	.274*
<i>Substance and medication sensitivity</i>	.364**	.343**	.287*
<i>Anxious expectation</i>	.270*	.285*	.302**
<i>Typical and atypical agoraphobia</i>	.227*	.194	.307**
<i>Illness phobia and hypochondriasis</i>	.204	.182	.266*
<i>Reassurance orientation</i>	.531**	.340**	.258*
<i>PAS Total</i>	.465**	.359**	.345**
** p< 0.01 * p< 0.05			

Table 5: BDI, BDII and MDD correlation with impulsivity and PAS cutoff 35.

	<i>Impulsivity</i>					
	PAScut35 +			PAScut35 -		
	Media	st.dev.	p	Media	st.dev.	p
BD I	7.4231	4.50931	.004	4.4154	3.72446	.002
BD II	7.2813	4.10534	.003	4.5227	3.38594	.002
MDD	4.0000	2.89015	.034	2.5952	2.79424	.034
**p<0.01 *p<0.05						

score and PAS-SR by cut-off 35 (OR=1.210). Finally seems to be an evident correlation between subthreshold anxiety (defined with PAS-SR cut-off 35) and impulsivity in mood disorder, especially in bipolar disorder with a score statistically much higher for impulsivity. Panic disorder diagnosis seems to be not correlate with impulsivity in mood disorders.

Discussion and Conclusion

Impulsivity is an individual's primal behaviour [45,46] and seems to be an essential part of control disruptive disorders [47] substance abuse [15] personality disorders [48] aggressive behaviours [49,50] bipolar disorder [51] suicidal behaviour [52] and some other potential violent and explosive behaviours [53]. Impulsivity is the rule and not the exception, like in our research, in BD and represents a core feature of BD [1,5,7,54] being a prominent component of mania and mixed mania [9,10] Still, impulsivity seems also to contribute to BD complications, such as suicide [11-13] and substance abuse [1,15-17]. Impulsivity displays a positive relationship with anxiety [24,25,55], impulsivity could be a stable trait in euthymic BD and a better trait impulse control may be associated with better treatment responsiveness [55-58]. It has been traditionally stated that impulsivity displays a negative relationship with anxiety [18,19] and epidemiological data revealed high rates of comorbidity between

anxiety disorders and impulse control disorders [21,22]. Of note, BD patients with a comorbid anxiety disorder seem to display significant higher levels of impulsivity when compared to patients without an anxiety disorder [22]. Moreover, the level of depression is significant in the intensity of impulsivity and anxiety, and the presence of anxiety, either as a comorbid disorder or as current anxiety symptoms, is associated with higher impulsivity in subjects with either BD or MDD [23,54]. In particular, epidemiological data demonstrated that panic disorder occurs frequently in BD and in some studies such a comorbidity seems to represent the rule rather than the exception [27,28]. Panic disorder comorbidity is BD is associated with poor response to treatment, earlier onset of BD, elevated rates of comorbid psychopathology, greater levels of depression, more suicidal ideation and increased familial risk of affective disorder [29,30]. Our data suggest not only that bipolar panic comorbidity but also that subthreshold panic symptoms in BD patients, constitutes a unique entity from a clinical, neurobiological and genetic point of view [31,32]. Moreover, euthymic BD patients with particular addictive and anxiety comorbid disorders have large number of depressive episodes, rapid cycling, mood instability, and high risk of suicidal behaviour [14].

Anxiety comorbidity and impulsivity

To our knowledge the majority of the literature study pay attention on mood disorder sample (bipolar disorder and major depressive disorder), especially to suicide-aggressive behaviours [59-62], nevertheless without a significant correlation to anxiety comorbidity.

Into the literature, the correlation of anxiety comorbidity and impulsivity in a sample of bipolar disorder is investigate by the single article of Taylor et al [22], in which the confirmatory regression analyses controlling for age, gender, current substance use disorder status, and presence or absence of a current mood episode entered together, all anxiety-related measures continued to provide unique significant prediction of the BIS total score (b range = .23-3.18, t range = 2.18-4.03, all p < .05). None of the added covariates, however, were significantly associated with the BIS total score.

It has been traditionally stated that impulsivity displays a negative relationship with anxiety [18,19]. This was mainly based on the assumption that anxiety alerts the individual to potential danger, and operates to inhibit behavior under conditions of heightened threat [20]. In reality, epidemiological data revealed high rates of comorbidity between anxiety disorders and impulse control disorders [21,22]. Moreover patients with impulse control disorders explain more anxiety arousal and tension before to commit impulsive acts [5], and this suggest a direct link between anxiety and impulsivity in bipolar disorder. Of note, BD patients with a comorbid anxiety disorder seem to display significant higher levels of impulsivity when compared to patients without an anxiety disorder [22].

Impulsivity and polarity of affective state

Euthymic bipolar patients express trait impulsivity at higher levels than healthy individuals [51], but they do not differ from manic bipolar patients [63]. Manic and eutimic bipolar patients present higher impulsivity level than healthy controls at BIS-11 factors: 'attention', 'motor' e 'non planning impulsiveness' [16,51,63,64].

Although anxiety disorder comorbidity may be critical for identifying high-risk bipolar patients, many important, well-designed studies of Suicidal Ideation and Suicidal Attempts in bipolar disorder have not examined the relationship of anxiety comorbidity with SA and SI [59-62].

By the use of MOOD-SR lifetime, and the rational creation of this impulsivity dimension, we can confirm that impulsivity is a stable component in mood disorders beyond illness episodes (manic, depressive and mixed state). In bipolar patients impulsivity seems to be much higher than depressive patients [51,63,64] and important during the illness episodes but also during the eutimic phase of the illness [1,51,63]. Aggressive behaviors and impulsive acts are related to bipolar manic state [65]. These data suggest that, in bipolar disorder, impulsivity has both state- and trait- dependent components, and is present irrespective of illness phase [51,63]. These remarks highlight two important reports: a) impulsivity is independent of illness phase; b) the association between impulsivity and bipolar disorder is a stable component during eutimic state, and this suggests that impulsivity is an independent psychopathological dimension from illness course and mood disorder clinical symptoms; c) impulsivity could underlie a specific clinical characteristic and illness bipolar course with a specific neurobiological mechanism [51,66,67]. Bipolar- impulsivity connection should be due to continuous mood fluctuations, in particular to manic phase [1,16,63,68] with a key role during suicidality in greater depressive episodes [39]. Second this could be an independent feature correlated to noradrenergic function in bipolar disorder [69,70] that is higher during manic episodes [66,71], and settles specific mood disorder endophenotypes [51,67].

Both possibilities are important to a better comprehension of bipolar disorder [51,63]. These possibilities should be important to a better understanding for bipolar disorder [51,63] and impulsivity could shape course and presentation of bipolar disorder. Moreover trait impulsivity seems to contribute to less therapeutic compliance and worse outcome [64].

Impulsivity and panic-agoraphobic spectrum

The panic-agoraphobic spectrum focused on its importance in identifying phenotypes of depressed patients who might present differently and respond differently to treatment. In such a situation, the authors consider identification of spectrum symptoms especially important because they may occur in the absence of diagnosable PD and still define an important depressive phenotype [30]. In the clinical practice, the spectrum model is extremely useful, even at the light of previous studies [72,73] thought some features, like affective instability and anxiety disorder comorbidity in bipolar patients, show complex clinical cases with major severity and worst course [74,75].

Moreover clinically significant lifetime panic spectrum was associated with female sex, higher levels of depression, a greater risk of suicidality, and a much longer time to remission of the index mood episode [30]. The spectrum approach, however, was developed to provide a more dimensional assessment of underlying symptom constellations. Categorical classification of panic disorder often fails to capture the broad array of atypical symptoms and related, yet enduring, temperamental features that can be associated with this core condition. In contrast, the PAS-SR casts a "wide net" to capture the lifetime experience of both classic panic symptoms as

well as related, yet subtle, manifestations of this core condition [30]. This may be advantageous, given the contention of Akiskal, Savino and others, that the affective instability and common anxiety-mood comorbidities of patients with BP disorder are often misdiagnosed as Axis II personality disorders, such as borderline personality disorder [30].

Moreover the assessment of a broad range of panic features (in particular atypical symptoms) than those represented by the DSM-IV criteria for panic disorder, seems to be an indicator of impulsive behaviours in bipolar disorder.

These represent a crucial point not only in mixed and depressed patients also too in bipolar eutimic patients where trait impulsivity is higher than healthy individuals [51].

Our clinical experience suggests that patients who are more sensitive to medical reassurance are generally those at the onset of the disorder, who present with a limited number of symptoms and are mostly concerned about an underlying physical illness not yet identified. These patients tend to ask repeatedly for lab tests or visits [76].

In our sample, bipolar I and II eutimic patients explain impulsivity correlated with reassurance orientation, substance and medication sensitivity and panic-like symptoms. Indeed impulsivity dimension we look into BIS-11 order factor motor impulsiveness and non-planning impulsiveness, and this would be interesting because it identifies a specific endophenotype among bipolar disorder patients "that tested themselves in dangerous situations", "that are more impulsive to reduce anxiety symptoms".

Limits of our study are: 1) only a 19.8% (49 patients of the total, 11 bipolar I, 15 bipolar II and 23 unipolar) of the sample show a panic disorder comorbidity following DSM-IV criteria, and in our knowledge is lower than literature data [more than half (51.2%) of patients with BD were identified as having a co-occurring anxiety disorder at some point in their lifetime, while 30.5% were diagnosed as having a current anxiety disorder [26]; 2) The impulsivity dimension used here was rationally constructed by reviewing MOOD-SR items based on items of Barratt Impulsiveness Scale (BIS-11) (Table 3). Between this dimension we essentially checked on motor-impulsiveness and non-planning impulsiveness order factors in the BIS-11 [43]; 3) We don't examine axis II comorbidity, because our intent was to study trait impulsivity in eutimic bipolar patients.; 4) we corroborate the conclusions of Taylor et al., [22], and we overcome a limit of this previous study, to be more precise the low size of bipolar patients, the lack of unipolar patients inside the sample; 5) we don't examine substance and alcohol abuse disorders, and suicidality wherefore the lower percent of substance/alcohol abuse disorders, and aggressive behaviours; 6) we don't examine the axis II disorder comorbidity; 7) next our proposal would be to value the correlations between BIS-11 and impulsivity dimension in a subsample of bipolar patients, to confirm internal validity of impulsivity dimension.

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