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IMPULSIVITY
IN ANXIETY DISORDERS

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SUMMARY

1. INTRODUCTION

1.1 Definition of impulsivity

1.2 Impulsivity in a psychiatric perspective

1.3 Impulsivity in a neurobiological and genetic perspective

1.4 Assessment tools
   1.4.1 Psychometric tools
   1.4.2 Behavioural tests

2. THE ROLE OF IMPULSIVITY IN MOOD AND ANXIETY DISORDERS

2.1 The role of impulsivity in Mood Disorders

2.2 The role of impulsivity in Anxiety Disorders
   2.2.1 Impulsivity in Panic Disorder
   2.2.2 Impulsivity in Generalized Anxiety Disorder
   2.2.3 Impulsivity in Social Anxiety Disorder
   2.2.4 Impulsivity in Obsessive-Compulsive Disorder

3. AIMS OF THE RESEARCH

4. METHOD

4.1 Evaluation procedure

5. RESULTS AND DISCUSSIONS

5.1 RESULTS AND DISCUSSION FOR HYPOTHESIS A
   5.1.1 Clinical sample and control subjects
   5.1.2 Statistical Analysis
   5.1.3 Demographic Characteristics
   5.1.4 Diagnostic distribution, comorbidity and treatment
   5.1.5 Symptomatological and personological evaluation
   5.1.6 Impulsivity assessment
   5.1.7. Discussion
5.2 RESULTS AND DISCUSSION FOR HYPOTHESIS B 67
  5.2.1 Clinical sample and control subjects 67
  5.2.2 Statistical Analysis 67
  5.2.3 Demographic Characteristics 68
  5.2.4 Symptomatological and personological evaluation 68
  5.2.5 Impulsivity assessment 69
  5.2.6 Discussion 71

5.3 RESULTS AND DISCUSSION FOR HYPOTHESIS C 76
  5.3.1 Clinical sample 76
  5.3.2 Statistical Analysis 76
  5.3.3 Diagnostic distribution and comorbidity 77
  5.3.4 Comparison between patients with anxiety disorders with and without cyclothymia 77
  5.3.5 Correlations between affective temperaments, mood symptoms and impulsivity 78
  5.3.6 Discussion 79

5.4 RESULTS AND DISCUSSION FOR HYPOTHESIS D 87
  5.4.1 Clinical sample and control subjects 87
  5.4.2 Statistical Analysis 87
  5.4.3 Demographic Characteristics and Diagnostic distribution 88
  5.4.4 Symptomatological, temperamental and personality traits evaluation 89
  5.4.5 Impulsivity evaluation 90
  5.4.6 Discussion 92

6. LIMITS STRENGTHS AND CONCLUSIONS 96

7. TABLES 99

8. REFERENCES 111

9. PUBLICATIONS 142
SUMMARY

Impulsivity is "a predisposition to react in a sudden and unplanned way to internal or external stimuli without regard to the possible negative consequences of these in relation to themselves or others". In the International Diagnostic System, as the DSM-V and ICD-10, impulsivity is mentioned among the operative criteria for many mental disorders and for some of them (impulse control disorders, personality disorders, substance abuse, bipolar disorders) represents a central aspect. The relationship between anxiety and impulsivity is controversial and has received little attention in the scientific literature. Historically, the two dimensions were considered orthogonal, although there are clinical evidences about their coexistence in some psychopathological conditions. Studies on impulsivity are also burdened with several methodological questions: impulsivity is a complex dimension (for example state/trait aspects) and researchers have debated its main constituents to improve the validity of the construct and to provide instrument for a correct evaluation.

The purpose of this research is to assess impulsivity in patients with primary anxiety disorders, using both state and trait measures, and to assess any differences from a control group matched for demographic characteristics. Furthermore, it explores the role of comorbidity with Cyclothymic Disorder (CD) and the relationships with affective temperaments. In particular, our hypotheses are: (a) impulsivity may be greater in patients with anxiety disorders compared to non-psychiatric controls; (b) impulsivity may not be related to the diagnosis of anxiety disorders in itself, but may be mediated by the presence of comorbidity with cyclothymic disorder; (c) there may be a
variability in the levels of impulsivity in relation to specific affective temperaments or to affective symptoms; (d) we tried to prove the preceding hypotheses, other than in a mixed case sample of subjects belonging to different diagnostic subtypes, in specific anxiety disorders, beginning with panic disorder.

For this purpose, we evaluated a sample of subjects suffering from anxiety disorders (panic disorder, social phobia, obsessive-compulsive disorder, generalized anxiety disorder) and a sample of control subjects, paired with demographic characteristics, education and occupation. All subjects were exposed to a diagnostic assessment using the Mini Neuropsychiatry Interview (MINI); to a symptomatological assessment by the Bach Raephelsen Depression and Mania Scale (BRDMS), the State-Trait Anxiety Inventory (STAI-Y), the Hypomania Checklist (HCL-32) and the Clinical Global Impression (CGI); to a temperamental and personality assessment by the Questionnaire for the Affective and Anxious Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified (TEMPS-M), the Separation Anxiety Sensitivity Index (SASI), the Interpersonal Sensitivity Symptoms Inventory (ISSI) and, finally, to a psychometric assessment of trait impulsivity using the Barratt Impulsiveness Scale (BIS) and a neurocognitive evaluation of state impulsivity, using the computerized test Immediate and Delayed Memory Task (IMT/DMT).

For testing hypothesis (a) we enrolled a sample of 47 subjects with different anxiety disorders and 45 matched controls in a period of about 1 year. The case-control comparison showed that subjects suffering from anxiety disorders resulted more impulsive than controls in all the explored measures (i.e. both trait and state components of impulsivity), and reached higher scores
on symptomatological and temperamental scales. Thus, patients with anxiety disorders but without a lifetime history of comorbid major mood episodes resulted to have greater trait and state impulsivity than controls.

For testing hypothesis (b) the initial sample of 47 patients has been divided into two subgroups (Cyclo+, n=26 and Cyclo-, n=21) according to the presence, or absence, of comorbidity for cyclothymic disorder. For the diagnosis of cyclothymic disorder, we used both the DSM-IV-TR criteria and also a modified threshold for hypomania with a duration of 2 days. Then we compared symptomatological, temperamental and impulsivity measures in Cyclo+, Cyclo− and controls. The comparisons showed that Cyclo+ are the most impulsive subjects in both trait and state measure and are characterized by greatest symptomatological impairment, highest scores in temperamental scales, and highest levels of interpersonal sensitivity and separation anxiety. Cyclo− subjects resulted to be more impulsive compared to controls concerning the retrospective trait measures, but not in the neuro-cognitive test, a measure of state impulsivity.

For testing hypothesis (c) we enrolled a larger case series of 78 outpatients suffering from anxiety disorders in a period of 2 years. We then correlate BIS and IMT/DMT scores with Brief-TEMPS-35 subscales and BRDMS scores. Correlational analyses showed that cyclothymic and irritable temperaments were significantly related to measure of trait impulsivity, while severity of hypomanic symptomatology to state impulsivity.

Finally, for testing hypothesis (d) we selected, from the previous case series, 64 outpatients who met the DSM-IV-TR criteria for Panic Disorder (PD) with or without Agoraphobia and 44 healthy subjects matched for demographic
features. Compared to healthy controls subjects with PD resulted more impulsive in all the explored measures (i.e. both trait and state components of impulsivity), also reporting higher scores in symptomatological and temperamental scales. The comparison between PD patients with (Cyclo+, n=20) and without (Cyclo−, n=44) comorbid cyclothymic disorder and controls (n=44) showed that Cyclo+ were the most impulsive subjects in all the investigated measures and were characterized by the greatest symptomatological impairment, the highest scores in temperamental scales, and the highest levels of interpersonal sensitivity and separation anxiety.

In conclusion, in our clinical records, as hypothesized, trait and state impulsivity resulted greater in patients with primary anxiety disorders than in matched controls. Moreover, impulsivity seemed not to be connected to the Anxiety Disorder diagnosis in itself, but it seemed to be mediated by comorbidity with cyclothymic disorder. Moreover, trait and/or state impulsivity levels resulted variable and seem to be associated with specific affective temperamental traits or with affective symptoms. In particular, trait impulsivity could be attributed to the temperament disposition, while state impulsivity to current hypomanic symptomatology. It was finally possible to replicate the results, previously obtained in a the mixed case sample of subjects belonging to different diagnostic disorder subtypes, in a sample of patients with panic disorder.
1. INTRODUCTION

1.1 Definition of impulsivity

Up against different conflicting tendencies that can intervene, man is able to decide what hinder and what let realize, according to affective and cognitive processes: this decision-making is called will. The voluntary act is considered at a conscious level as a responsible choice in which the self realizes itself in complete independence (Sarteschi and Maggini 1989).

Impulsivity is a component of normal and pathological behaviour that characterizes the transition from the intention to action (Barratt, Patton et al. 1983; Evenden 1999). The concept ‘impulsivity’ has been used to refer to a wide range of seemingly unrelated mal-adaptive behaviours including inability to wait, difficulty withholding responses and insensitivity to negative or delayed consequences. Examples of previous definitions of the term are: a passage to the act not premeditated or without mindful judgment (Hinsie and Shatzky 1940), an adoption of a behaviour without an adequate reflection (Smith 1952), or a tendency to act with lower premeditation if compared to the most of the subjects in the similar cultural extraction (Dickman, McCown et al. 1993).

Impulsivity research has historically focused in defining and assessing the construct according to different perspectives and in literature there has not been an operational definition for years, because of the difficulty to unambiguously identify its essential elements (Oas 1985).

From the personological viewpoint, Eysenck was the first connecting impulsivity to risk taking and considering it as a lack of planning and tendency to hastily take a decision. According to the behavioural theories, impulsivity is
defined as a wide range of actions that are poorly planned, prematurely expressed, too risky and inappropriate to situations, and often give rise to undesirable results (Evenden 1999; de Wit 2009). More simply, Monterosso and Ainslie (Ainslie 1975) describe it as an inability to delay gratification or as a self-control lack. Ho et al. (Ho, Al Zahrani et al. 1998) have integrated the previous conceptualization emphasizing the lack of punishment sensitivity and defining impulsivity as "the tendency to choose small immediate gratification rather than larger later rewards, or the tendency to avoid small immediate punishment even at the cost of incurring to later greater punishment". According to a bio-psycho-social perspective, Moeller, Barratt, Dougherty, Schmitz and Swann (Moeller, Barratt et al. 2001) suppose that a definition of impulsivity should include, at least, the following elements: a) rapid, unplanned reactions to stimuli before a complete information processing; b) lack of foresight of the negative effects of behaviour; c) lack of consideration for the long-term consequences in the area of decision making. According to this perspective, they have defined impulsivity as "a predisposition to react in a sudden and unplanned way to internal or external stimuli without regard to the possible negative consequences of these in relation to themselves or others" (Moeller, Barratt et al. 2001). Impulsivity would therefore be a predisposition, being part of a behavioural model and would include rapid and unplanned actions occurring before considering the consequences of an act. Finally, in DSM-V (APA 2013) impulsivity has been referred to “hasty actions that occur in the moment without forethought and that have high potential for harm to the individual that may reflect a desire for immediate rewards or an inability to delay gratification”. More in detail, throughout the manual, impulsivity is considered both as an “individual temperament” when related to the propensity to develop a substance use disorder as well as a “personality trait”
that may affect treatment outcomes. Moreover, in the Section of Emerging Alternative Model for Personality Disorders impulsivity is potentially considered a facet of a broad complex personality trait domain called “Disinhibition” and, in this meaning, impulsivity should comprise “acting on the spur of the moment in response to immediate stimuli, acting on a momentary basis without a plan or consideration of outcomes, difficulty establishing and following plans, a sense of urgency and self-harming behavior under emotional distress”.

It is clear from these quotations that a correct and unambiguous definition of impulsivity is not easy manageable because it should include a great variety of aspects. That is, several neurobiological processes may lead to impulsive behaviours. However, a non-unitary nature is more typical than atypical when comparing impulsivity with other psychological concepts. Therefore, researchers have been stimulated to subdivide impulsivity in main different components to improve the validity of the construct, to differentiate it from other neuropsychological elements as well as in an attempt to provide instrument for a correct operationalization.

1.2 Impulsivity in a psychiatric perspective

In the international diagnostic systems, the DSM-V and ICD-10, impulsivity is not defined in a separate diagnostic category, but is frequently mentioned and included in the operational criteria of many Axis I and II disorders, representing a central element of some of them: for example, mood disorders (Najt, Perez et al. 2007), conduct disorder (Schatz and Rostain 2006), attention deficit and hyperactivity disorder (Barkley, Edwards et al. 2001), personality disorders (Links, Heslegrave et al. 1999), substance use disorders (McCown 1988). Besides the epidemiological importance, the interest in the role of
impulsivity in psychiatric diseases is powered by the consequences of its related behavioural phenomena on the social level and welfare. Since impulsivity is a key characteristic of many disorder treating it in a proper manner may represent a important intervention strategy. For several pharmacological classes, such as selective serotonergic antidepressants, anticonvulsants with mood stabilizing properties, new antipsychotics with dopaminergic and serotonergic combined action, there are many clinical evidence of an effective regulatory modulation on impulsive and aggressive conduct. Thus, a pronounced pressure stimulates researchers to a better definition of the indications and the spectrum of effectiveness of these instruments.

1.3 Impulsivity in a neurobiological and genetic perspective

A growing body of data has confirmed that impulsivity is heterogeneous. It consists in several behavioural phenomena that are dissociable at the neuroanatomical as well as at the neurochemical levels. Mainly, behavioural expressions of impulsivity range from difficulty in inhibit actions (impulsive action/response dis-inhibition) and inability to postpone rewards (impulsive choice/delay aversion). Debate currently endures regarding the number and identity of domains into which impulsivity might be fractionated, with 2 or (possibly) more domains typically identified (Fineberg, Chamberlain et al. 2014).

In particular, proposed domains may include:

(a) insufficient information sampling before giving a response with an inadequate sensory evidences (reflectional or dis-attentional impulsivity);

(b) a tendency to pre-potent motor disinhibition (motor impulsivity or impulsive action);
(c) difficulty in delaying gratification and choosing immediate small rewards despite negative long-term consequences (impulsive choice);

(d) a tendency towards complex decision-making deficits (decision-making impulsivity).

It should be clearly noted that these represent “working expression” of impulsivity that have been defined not primarily at a clinical level but, rather, on the basis of a number of neurocognitive paradigms, better described below.

Similarly, there has been considerable convergence in recent years on the neuroanatomical substrates of impulsivity both in experimental animals as well as in clinical patients groups. It has been suggested that impulsivity encompasses various sets of neural regions: prefrontal cortex (PFC), right inferior frontal gyrus (RIFG), infra-limbic cortex (IL), pre-supplementary motor area (pre-SMA), anterior cingulate cortex (ACC), orbito-frontal cortex (OFC), distinct sub-regions of the basal ganglia (ventral and dorsal striatum, nucleus accumbens including core and shell), hippocampus (HC), amygdala (AMG) (Dalley, Mar et al. 2008; Dalley, Everitt et al. 2011; Fineberg, Chamberlain et al. 2014).

In a neurophysiological perspective, impulsivity would result from an alteration in the cortico-subcortical circuitry: hyperactivity within the circuitry that includes the basal ganglia and their limbic cortical inputs and/or abnormalities (presumably hypoactivity) in the “top-down” control exerted by prefrontal region, may result in an increased automatic tendency for executing impulsive behaviours (Dalley, Mar et al. 2008; Dalley, Everitt et al. 2011; Fineberg, Chamberlain et al. 2014).
Moreover, there is also a growing body of data that confirm, as reviewed by Dalley et al. (Dalley, Mar et al. 2008; Dalley, Everitt et al. 2011), a functional specialization in the neural systems facilitating the two major sub-forms of impulsivity i.e. delay aversion and response dis-inhibition. Although, more work is needed to elucidate the precise mechanisms of these fronto-striatal dysfunctions (i.e., specific circuitry involved), these findings seem in line with earlier observations showing a partially dissociable roles of principal neurotransmitters dopamine and serotonin in modulating impulsive choice and impulsive action (Dalley and Roiser 2012). This latter evidence is supported by psychopharmacological investigations, in which different laboratory measures of impulsivity appear to be differentially sensitive to experimental neurotransmitters manipulations: for example, L-dopa appears to increase delay discounting (Pine, Shiner et al. 2010), but has no effect on SSRT performance (Obeso, Wilkinson et al. 2011). Nevertheless, the neuropharmacology of impulsive behaviour depends on interactions between different neurotransmitters systems. Thus, both dissociation as well as some overlap, have been described in singular studies. Additionally, recent studies have also implicated noradrenergic (Chamberlain and Robbins 2013) glutamatergic (Floresco, Tse et al. 2008) and cannabinoid (Navarrete, Perez-Ortiz et al. 2012) signalling in different form of impulsive behaviour in rats.

Concerning the role of genes, there is significant support from twin studies that heritability of self report measure of impulsivity is approximately 45% (Hur and Bouchard 1997). The genetic contributions to impulsivity are mediated mainly through functional polymorphisms impacting the same neurotransmitter systems described above; among these, several genes regulating dopaminergic and serotoninergic function have received
considerable interest (Congdon and Canli 2008). For example, variants of the dopamine D4 receptor gene (DRD4) and, more recently, of the dopamine D2 gene (DRD2) as well as of the dopamine transporter (DAT) may be associated with measures of impulsivity (Congdon, Lesch et al. 2008; Hamidovic, Dlugos et al. 2009). Similarly, the serotonin system genes regulating the synaptic availability through the control of the synthesis (tryptophan hydroxylase, TRP) or of the reuptake (SERT/SLC6A4) (Oades, Lasky-Su et al. 2008; Walderhaug, Herman et al. 2010) have been extensively studied. Controversial data linking genes for pre and post-synaptic serotonin receptors (for example 5HT2b, 5HT1A, 5HT1B, 5HT3B) to impulsivity should be clarified in future research (Lappalainen, Long et al. 1998; Lesch and Merschkorf 2000; Oades, Lasky-Su et al. 2008; Bevilacqua, Doly et al. 2010). A number of studies have also examined the role of MAOA and COMT genes in impulsive and aggressive behaviours (Malloy-Diniz, Lage et al. 2013; Soeiro-De-Souza, aacute et al. 2013; Iofrida, Palumbo et al. 2014). Lastly, there are several recent contributions suggesting epigenetic processes underlying the final outcome of pathological impulsivity in neuropsychiatric disorders (Archer, Oscar-Berman et al. 2012).

1.4 Assessment tools

The need (and validity) of exploring impulsivity from different perspectives has been long established because impulsivity is a multidimensional construct of not definitive theoretical modelling and practical operationalization. Consequently a variety of tests has been developed and used in both human and nonhuman subjects to measure different forms of impulsive behaviours.

The assessment tools for impulsivity currently belong to different broad categories: questionnaires, rating scales, behavioural tests and
neurophysiological investigations. Many studies have also clearly demonstrated that the various impulsivity measures probably reflect the existence of separate underlying neurophysiological processes (Reynolds, Ortengren et al. 2006).

1.4.1 Psychometric Tools

The majority of research into impulsivity at a clinical level involves the use of self-report questionnaires designed to measure impulsive tendencies. Instruments such as the Barratt Impulsiveness Scale (BIS) (Patton, Stanford et al. 1995) and the Eysenck Impulsiveness Questionnaire (Eysenck, McCown et al. 1993) have the advantage of allowing researchers to obtain information on a wide range of actions and the possibility they constitute, in the long term, stable behavioural patterns of the subject. “I act on impulse” or "I organize carefully the assigned tasks ” are some examples of items used. A disadvantage is the need to be sure of the reliability of the answers given in the questionnaire: self-report instruments are obviously reflective of subjective assessment, so recall biases could not be excluded. These tools are then not completely suitable to be administered several times, and this aspect limits their use in treatment trials. Therefore, self-report questionnaires have been considered measure of “trait impulsivity”, focused on long-standing behavioural tendencies (trait), less suited to repeated evaluation over short periods of time.

Probably, the most widely used psychometric instrument for the assessment of impulsivity is the Barratt Impulsiveness Scale (Patton, Stanford et al. 1995; Stanford, Mathias et al. 2009). The current version of the BIS (Patton, Stanford et al. 1995) is composed of 30 items describing common impulsive or non-impulsive (for reverse scored items) behaviours and preferences. Items are rated on a four-point Likert scale with anchors of rarely/never to almost
always. Individual items are summed to create an overall score, with higher scores representing greater levels of impulsiveness. These researchers have identified three higher-order factors, which they argue reflect the components of impulsivity: attentional (the ability to focus on the tasks at hand and cognitive instability), motor (acting on the spur of the moment and perseverance), and non-planning impulsivity (self-control and cognitive complexity). Subsequently, the same authors have proposed an interesting conceptualization of impulsivity based on a 3-factor model, in which a marked motor activation together with a decrease in attention and an impairment of plan capacity would represent key aspects (Patton, Stanford et al. 1995).

Previous research has established that the BIS had strong psychometric properties in both psychiatric and non-clinical populations (Patton, Stanford et al. 1995; Stanford, Mathias et al. 2009). As an example, a wide series of studies using the BIS for measuring trait impulsivity in bipolar disorder is available. Some cross-sectional researches have explored (Peluso et al., 2005) impulsivity using the BIS in healthy subjects and bipolar patients across different mood phases (depressed, mixed, manic and euthymic) (Swann, Anderson et al. 2001; Swann, Lijffijt et al. 2009; Strakowski, Fleck et al. 2010). In general, bipolar patients tended to score higher than healthy controls, no mattering clinical states and comprising euthymic phases. The findings supported the existence of trait-dependent impulsivity features in bipolar disorder, which seem to be present regardless of the phase of the illness (Najt, Perez et al. 2007; Peluso, Hatch et al. 2007; Swann 2010).
1.4.2 Behavioural tests

The computerized tests used to measure impulsivity derive from a behavioural perspective. These tools offer some advantages if compared to the previous ones: first, they derived from animal models and therefore, through their continuous development, it is possible to select specific endophenotype which behavioural task have to be refined on. Moreover, they are not influenced by subjective report bias and permit to assess aspects that are partially independent from those explored by the scales, so they may represent useful supports to be added to diagnostic batteries. Finally, since these tests have showed a sensitivity to transient variations in levels of impulsivity (such as those which may be determined by the administration of different pharmacological agents) they seem to provide information that could be referred to a “state dependent” component of impulsivity (Dougherty, Marsh et al. 2000).

Focusing on the specificity of the computerized tasks, as it happens for every behavioural measure, the study of the multiple expressions of impulsive behaviour needs a precise connection to the biological basis of such behaviour. Investigation of the neuropsychological basis of impulsivity has been greatly aided by the fact that, although there may be a variety of methods for measuring impulsive acts in human volunteers, many of these methods have analogues in animal behaviour. Specific behavioural tasks have been developed to investigate different components of impulsivity. In practice they can be grouped according to the different paradigms they refer to. In particular, animal models fall into two broad categories: the Response Inhibition
paradigms (Rapid Decision or Rapid Response paradigms (Halperin, Wolf et al. 1991; Matthys, van Goozen et al. 1998; Dougherty, Moeller et al. 1999) on one side and Reward-direct paradigms (delay discounting) (Ainslie 1975) on the other.

The Response Inhibition paradigms (Rapid Decision or Rapid Response paradigms) have been originally developed according to a model that defines impulsivity as an inability to align the behavioural response to the environmental context. This impulsive behaviour induces errors in the execution of those tasks which require an accurate processing of the stimulus and/or an accurate context assessment and/or the ability of inhibition (Evenden 1999). According to this perspective, a behavioural response can be considered "impulsive" when there is at least one of the following characteristics:

a) it must be hasty, probably induced by the subject inability to hold in providing it, without having adequately assessed the stimulus (response disinhibition/dis-attentional paradigms) (Halperin, Wolf et al. 1991; Dougherty, Moeller et al. 1999). Therefore, successful performance in this paradigm requires good attention processing because impulsive answer is represented by anticipatory and incomplete stimulus processing that leads to rapid, but incorrect, responding. A commonly used behavioural task that reliably measure this aspect is the Immediate and Delayed Memory Task (IMT/DMT) developed by Dougherty and colleagues that has been validated to measure dis-inhibitional/dis-attentional impulsivity in various clinical population and healthy subjects. It is a modified version of the Continuous Performance Test (Rosvold, Mirsky et al. 1956), a test used for the attention and working memory assessment, and it is a more demanding version. The IMT/DMT consists of two task components (IMT and DMT) that each feature two 5 min blocks. The order
of the blocks was the same for each subject (i.e., IMT/DMT/IMT/DMT) and blocks were separated by a 30 sec rest period, resulting in total test duration of 21.5 min. In the IMT five number strings appear in sequence on a computer screen with an interval of 0.5 sec: the subject is instructed to compare strings and to respond only when the string of numbers is displayed exactly identical to the previous one, through a mouse click. Among the various responses obtained in a task of this type, three are particularly significant in reaction to the different types of stimuli that are presented in a testing session: 1. a correct response (correct detection, hit), if the subject clicks on the mouse after identifying a sequence (target stimulus, there is a 33% probability of a target stimulus) which is identical to the previous one; 2. an impulsive response (commission error, false alarms), if the subject responds to a series (catch stimulus, there is a 33% probability that a catch stimulus will appear) which is not identical to the previous one because having in common four of the five numbers. It is important to note that the position and value of the only one number that is different is determined randomly; 3. filler errors, representing unnecessary responses to novel stimuli (random numbers that always follow a catch or a target stimulus). Commission errors are considered impulsive type errors, induced by the tendency to give a quick but incorrect response when there is a series similar enough (4 of 5 numbers) to the target, so before having assessed the actual difference. In the DMT a distracter stimulus, which is to be ignored, appears 3 times between each of the testing series. The task was designed to measure a participant’s ability to retain and subsequently identify a stimulus kept in memory for a longer period of time (compared to the IMT). In particular, the major difference between the IMT (above) and this task is that stimuli (including target, catch and filler) are separated by three presentations of the number 12345, which appear at the same rate and duration as all other
stimuli. For example, a possible sequence involving a target stimulus might be 59213 ... 12345 ... 12345 ... 12345 ... 59213. Here, participants are told to ignore the 12345 stimuli and to remember and compare only the stimuli separated by the series of 12345 presentations. The 12345 stimuli are the distracter stimuli. The primary dependent impulsive action measure for both IMT and DMT is the ratio of commission errors to correct detections (IMT or DMT Ratio). A preclinical example of equivalent task is the 5 choice serial reaction time task that measure impulsive responses in the contest of general attentive capacities in experimental animals (Robbins 2002).

b) it must be perpetrated and not interrupted due to a change of environment, so as to be inadequate to the new context, and then punished or, at least, not rewarded (punished and/or extinction and/or action cancellation and/or response inhibition paradigms) (Matthys, van Goozen et al. 1998). In this case, impulsive answer is determined by an inability to inhibit an already initiated response rather than in choice selection. An example of test developed according to these second paradigms is the “stop-signal reaction time task” (Logan 1994) in which subjects are trained to respond as quickly as possible in a reaction time task. On a proportion of trials, a “stop-signal” is sounded, which indicates that the subject has to cancel responding on that trial. Presentation of the stop-signal occurs at different time-points after the imperative signal, so it is much more difficult for subjects to cancel the response with increasing delay after the imperative signal than when the stop signal occurs immediately. SSRT involves the cancellation of an already selected response thus represent an example of “action cancellation” task. Another task of this type is represented by the Go/NoGo procedure in which the subject has to choose between a stimulus associated with reward and another stimulus that cues inhibition of
responding. In the Go/NoGo is implicated a response choice selection as well as action restraint, whereas SSRT, as discussed above, involves the cancellation of an already selected response (representing a reaction time measure). It is important to take into account the precise processes involved in these apparently similar tasks: in an interesting review, for example, Eagle et al. (Eagle, Bari et al. 2008) presented evidence to determine if the stop-signal task and the go/no-go task have similar neuroanatomical and neurochemical modulation. The authors suggested that whilst performance of the stop-signal and go/no-go tasks is modulated across only subtly different anatomical networks, serotonin (5-HT) is strongly implicated in inhibitory control on the go/no-go but not the stop-signal task, whereas the stop-signal reaction time appears more sensitive to the action of noradrenaline. Thus, response inhibition may involve different sub-processes, depending on the precise programming of the action (Dalley, Everitt et al. 2011).

The **Reward-directed paradigms**, the second broad category of behavioural tasks, originate from models developed for the study of operant behaviour in animals. Typically, in these delayed reinforcement tasks rats are faced with a choice between two response options. One option is associated with small and immediate food reward, whereas the second option results in larger but delayed food reward. Clearly, the second response option is more beneficial, but the subjective value of the large food reward declines with the delay of its delivery. Similarly, individuals that are more impulsive in these paradigms are generally more delay averse, because the participant does not tolerate the delay necessary for the larger reward: in other words, the delay discounts its value over time (this phenomena can usually be characterized mathematically as hyperbolic discounting). Human discounting tasks have also
been developed, in which subjects receive delays and rewards in real time, and which can be sensitive to acute pharmacological manipulations (Reynolds and Schiffbauer 2004; Reynolds, Ortengren et al. 2006). Despite their wide applications, some methodological questions concerning these types of paradigms are still debated, mainly concerning their validity. The paradigms vary considerably and these differences in methodology can be a crucial factor in influencing drug manipulations. Nevertheless, as with the human data, there is a general concordance in the output in that nearly all variants of the task can distinguish high and low impulsive subgroups, and can be used to estimate a delay-discounting curve (Winstanley 2011). Delay-discounting tasks have probably been the most successful in terms of modelling the inability to prioritize future rewards over satisfying the need for more immediate gratification. Forms of discounting choices almost certainly contribute to performances in more complex tasks such as the Iowa Gambling Task (Bechara 2003) or the Balloon Analogue Risk Task (Lejuez, Read et al. 2002), selectively targeting aspects of decision-making and frequently included in batteries evaluating impulsive behaviours.

All the examined instruments have been validated on populations of patients with psychiatric disorders and received empirical support as a behavioural index of impulsivity. Several research groups have projected specific studies in which different measures, including self-report personality questionnaires and a varieties of behavioural tasks, have employed in case series of healthy and clinical populations aiming of evaluate the interrelations between different instruments (Reynolds, Ortengren et al. 2006). Although the correlations among the various self-report questionnaires were found to be high, self-report measures and behavioural-task resulted not correlated
Moreover, singular behavioural task failed to inter-correlate with each other (Sonuga-Barke 2002; Swann, Bjork et al. 2002). This general lack of inter-correlation in behavioural-task means that, although they share some common features, they probably reflect separate underlying processes, controlled by different neural structures (Dalley, Mar et al. 2008; de Wit 2009; Dalley, Everitt et al. 2011).

2. THE ROLE OF IMPULSIVITY IN MOOD AND ANXIETY DISORDERS

According to DSM-V (APA 2013), impulsivity has been referred to “hasty actions that occur in the moment without forethought and that have high potential for harm to the individual that may reflect a desire for immediate rewards or an inability to delay gratification”.

Although impulsivity could be present in any individual, it is definitely more easily seen in individuals suffering from certain mental disorders: a number of psychiatric disorders listed in the DSM-V are conditions in which various types of impulsive behaviours are comprised in their definition; examples include bulimia nervosa, substance abuse, borderline and antisocial personality disorders. Impulsivity may also be a symptom or manifestation or a complication of various psychiatric disorders: for example, borderline personality disorder (BPD) is associated with significant morbidity and mortality as a consequence of impulsivity; hence, impulsivity is considered a core symptom of BPD (Oquendo and Mann 2000). Accordingly, at least in part, the association between psychiatric disorders and impulsivity is due to the way they have been defined in diagnostic systems, which often includes, among their criteria and/or symptoms and/or complications, different forms of deficit
in the ability of behavioural inhibition (Moeller, Barratt et al. 2001). Moreover, the previous edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA 2000) included a class of other disorders, in which behavioural impulsivity was a specific core feature, designated as “Impulse-Control Disorders Not Otherwise Specified”. Impulse-control disorders comprised pathological gambling, kleptomania, pyromania, trichotillomania (compulsive hair pulling), and intermittent explosive disorder. However, this specific class represented a "residual" category, which included conditions of not definitely systematization. Several authors have dealt with this topic, reflecting on the ambiguity at the nosographic level. Most of them, on the base of epidemiological and clinical data, have discussed the nosological validity of the impulse-control disorders “not elsewhere classified” as a class and tended to consider these disorders as related to other clinical syndromes: for example the "affective spectrum" for McElroy (McElroy, Hudson et al. 1992), the "compulsive-impulsive continuum" for Hollander et al. (Hollander, Kwon et al. 1996; Hollander, Posner et al. 2002), a "convergence of mood, impulsive and compulsive disorders" by Kafka and Coleman (Kafka and Coleman 1991).

In any case, despite impulsivity seems to be a central clinical aspect for several mental disorders, with multiple expressions in within the different syndromic groupings, there is a clear ambiguity in previous and current diagnostic systems on this dimension. Now, the more recent DSM-V (APA 2013), published in 2013, includes a new chapter (not comprised in DSM-IV-TR) on Disruptive, Impulse-Control, and Conduct Disorders covering disorders "characterized by problems in emotional and behavioural self-control". Furthermore, the class of “Impulse-Control Disorders Not Otherwise Specified” has been reviewed, and, actually, it encompasses intermittent explosive disorder, pyromania, and kleptomania. Trichotillomania has been arranged in a
new “Obsessive-Compulsive and Related Disorders (OCRDs)” chapter that also comprises obsessive-compulsive disorder and skin-picking disorder. These latter disorders are, actually, considered as either impulsive or compulsive, suggesting a significant shift in taxonomic perspective.

The main reason of these nosographic difficulties lies in the fact that the research on impulsivity has been limited by a long-lasting lack of consistency in defining and assessing the construct. Historically, the term has been used to refer to a wide range of seemingly “unrelated” mal-adaptive behaviours, including inability to wait, difficulty withholding responses and insensitivity to negative or delayed consequences. There is now a consensus that impulsivity is multi-dimensional, and that the various impulsivity models reflect separate underlying processes (Moeller, Barratt et al. 2001; Reynolds, Ortengren et al. 2006). Actually, it is also clear enough that different mental disorders are associated with impulsivity through combinations of these separate and dissociable mechanisms. However, these latter need to be further characterized and understood in their specific roles in the development and consequences of various disorders.

2.1 The role of impulsivity in Mood Disorders

The relationship between impulsivity and mood disorders has been widely documented. Concerning the distinct affective phases, it is intuitive that it is virtually impossible to satisfy the DSM-IV as well as the DSM-V criteria for a manic episode in absence of impulsive behaviours. Swann et al. (Swann, Janicak et al. 2001) have shown how in manic episodes, while the other symptom characteristics vary widely, impulsivity represents a persistent
feature to be considered a fundamental dimension in the clinical picture. Impulsivity may also be present in depressive episodes and, in this case, it tends to be associated to an increase of auto-aggressive conduct (Corruble, Damy et al. 1999; Pompili, Innamorati et al. 2008).

In the context of bipolar disorder (BD), it has been clearly demonstrated that episodes of illness are associated with impulsivity, as well as the euthymic periods (Najt, Perez et al. 2007). In one of the first study that combined a psychometric and a neurocognitive evaluation, Swann et al. (Swann, Pazzaglia et al. 2003) measured impulsivity in bipolar patients who had not met episode criteria for at least 6 months (i.e. in an euthymic phase), in patients who were manic, and in healthy control subjects. Impulsivity was assessed using the Barratt Impulsiveness Scale (BIS) and performances on the computerized Immediate and Delayed Memory Task (IMT/DMT). BIS scores resulted almost identical in euthymic and manic bipolar subjects, and significantly elevated compared to controls. On the other hand, the impulsive responses on the IMT/DMT resulted elevated in manic subjects but were identical to controls in euthymic subjects. Subsequently, the findings were replicated and extended by Strakowski et al. (Strakowski, Fleck et al. 2010) in a wide sample of 108 bipolar I patients recruited when in a manic or mixed phase. The subjects underwent a neurocognitive evaluation of impulsivity (using three different type of task: a stop signal task, a delayed reward task, and a classical continuous performance task) as well as a psychometric evaluation with the BIS. Patients were compared to healthy controls at baseline and then followed up to one year: during this period, if they developed depression or euthymia they were reassessed with the same measures. As main results bipolar subjects demonstrated, at baseline, significant more impulsive responding in all the three tasks as compared to
healthy subjects. Interestingly, performance on the three behavioural tasks normalized (independently from the specific task) upon switching to depression or developing euthymia. In contrast, BIS-11 scores were elevated during mania and mixed state and persisted elevated across the various phases of illness, i.e. when bipolar subjects developed depression or achieved euthymia. Taken as a whole, these results suggested that in bipolar disorder impulsivity has different components: a state component linked to the current affective-state and a trait component linked to a more persistent structural disposition (Najt, Perez et al. 2007; Swann 2010).

Further studies have shown that many specific clinical characteristics of bipolar disorder could account for an additional increasing in state or trait impulsivity and/or for a modified interaction between these two components. For example, BIS scores (i.e. trait impulsivity) resulted higher in bipolar patients presenting early onset, many previous episodes, substance/alcohol use disorders, and histories of suicidal behaviour when compared to bipolar subjects without such clinical characteristics (Swann, Lijffijt et al. 2009). These relationships persisted when age, gender, and education were taken into account. The same trend was also detectable for neurocognitive measure (both rapid-response and reward-delay measure of impulsivity) suggesting that an additional increment of state impulsivity could be associated with a more severe course of illness (Swann, Lijffijt et al. 2009). Moreover, it is particularly interesting that in bipolar patients a co-existing substance-use disorder not only increased all behavioural manifestation of impulsivity but also tends to blur the distinction between its trait and state components: for example, Swann et al. (Swann, Dougherty et al. 2004) showed how state impulsivity resulted increased in inter-episode bipolar subjects with substance abuse similarly to
manic subjects without substance abuse. Finally, impulsivity and anxiety are common features of bipolar disorder, each associated with a number of negative outcomes and sequelae. The relationship between anxiety and impulsivity, still, has not been a clear focus of study in BD. Nevertheless, in an interesting research of Taylor et al. (Taylor, Hirshfeld-Becker et al. 2008) the authors evaluated this association measuring impulsivity by the Barratt impulsiveness scale (BIS-11) in 114 outpatients with BD with or without comorbidity with anxiety disorders. The main results revealed that patients with a comorbid anxiety disorder displayed significantly higher levels of trait impulsivity relative to patients without an anxiety disorder. Moreover, a broad range of anxiety-related symptom domains was associated with greater levels of impulsivity. Exploratory analyses also revealed that baseline anxiety symptoms were associated with elevated impulsivity at 9-month follow-up, although these relationships were less robust after covariate adjustment. A particular strength of the research was the use of both diagnostic and dimensional assessments of anxiety, which bolsters confidence in the robustness of the anxiety–impulsivity relationship observed in bipolar patients. The authors found no evidence that specific symptom domains of anxiety were exclusively related to impulsivity. These data has been interpreted as the confirm that, although anxiety is not a unitary concept, anxiety displayed a non-specific positive association with impulsivity in bipolar disorder, suggesting also that it is not just one specific aspect of the anxiety experience that accounts for that relationship.

Summarizing, though there is little quantitative information available, the relationship between bipolar disorder and impulsivity goes beyond the phases of illness. This statement is therefore not surprising given that impulsivity is
increased in other psychiatric disorders that involve affective or behavioural instability (Swann 2010).

Classically, trait impulsivity in bipolar disorder has been included among temperamental features (Akiskal and Mallya 1987; Akiskal, Hantouche et al. 2003; Signoretta, Maremmani et al. 2005). Affective temperament has been conceptualized as biological disposition, corresponding to a constitutional substrate expressed through a series of signs and features, usually manifested by a certain stability since the childhood, of affectivity and mood, attitudes toward the environment, sensitivity to external stimuli and characteristic modes of reaction (Akiskal 1996). In their extreme manifestations ‘dysthymic’ and ‘cyclothymic’ dispositions have received official sanction in the contemporary psychiatric nomenclature as dysthymic and cyclothymic disorders, while irritable and hyperthymic have not.

The DSM-V (APA 2013) lists “Cyclothymic Disorder” (CD) as a “chronic fluctuating mood disturbance” involving “numerous periods with hypomanic symptoms that do not meet criteria for a hypomanic episode and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode” usually beginning in adolescence or early adult life. The diagnosis of cyclothymic disorder could be made only if the criteria for a major depressive, manic, or hypomanic episode have never been met. Mood instability needs to be present for 2 years (one year for children or adolescents), although symptom-free intervals can last no longer than 2 months. After 2 years, hypomanic, manic or major depressive episodes may be “superimposed” thus the diagnoses of unspecified bipolar and related disorder (sub-classified as hypomanic episode without prior major depressive episode) or bipolar I, or bipolar II, disorder can be made. In this case he cyclothymic disorder diagnosis
is dropped. The disorder cannot be secondary to medical conditions or substance effects, and must be associated with “clinically significant distress or impairment.”

As in the previous editions, the DSM definition of cyclothymic disorder continues to focus on “fluctuating mood disturbances” without any mention of temperament or predisposition. As a consequence, the diagnosis is not commonly made in clinical practice and frequently neglected especially in patients presenting a Major Depressive Episode, as better described below (Akiskal, Akiskal et al. 2006).

According to some authors, cyclothymia is better defined as an exaggeration of a “temperamental style” (Akiskal, Khani et al. 1979), present during a long lasting part of life and starting from childhood to adolescence. The criteria for cyclothymic temperament proposed by Akiskal et al. (Akiskal, Khani et al. 1979) reflect the classic descriptions and require the presence, throughout much of the patient’s life and starting from childhood/adolescence, of sudden mood swings and three (out of five) opposed conditions of each of the following two sets. The first set includes: (1) hypersomnia vs decreased need for sleep; (2) introverted self-absorption vs uninhibited people-seeking; (3) taciturnity vs talkativeness; (4) unexplained tearfulness vs buoyant jocularity; (5) psychomotor inertia vs restless pursuit of activities. The second set includes: (1) lethargy and somatic discomfort vs eutonia; (2) dulling of senses vs keen perceptions; (3) slow-witted vs sharpened thinking; (4) shaky self-esteem alternating between low self-confidence and overconfidence; (5) pessimistic brooding vs optimism and carefree attitudes.

In this perspective, to configure a full blown “cyclothymic disorder” some essential components are additionally needed: besides affective instability with
the classical biphasic ups-and-downs in activity, energy and mood, there should be present mood reactivity, excessive emotional sensitivity to environmental cues, as well as changes in behaviour accompanying the mood shift. Negative consequences (e.g., school, work, love and family) and repetitive sabotage of opportunities to become stable and have a serene lifestyle are generally the rule in these patients (Hantouche and Perugi 2012).

The clinical presentation of cyclothymic disorder is highly heterogeneous. Some people may be dysthymic nearly all the time with rare days of hypomania, whereas others may shift from feeling depressed to feeling hypomanic multiple times in a single day (Howland and Thase 1993). Similarly, although periods of both depressive and hypomanic symptoms occur, and may do so in ways that appear episodic, more often the presentation is mixed, without clear demarcation between different moods (Akiskal, Djenderedjian et al. 1977). Furthermore, depressed periods often include hypomanic symptoms, resulting in a more agitated presentation (Howland and Thase 1993). The quality of hypomanic symptoms also can vary between positive versus restless and irritable shades, which have greater likelihood of negative outcomes (Hantouche, Angst et al. 2003). Moreover, adults and youth with cyclothymic disorder tend to have high rates of concomitant psychopathological manifestations and comorbidities (Perugi and Akiskal 2002; Perugi, Toni et al. 2003; Hantouche and Perugi 2012; Van Meter, Youngstrom et al. 2012). Among them, anxiety comorbidity is often the rule in these subjects (Tomba, Rafa\'nelli et al. 2012): they could report panic disorder (MacKinnon, Zandi et al. 2003; Perugi, Toni et al. 2003), separation anxiety (Pini, Abelli et al. 2005); social phobia (Himmelhoch 1998), obsessive compulsive disturbances (Hantouche, Angst et al. 2003; D’Ambrosio, Albert et al. 2010). In particular, taking into
account the high rates of lifetime and familiar comorbidity with panic disorder, some authors have hypothesized that the relationship between panic disorder (PD) and CD could not simply viewed as an association between two separate disorders. Indeed, some available data suggest that panic attacks and rapid mood switching could be considered as a specific subtype of familial bipolarity (MacKinnon, McMahon et al. 1997; MacKinnon, Zandi et al. 2003; MacKinnon and Pies 2006; MacKinnon and Zamoiski 2006). More in detail, MacKinnon et al. (MacKinnon, Zandi et al. 2003; MacKinnon and Pies 2006) have carried out a series of clinical and family studies on bipolar subjects with rapid mood switches, whose characteristics in many ways resulted similar to those of cyclothymic patients (MacKinnon, McMahon et al. 1997; MacKinnon, Zandi et al. 2003; MacKinnon and Pies 2006; MacKinnon and Zamoiski 2006). The presence of rapid mood fluctuations was associated with a high familial load for mood and anxiety disorders, early onset, marked suicidal risk and high rates of comorbidity with PD. These results are in line with the results of the studies carried on bipolar disorder in children and adolescents by Perugi et al. (Masi, Perugi et al. 2007), pointing out the same characteristics of high familial loading, comorbidity with multiple anxiety disorders and rapid circadian switches. Taken as a whole, these findings seem to suggest that the association between panic disorder and rapid mood switches could be interpreted as a particular familial subtype of bipolar disorder characterized by early onset and cyclothymic instability (Masi, Perugi et al. 2007; Nwulia, Zandi et al. 2008).

Moreover, the coexistence of cyclothymia with impulsivity, both in terms of vulnerability to impulsive reactions (Hantouche, Angst et al. 2003) as well as in terms of comorbidity with impulse control disorders, is well established (Perugi and Akiskal 2002; Perugi, Toni et al. 2006). Substantial additional
comorbidity associated with cyclothymia includes: attention deficit hyperactivity disorder (Landaas, Halmo et al. 2012); eating disorders, especially those that include impulsive conducts towards food, such as bulimia (Perugi, Toni et al. 2006); substance abuse (Maremmani, Perugi et al. 2006; Vyssoki, Bluml et al. 2011); suicidality (Pompili, Innamorati et al. 2012); Cluster B personality disorders (Perugi, Fornaro et al. 2011). Finally, many cyclothymic patients could be diagnosed as affected by personality disorders, especially those with frequent relapses, severe impulsivity and extreme mood instability (Perugi and Akiskal 2002; Perugi, Toni et al. 2006).

Among the various subtypes of mood disorders, Cyclothymia has probably received the least attention in epidemiological studies. In the available researches, that did report rates of cyclothymia, the prevalence in the general population ranged from 0.4% to 2.5% (Van Meter, Youngstrom et al. 2012). However, these rates seem to reflect the infrequent usage and relatively poor understanding of the cyclothymic diagnosis, rather than a valid prevalence of the condition (Van Meter, Youngstrom et al. 2012). Nevertheless, Angst (Angst and Marneros 2001) reported lifetime prevalence rates for brief episodes of hypomania associated with brief depression ranged between 5 and 8%. More in detail, the same authors suggested that the average length of a hypomanic episode in general population seems to be 2 days, while in many cyclothymic patients elated episodes are shorter than 1 day and, often, associated with environmental stimuli or substance misuse. Based on these observations, the 4-day threshold proposed by DSM-IV for the definition of hypomanic episode has been criticized (Akiskal 2007). It is important to consider that the proportion of subjects with depressive symptoms in the general population who should be diagnosed as cyclothymic will significantly grow if the 4-day threshold for the
hypomanic episode proposed by the DSM IV is reconsidered. On the other hand, high rates of cyclothymia has been observed in clinical populations: more than 30% of depressed patients seen in psychiatric outpatient settings as reported by Hantouche et al. (Akiskal, Akiskal et al. 2006) and 50% of patients presenting obsessive–compulsive disorder (Hantouche, Angst et al. 2003) in the same setting. A similar figure has been prospectively evaluated in a general practice setting (Manning, Haykal et al. 1997).

In conclusion cyclothymia seems to represent a very common phenotype of mood disorder (Akiskal, Akiskal et al. 2006; Akiskal, Akiskal et al. 2006). Nevertheless, many essential aspects of cyclothymia remain understudied, remarkably for a condition that has been recognized for more than a century (Baldessarini, Vázquez et al. 2011). Moreover, cyclothymia represents a plausible basic foundation for both anxious/inhibited as well as impulsive/disinhibited manifestations, pertaining to a large number of patients. This matrix, which, in other words, makes the same individual susceptible to anxiety, impulse-control, eating and substance-use disorders, should be considered a substantial challenge for clinicians and a focus for the future research.

2.2 The role of impulsivity in Anxiety Disorders

The relationship between anxiety and impulsivity is controversial. Traditional conceptualizations suggested that impulsivity might display a negative relationship with anxiety (Barratt 1965; Askenazy, Caci et al. 2000), mainly because anxiety has been, classically, thought to alert to potential danger and to inhibit behaviour under conditions of heightened threat (Gray
Though, characteristic features of anxiety such as behavioural inhibition, harm avoidance, safety-seeking, and anxious apprehension (Zinbarg and Barlow 1996) may seem initially inconsistent with characteristics of impulsivity, such as increased risk-seeking, acting without forethought, and decreased anticipation of the consequences of one’s behaviour. Similarly, others authors have speculated that anxiety might serve as a protective factor against disinhibited, potentially dangerous activities or behaviours that could lead to early mortality (Lee, Wadsworth et al. 2006). Consequently, one might hypothesize that anxiety would be protective against impulsivity.

On the other hand, despite the classical conceptualization, there is an extensive clinical literature, which supports a close association between these two dimensions, at least in some psychiatric populations. You may think of the coexistence between anxiety and impulsivity in subjects presenting behavioural disorders characterized by lack of self control such as pathological gambling (Roy, Adinoff et al. 1988; Barrault and Varescon 2013), eating disorders (Waxman 2009), personality disorders characterized by self injuring (Simeon, Stanley et al. 1992). Furthermore, there are several researches documenting a high comorbidity between anxiety disorders and conditions characterized by elevated levels of impulsivity, such as attention deficit disorder and hyperactivity (Schatz and Rostain 2006; Baldwin and Dadds 2008) and conduct disorders in adolescents and young adults (Askenazy, Sorci et al. 2003). Epidemiological data, also, reveals high rates of comorbidity between anxiety disorders and impulse control disorders (Kessler, Chiu et al. 2005). Finally, after great debate in the literature, anxiety disorders have been clearly associated at least with some behavioural aspects of impulsivity such as suicidality, beyond the effects of co-occurring confounding factors, especially depressive symptoms (Sareen, Cox et al. 2005; Nepon, Belik et al. 2010; Thibodeau, Welch et al. 2013).
Notwithstanding the high rates of co-occurrence in clinical populations, relatively little attention has been paid on study in deep the relationship between impulsivity and anxiety, both in a categorical as well as in a dimensional perspective. In a dimensional approach, several previous studies have evaluated the relationships between various psychopathological dimensions such as anxiety, anger, and impulsivity in order to predict the risk of suicide and/or violent behaviours (Apter, van Praag et al. 1990; Apter, Kotler et al. 1991; Apter, Plutchik et al. 1993), but few have focused exclusively on anxiety and impulsivity. For example, in a study conducted by Apter et al. (Apter, Plutchik et al. 1993), sixty psychiatric patients were evaluated regarding suicide and violence risk, anxiety, anger, impulsivity and mood. The authors reported that trait anxiety, assessed by the Spielberger State-Trait Anxiety Scale (Spielberger 1983), tended to decrease the risk of violent behaviour (but not the risk for suicidality). Other studies on groups of violent adolescents with high levels of impulsivity (Askenazy, Caci et al. 2000) reported a lack of correlation between anxiety, assessed by the Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959), and impulsivity, as assessed through the Impulsivity Rating Scale (IRS) (Lecrubier, Braconnier et al. 1995). Similarly, a lack of correlation between anxiety and impulsivity has been reported in healthy adolescents (Caci, Askenazy et al. 1998). On the other hand, a positive correlation was found in a sample of patients suffering from eating disorders with high anxious comorbidity, who resulted characterized by impulsive behaviour but not by violent behaviour (Askenazy, Candito et al. 1998). Interestingly, the relationship between anxiety and impulsivity was the focus of a study conducted by Ashkenazy et al. (Askenazy, Sorci et al. 2003) in a sample of adolescents hospitalized for a broad spectrum of behavioural disturbances (first or recurrent suicide attempt, self-mutilation, violence and assault, delinquency, alcohol and
drug abuse, eating disorders). During a 1-year period, 69 in-patients admitted for one of the cited behaviours were evaluated, irrespective of their psychiatric diagnosis. The subjects were then divided into four subgroups, according to a psychometric evaluation of the levels of anxiety and impulsivity: impulsive and anxious (IA); impulsive and not anxious (Ia); not impulsive and anxious (iA); not impulsive and not anxious (ia). As main results, in the IA group, mood disorders were prominent, with 62% of the subjects currently reaching criteria for a hypomanic episode, while 48% presented a major depressive episode. The commonest behaviour observed was recurrent suicide attempts, presented in the 87% of the subjects. Notably, out of the six behavioural disturbances explored (first and recurrent suicide attempt, self-mutilation, violence and assault, delinquency, substance abuse, and eating disorders), three were present in 95% of the subjects of this group. Finally, 67% used cannabis. In the group Ia, almost all subjects, 93%, were boys (other groups were mainly composed of girls). Almost all of them (87%) had a positive anamnesis for conduct disorder: this diagnosis was rather specific to this group. The 80% was also positive for delinquent episodes. Also in this group the use of cannabinoids was frequent (67% of subjects, as for the group IA) and 20% of the subjects was positive for hypomanic episodes. In the iA group, a high percentage of subjects were positive for major depressive episode (87%) as well as for nervous anorexia (73%). Finally, the group ia did not show a positive anamnesis for violent forms of behaviour. Only one subject reached criteria for major depressive episode, with an overall reduced risk of suicidal behaviour. The results observed in the four sub-groups were surprisingly relevant. The characteristics of the IA group were associated with at-risk behaviours, such as violent suicide attempt, and a high prevalence of depressive and hypomanic episodes. These data, primarily, suggest that when impulsivity and anxiety are associated with mood
disturbances they result highly prognostic of suicide attempts: in other words, the combination of mood and anxiety disturbances in an impulsive population doesn’t seem to protect from the tendency to behavioural dyscontrol, but, in some way, it seems to express aggression in a self-directed sense. On the other hand, delinquency and conduct disorders were observed in the Ia population: thus impulsivity, in absence of anxiety, seems to connect to antisocial and violent behaviour. Furthermore, it is interesting to notice that both the IA and Ia subgroup presented affective disturbance with current or lifetime mood episodes. The authors suggested that this findings tends to corroborate the hypothesis that behavioural dyscontrol may be an initial manifestation of prepubertal-onset bipolar disorder (Kovacs and Pollock, 1995), emphasising the importance of identifying a bipolar spectrum diathesis as described by Akiskal and Pinto (Akiskal and Pinto 1999). Finally, substance abuse seemed to be associated to both impulsivity and anxiety. Indeed, in both IA as well as Ia groups the researchers observed a wide representation of cannabis abuse.

In contrast to the theories that consider anxiety as orthogonal and protective against impulsivity, but keeping in mind the previously reported findings, it is also relevant to mention how the presence of co-morbid anxiety disorders in patients with mood disorders increases the risk of suicide attempts, as clearly demonstrated by Sareen et al. (Sareen, Cox et al. 2005). Similarly, the presence of a comorbid anxiety disorder was found to increase the levels of trait impulsivity, specifically measured with the BIS, in a sample 114 bipolar outpatient, as described by Taylor et al. (Taylor, Hirshfeld-Becker et al. 2008). Moreover, in a recent study conducted by Erche et al. (Ersche, Turton et al. 2012), with the aim to identify cognitive, emotional, and personality markers of stimulant dependence vulnerability, the presence of high levels of impulsivity, measured with the BIS, in association with high levels of trait anxiety, measured
with the STAI (Spielberger 1983), has been associated with stimulant
dependence predisposition, in both stimulant-dependent individuals as well as
in their non-drug-dependent siblings compared to healthy unrelated
volunteers. The authors suggested that higher levels of a putative “anxious-
impulsive” trait in the sibling pairs imply underlying deficits in emotion
regulation, possibly laying the foundation for individual risk in addiction
psychopathologies, together with the abnormalities in domains of executive
cognitive and response control also shared in the siblings.

Interestingly, an “anxious-impulsive” trait has previously described by
Newman and Wallace (Newman and Wallace 1993) as a breakdown of
inhibitory control showed by anxious patients in situations of negative urgency
and/or when the escape from aversive consequences appears impossible. In
other words, anxious patients were thought to be prone to impairments in
response modulation, especially in stimulus contexts to which they are most
sensitive (i.e. uncertainty and negative urgency), leading the subjects towards
unchecked impulsive reactions. Newman and his colleagues have identified
this pathway of anxious-impulsive responding on the base of several
experimental observations (Bachorowski and Newman 1990). The authors
considered this predisposition as a “trait” that could be exerted in some
conditions. Moreover, they also suggested that the tendency of some anxious
patients to acquire a variety of maladaptive behaviours, such as reactive
aggression, could be interpreted in that perspective.

More recently, higher levels of trait anxiety have also been associated with
disturbances in specific executive functions, such as attention and inhibitory
control, as well as task shifting (see Ansari et al. (Ansari and Derakshan 2011)
and Eysenck et al. (Eysenck, Derakshan et al. 2007) for reviews). Mainly,
anxiety is thought to increase excessively the influence of stimulus-driven
processes over efficient top-down control. Although speculatively, it cannot be excluded that anxiety-dependent imbalances in these systems could play a role in arising the risk of more complex impairments in response modulation, leading anxious subjects prone, at least, to subtypes of impulsivity, for example to its disinhibitional/disattentional forms. Moreover, partly supporting this hypothesis, there is some evidence to suggest a possible relationship between anxiety and complex decision-making. Two recent studies conducted by Miu et al. (Miu, Heilman et al. 2008) and de Visser et al. (de Visser, van der Knaap et al. 2010) investigated the effects of high levels of trait anxiety on decision-making of subjects playing Iowa Gambling Task. Both studies reported that participants with high levels of trait anxiety showed a higher tendency to risk taking behaviour when compared to normal participants.

Thus, although both anxiety as well as impulsivity are not a unitary concept, it is legitimate to hypothesize that anxiety might display positive association with impulsivity, in some psycho-physiological perspective. This statement is clearly consistent with the only published study, conducted by Summerfeldt et al. (Summerfeldt, Hood et al. 2004), examining impulsivity (as a trait) in a sample of patients with primary anxiety disorders. The authors administered to both cases (40 patients with obsessive-compulsive disorder, 37 with panic disorder and 24 with social anxiety disorder) and healthy controls several self-assessment questionnaires, including the Barratt Impulsiveness Scale. Among the various results obtained, anxiety disorders patients reported significantly higher levels of trait impulsivity when compared to controls, with no differences among diagnostic subtypes. More specifically, the authors have found significant differences in the “cognitive domain” of impulsivity as measured by the “attentional” and “non planning” subscales of the BIS, with
the attentional subscale that accounted for the greatest amount of variance across clinical and non-clinical groups.

Finally, although the relationship between anxiety disorders and impulsivity has not been a focus of a large number of studies, the data obtained by Summerfeldt et al. (Summerfeldt, Hood et al. 2004) as well as the data revised above are likewise consistent with several records acquired, from different research groups, in specific diagnostic subtypes of anxiety disorders, as better described in the next sections.

2.2.1 Impulsivity in Panic Disorder

The relationship between Panic Disorder (PD) and impulsivity has not been adequately studied. The studies conducted so far lead to conflicting and mixed data mainly on some behavioural aspects of impulsivity such as suicidality and aggression (George, Anderson et al. 1989; Weissman, Klerman et al. 1989; Beck, Steer et al. 1991; Lepine, Chignon et al. 1993; Korn, Plutchik et al. 1997; Pilowsky, Wu et al. 1999).

Several studies (Weissman, Klerman et al. 1989; Pilowsky, Wu et al. 1999) have reported a higher incidence of suicidal ideation and suicide attempts in subjects with panic attacks. In other reports (Vickers and McNally 2004) a lifetime history of PD was not related with an increased risk of suicide attempts and, similarly, people with PD that have a higher risk of suicide attempts would be only those characterized by the presence of any comorbidities. In particular, high rates of suicidal ideation and behaviour were detectable in patients with panic attacks when associated with depression, substance abuse or borderline personality disorder (Lepine, Chignon et al. 1993). A recent study
(Huang, Yen et al. 2010) showed that 31.7% of a sample of outpatients with PD had experienced suicidal ideation in the previous 2 weeks, associated with young age, early onset of symptoms, alcohol consumption, symptom severity, reduced social support and sensitivity to drugs. Similarly, although aggressive behaviours have been reported in people with panic attacks (George, Anderson et al. 1989; Korn, Plutchik et al. 1997), the relationship between aggression and PD is unclear. However, in PD patients the comorbidity with depression seems to increase the prevalence of property destruction and aggression, as well as homicidal ideation, other than suicidal ideation (Korn, Plutchik et al. 1997).

Lastly, there is one single study conducted by Jakuszkowiak-Wojten et al. (Jakuszkowiak-Wojten, Gałuszko-Wegielnik et al. 2013) in which the authors explored the prevalence of trait impulsivity in a sample of subjects affected by Panic Disorder. The case series consisted of eleven patients diagnosed with panic disorder (DSM-IV-TR) and nine healthy volunteers, who were evaluated with the Barratt Impulsiveness Scale and with several neuropsychological test to assess cognitive functions. As main result, trait impulsivity, measured with the BIS, resulted higher in the experimental group compared to control group. Unfortunately, these preliminary findings have been obtained in a small sample, so the occurrence of trait impulsivity in the contest of primary panic disorder is not adequately explored.

2.2.2 Impulsivity in Generalized Anxiety Disorder

In literature, the relationship between Generalized Anxiety Disorder (GAD) and impulsivity has been widely neglected. Likewise, it is somewhat surprising the scarcity of studies regarding main behavioural correlates of impulsivity such as suicidality (Ma, Xiang et al. 2009; Thibodeau, Welch et al.
On the contrary, few studies have examined the relationship between anger and GAD suggesting that anger may be an important emotion associated with the disorder (Erdem 2009; Hawkins and Cougle 2011; Deschenes, Dugas et al. 2012). For example, Erdem (Erdem 2009) found that individuals with GAD had greater levels of trait anger and lower anger control, both in an externalized as well as in an internalized expression, than did non-anxious individuals. However, the relative contribution of each anger dimension to GAD is actually unclear: for example, Hawkins et al. (Hawkins and Cougle 2011) suggested that a diagnosis of GAD was related to a greater tendency to express anger externally, while Deschenes et al. (Deschenes, Dugas et al. 2012) found that an internalized anger expression was a stronger predictor of GAD diagnosis. Finally, there is only one study, conducted by Pierò (Piero' 2010), in which the Barratt Impulsiveness Scale, was administered in association to the Temperament and Character Inventory (TCI) to a sample of 79 subjects affected by GAD. As main finding, a high level of NS, measured by TCI, resulted correlated to higher levels of trait impulsivity as measured with the BIS in the case series. Unfortunately, a major limit of the study was the lack of a control group, requiring further studies to clarify the prevalence and the role of trait impulsivity in GAD.

2.2.3 Impulsivity in Social Anxiety Disorder

Social Anxiety Disorder (SAD) is characterized by an intense fear and avoidance of social situations where there is potential for evaluation or rejection by others (APA 2013). The prototypical patient affected by SAD has traditionally been described as shy, submissive, behaviourally inhibited, and risk averse (Crozier and Alden 2001). However, al least in a subgroup of
patients, the disorder appears to be correlated with a particular disposition towards risk-taking behaviours, impulsivity, affective and relational instability (Erwin, Heimberg et al. 2003; Leary, Twenge et al. 2006; Kashdan and Hofmann 2008; Kashdan, McKnight et al. 2009). For example, several authors have documented in these patients the occurrence of impulsive/aggressive reactions to rejection (real or perceived) (Leary, Twenge et al. 2006). Furthermore, having assumed the potential to subtype patients with social anxiety on the basis of the novelty seeking level, Kashdan et al. (Kashdan and Hofmann 2008) have identified an association with impulsive type behaviours (risk-prone and disinhibited behaviour) as well as a high comorbidity with substance use, in a subgroup of patients characterized by high levels of novelty-seeking tendencies. Later, the same authors (Kashdan, McKnight et al. 2009) have drawn, from the database of the National Comorbidity Survey-Replication (NCS-R) dataset, the clinical features of patients suffering from not prototypical social anxiety, selected on the basis of NCS-R risk-prone items. Subsequently, the former subgroup of patients was compared with patients suffering from the prototypical inhibited form (with a classical pattern of behavioural inhibition and risk aversion): the not prototypical subjects resulted younger, with higher rates of concomitant psychopathology (obsessive symptoms, anger, aggression, hyper sexuality) and, in an interesting way, with high comorbidity with impulse control disorders, substance use disorders, other anxiety disorders and mood disorders. The authors, among the various possible interpretations, supposed a biological-hereditary substratum, which can prepare those patients to these impulsive-uninhibited manifestations. It is interesting to underline how the psychopathological features and the course of these syndromes are superimposable on those of recent descriptions of some forms of soft bipolar spectrum, such as cyclothymia (Perugi and Akiskal 2002).
2.2.4 Impulsivity in Obsessive-Compulsive Disorder

In the previous edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) Obsessive-Compulsive Disorder (OCD) was comprised in the chapter of Anxiety Disorders, reflecting a sharing of the core symptom of anxiety. Notwithstanding, even though formerly considered a type of anxiety disorder, a special position has been traditionally reserved to OCD. The question of whether OCD should be maintained within the anxiety disorders has been vastly debated in literature (Stein, Fineberg et al. 2010), bearing in mind the possibility that certain disorders may be better characterized as OC-spectrum disorders. On the basis of a range of external validators and considering clinical utility, in DSM-V (APA 2013) the disorder is regarded as a unique condition, clustered separately from the Anxiety Disorders and arranged in a new Obsessive-Compulsive and Related Disorders (OCRDs). The OCRDs chapter comprises disorders such as trichotillomania and skin-picking disorder that can be considered as either impulsive or compulsive.

Commonly, OCD and impulsive behaviours are conceptualized as representing opposite ends of a continuum. This is partly due to the distance that seems to exist between the OCD manifestations, predictable, repetitive and high on harm-avoidance and the unpredictable reward-seeking traits that characterizes impulsive behaviour (Hollander and Wong 1995). Nevertheless, studies on OCD led to controversial data concerning the relationship with impulsivity. Consistently with the former conceptualization, BIS was given to OCD patients (recruited in the Field trial of the DSM-IV about the disorder) in order to investigate any relationship between impulsivity and compulsivity. The main results were as follows: a) patients with OCD did not differ from a control sample of young students in BIS scores; b) the scores obtained in the
attentional and non planning subscales of the BIS resulted positively correlated with the clinical severity of OCD; c) total BIS score positively correlated with the presence of symptoms characterized by aggressive and sexual impulses, and negatively with the control and cleaning rituals, d) finally, the BIS scores did not seem to correlate significantly with the treatment outcome (Stein, Hollander et al. 1994). Conversely, more recent studies showed an association between OCD and trait impulsivity as measured by the BIS (Summerfeldt, Hood et al. 2004; Ettelt, Ruhrmann et al. 2007; Boisseau, Thompson-Brenner et al. 2012; Benatti, Dell’Osso et al. 2014), particularly in the attentional area, suggesting a potential implication, at least, in subtypes of impulsive behaviour predisposition (i.e. dishinibitional/disattentional impulsivity).

Consistently with this latter hypothesis, other recent contributions induce to the recognition that the relationship between impulsivity and OCD may be more complex than previously conceptualized and not mutually exclusive. For example, it has been clearly demonstrated that OCD patients showed impaired response inhibition in a classical stop signal task compared to controls (Chamberlain, Fineberg et al. 2006; Penades, Catalan et al. 2007). Recent evidence has further suggested, using a stop signal task, that there are structural brain imbalances linked to inhibitory processing distinguishing both OCD patients and their unaffected first-degree relatives from healthy controls (Menzies, Achard et al. 2007; Chamberlain and Menzies 2009). Therefore, dysfunction of inhibitory control has been proposed as an endophenotype for OCD (Chamberlain and Menzies 2009). Subsequently, the response inhibition difficulties exhibited in OCD patients raise the intriguing possibility that behavioural mechanisms that are usually considered to contribute toward impulsive behaviour may, additionally, contribute to disorders characterized by high levels of compulsivity and/or the tendencies to perform compulsive acts.
There is also a growing consensus on assuming that this type of shared tendency toward behavioural disinhibition could result from a failure in “top-down” cortical control of fronto-striatal brain circuits, (or alternatively from over-activity within striatal neural circuitry) (Fineberg, Chamberlain et al. 2014). Actually, available data tend to confirm this modelling: for example, in a case report described by Luigjes et al. (Luigjes, Mantione et al. 2011) increasing the voltage of deep brain stimulation targeted at the nucleus accumbens increased impulsivity in two OCD patients and was reversed only after lowering the voltage. Possibly, the stimulation in the area of the nucleus accumbens at different voltages differently affects the cortico-striatal circuitry, which seems subsequently to play an important role in both forms of behaviour. Thereby, according to the speculation that impulsivity and compulsivity may share common neurobiological mechanisms some authors postulated an “impulsive–compulsive diathesis” (Fontenelle, Oostermeijer et al. 2011; Fineberg, Chamberlain et al. 2014).

However, further research is necessary to confirming a link between OCD and impulsivity: for example, data concerning investigations on delay discounting and relative mechanisms (i.e. choice impulsivity) in OCD patients are still needed.
3. AIMS OF THE RESEARCH

Our research aims to evaluate the presence and severity of impulsivity in patients with primary anxiety disorders using survey instruments that reflect different models of interpretation. It also aims to assess any differences from a control group coupled for demographic characteristics. Finally it explores the role of comorbidities with cyclothymic disorder and the relationships with affective temperaments and mood symptomatology.

The hypotheses are as follows:

A. Both trait and state impulsivity may be greater in patients with anxiety disorders if compared to controls.

B. Impulsivity may not be connected to Anxiety Disorder diagnosis in itself (Panic Attacks, Social Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder), but it is mediated by comorbidity with mood spectrum disorders, in particular with cyclothymia.

C. There may be variability in the impulsivity levels, in its trait and/or state components, related to specific affective temperamental traits or to affective symptoms.

D. We tried to verify the preceding hypotheses, other than in a mixed case sample of subjects belonging to different diagnostic anxiety subtypes, in specific anxiety disorders, beginning with panic disorder.
4. METHOD

4.1 Evaluation procedure

The study was approved by the local Ethics Committee of the “Azienda Ospedaliero-Universitaria Pisana”. Each subject included in the study was extensively informed about the study procedures and gave his/her own written informed consent before starting any evaluation.

All subjects gave their informed consent and were evaluated by a psychiatrist (ADC) supervised by a senior psychiatrist (GP). The psychiatrist underwent a specific training for the administration of the rating tools for symptoms, affective temperaments and personality aspects, as well as for impulsivity.

The diagnostic evaluation was performed using the Mini Neuropsychiatric Interview (MINI) a brief structured interview used to make the diagnosis of major Axis I syndromes, on the basis of criteria provided by DSM-III-R for specific nosographic entities.

The diagnosis of cyclothymic disorder was made considering two sets of criteria:

1. On the basis of the DSM IV-R diagnostic criteria that require the presence, for at least 2 years, of numerous periods with hypomanic symptoms not meeting Manic Episode criteria associated with numerous periods with depressive symptoms not meeting Major Depressive Episode criteria. It is not necessary that the periods of hypomanic symptoms meet either the duration or symptoms threshold criterion for a Hypomanic Episode;

2. On the basis of a broader approach that considers the criteria for Hypomanic Episode satisfied when symptoms occur for at least two days. More
specifically, we adopted the criteria for hypomania based on Akiskal et al. (Akiskal, Djenderedjian et al. 1977): patients must satisfy at least three of Washington University criteria (Feighner, Robins et al. 1972) for mania but at sub-syndromal level, for a period not longer than two days, without having psychotic features and without presenting a significant impairment of functioning during the period of mood elevation. In particular, the following must be absent: difficulty to maintain a proper conversation over time; euphoric mood that turns into a vindictive hostility; hallucinations or delusions about patient's own capacities or identity; persecutory delusions, auto-referential delusions, erotomanic delusions, and critical lack of insight to such an extent that leads to a significant social impairment. The validity of the 2 days threshold for hypomania has been confirmed in studies examining the family history and longitudinal course of a large clinical and control group population as shown in the International Exchange on Bipolar Disorders (Akiskal, Bourgeois et al. 2000; Angst and Marneros 2001). Moreover Angst (Angst and Marneros 2001) reported lifetime prevalence rates for brief episodes of hypomania associated with brief depression ranged between 5 and 8%. More in detail, the authors suggested that the average length of a hypomanic episode in general population seems to be 2 days, while in many cyclothymic patients elated episodes are shorter than 1 day and, often, associated with environmental stimuli or substance misuse.

The symptomatological evaluation was done by:

- the Bach-Raphaelsen Depression and Mania Scale (BRMS) (Bech, Bolwig et al. 1979; Bech 1988), a hetero-administered questionnaire that assesses the presence of depressive and manic symptoms, exploring the various aspects of the depressive or manic syndromes;
• the State-Trait Anxiety Inventory (STAI) (Spielberger 1983), a self-report inventory based on a 4-point Likert scale with 40 items. The STAI measures two types of anxiety: state anxiety, or anxiety about an event, and trait anxiety, or anxiety level as a personal characteristic;

• the Hypomania Check List (HCL - 32) (Angst, Adolfsson et al. 2005) is a self-report questionnaire, translated into several languages, that comprises a list of hypomanic symptoms that the subject must mark as "present" (or typical) or "absent" (or not-typical). The questionnaire includes other eight items assessing the severity and impact of the symptoms on different functional areas. The total score is obtained by adding the marked symptoms. The questionnaire was developed for the screening of clinical conditions belonging to the bipolar spectrum (Angst, Adolfsson et al. 2005; Vieta, Sánchez-Moreno et al. 2007). In particular, the questionnaire focuses on hypomania, crucial for the distinction between recurrent major depressive disorder and type II bipolar disorder: a score greater than 14 showed a good sensitivity (0.8) and a good specificity (0.51) to differentiate the subjects affected by unipolar or bipolar mood disorders, once subjected to standardized diagnostic evaluation (Vieta, Sánchez-Moreno et al. 2007). The questionnaire is not specific enough to differentiate between clinical subtypes (i.e. type I or II bipolar disorder). However, it presents an interesting independence from the current mood state of the subject at the evaluation time, making it a tool useful in symptomatic patients (Angst, Adolfsson et al. 2005).

• the Clinical Global Impression Severity and Improvement (CGI) (Guy 1976) is probably the most frequently used scale for the assessment of general psychopathology. It requires the formulation of a clinical judgment in 3
areas: the severity of the disease, the overall improvement and the treatment outcome. We have administered the first subscale (CGI-Severity), which explores, through a 7-point scale, the severity of the global symptomatology.

The temperamental and personality trait evaluation was carried out using:

- the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Modified (TEMPS-M) (Erfurth, Gerlach et al. 2005), a self-evaluation questionnaire consisting of 35 items that detect the affective and anxious temperamental characteristics according to Akiskal and Mallya criteria (Akiskal and Mallya 1987). The questionnaire is composed of five subscales and each of them considers, in a quantitative way, the presence of depressive, cyclothymic, hyperthymic, irritable or anxious temperamental features;

- the Separation Anxiety Symptoms Inventory (SASI) (Silove, Manicavasagar et al. 1993), a self-evaluation form made up of 15 items which explores the separation anxiety symptoms of the first eighteen years of age;

- the Interpersonal Sensitivity Symptoms Inventory (ISSI) (Davidson, Zisook et al. 1989), a self-evaluation form composed of 36 items which investigates the judgement and criticism sensitivity of the subject and the way the subject relates to others.

The impulsivity evaluation has been carried through:

- the Barratt Impulsiveness Scale (BIS) (Patton, Stanford et al. 1995), a self-administered questionnaire made up of 30 questions with four possible answers in an increasing scale which assesses the degree and type of trait impulsivity in a subject. The total score (ranging from 30 to 120) provides a
quantitative evaluation resulting from a combination of three factors: attentional impulsivity (inattention and cognitive instability with minimum score: 8; maximum: 32), motor impulsivity (motor impulsiveness and lack of perseverance with minimum score: 11, maximum: 44) and non-planning impulsivity (lack of self control and intolerance of cognitive complexity with minimum score: 11, maximum: 44);

• the Immediate And Delayed Memory Task (IMT/DMT) (Dougherty and Marsh 2003) a modified and more challenging version of the Continuous Performance Test (Rosvold, Mirsky et al. 1956), a test used for the assessment of attention and working memory. In the first task, the IMT, strings of five numbers appear in a sequence on a computer screen with a 0.5 sec interval: the subject is instructed to compare the strings and to respond with a mouse click, only when the latter string displayed is exactly as the former one. Three types of responses are particularly significant: 1. the correct answers (correct detection, hit) if the person clicks the mouse after identifying a sequence that corresponds to the previous one; 2. the incorrect answers (random error) if the subject chooses a sequence which is not identical to the previous one; 3. the false alarms (commission error) in which the subject responds by clicking a sequence that resembles but it is not identical to the previous one, having in common four of its five numbers. These latter ones are considered the impulsive type errors, induced by the tendency of the subject to respond, in the presence of a stimulus similar to the target, in a quickly but incorrect way, that is, before having assessed the actual difference. The delayed memory task is similar but for the presence, between sets of numbers to be matched, of three “distracting stimulus” consisting of the string “12345” shown for 0.5 s at 0.5-second intervals. In the
results we report only correct detections and commission errors; random errors never exceeded 5% and did not vary across any experimental groups.
5. RESULTS AND DISCUSSIONS

5.1 RESULTS AND DISCUSSION FOR HYPOTHESIS A

Impulsivity, in its trait and/or state component, may be greater in patients with anxiety disorders if compared to controls.

5.1.1 Clinical sample and control subjects

In the initial phase of the research design we enrolled a sample of 47 subjects in a period of about 1 year: all subjects were afferent to the outpatient services of the “Unità Operativa di Psichiatria 1 dell’Azienda Ospedaliero-Universitaria Pisana”. The sample includes 30 (63.8%) females and 17 (36.2%) males with a mean age of 34.5 years (sd = 10.3, range 19-63) who meet the DSM-IV-TR criteria for at least one Anxiety Disorder (Panic Disorder, Obsessive Compulsive Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder). Patients who present comorbidity for lifetime schizophrenia or other psychotic disorders, organic psychiatric syndromes and severe somatic disorders were excluded.

We additionally recruited a group of 45 control subjects matched for age, sex, education and employment including 28 (62.2%) females and 17 (37.8%) males with a mean age of 34.8 years (sd = 10.2, range 19-63); they did not satisfy the diagnostic criteria for any psychiatric disease or general medical condition with psychiatric significance.

All the subjects (n = 92) provided written informed consent to participate in the study.
5.1.2 Statistical Analysis

Comparative analysis for familial, epidemiologic, clinical features and course of different subgroups was performed using the t-student test for dimensional variables (Mann-Whitney U-test, when appropriate) and the chi-square test for categorical variables (Fisher exact-test, when appropriated). Due to the number of subjects and the confirmatory nature of our study, we considered, in a conservative way, two-tails significance levels with threshold at $p < 0.05$.

5.1.3 Demographic Characteristics

Table A1 shows the demographic features of the initial sample of patients with anxiety disorder ($n = 47$) and controls ($n = 45$). The comparison of the two groups did not show significant differences with regard to gender distribution, average age, schooling, occupation and marital status. It should be noted that the investigator team has paid special attention in selecting the group of control subjects matching age, education, occupation and social class, since all of these could influence measures of impulsivity (Dougherty, Marsh et al. 2002).

5.1.4 Diagnostic distribution, comorbidity and treatment

The diagnostic profile among the anxiety disorder patients ($n = 45$) is shown in Table A2. The most frequent diagnosis was panic disorder: in particular, 26 subjects (55.3%) met diagnostic criteria for panic disorder with agoraphobia, 11 subjects (23.4%) for panic disorder without agoraphobia, and only one subject met the criteria for agoraphobia without panic disorder. As for the other anxiety disorders, 12 subjects (25.5%) met the criteria for obsessive-compulsive disorder, 9 subjects (19.1%) met the criteria for a generalized anxiety disorder and 7 (14.9%) for social anxiety disorder. In some cases it was
possible that the subjects met the diagnostic criteria for more than one anxiety disorder.

Table A3 shows the distribution of psychiatric conditions in comorbidity. In the initial sample of patients with anxiety disorder, 9 (19.1%) reported a spontaneous hypomanic episode and 10 (21.3%) a hypomanic episode induced by pharmacological treatment. In 5 subjects (10.6%) it was possible to perform the diagnosis of cyclothymic disorder according to DSM-IV-TR criteria, while in a much greater number, 26 subjects (55.3%), it was possible to diagnose cyclothymic disorder using modified criteria for hypomania based on 2 days threshold (Akiskal, Djenderedjian et al. 1977; Angst and Marneros 2001). The control subjects (n = 42) did not meet the diagnostic criteria for any psychiatric disorder according to DSM-IV-TR criteria.

Table A4 shows the current psychopharmacological treatment of anxiety disorder patients. At the time of observation, 12 patients (25.5%) were receiving antiepileptic drugs (mainly gabapentin or pregabalin), 23 subjects (48.9%) SSRI, 3 (6.5%) SNRI, 7 (15.2%) TCA, 8 (17.4%) other antidepressants (bupropion, mirtazapine, trazodone). A small percentage of patients (n = 3, 6.5%) was treated with a typical or atypical antipsychotic in combination with antidepressant therapy; 5 patients (10.6%) took anxiolytics and / or hypnotics.

5.1.5 Symptomatological and personological evaluation

Table A5 shows the clinical scale scores obtained by subjects with anxiety disorder and healthy controls. With regard to the affective symptoms individuals with anxiety disorder differed from controls showing higher scores in the Bach-Raphaelsen Mania scale (BRMS) (p = .001), the Bach-Raphaelsen Depression scale (BRDS) (p = .004), in the STAI, both as regards the state
component (STAI-S) both as regards the trait component (STAI-S) (both \( p < .001 \)), as well as in hypomania check list (HCL32) (\( p < .001 \)). For this latter we calculated, for each group, the subjects percentage who achieved a \( \geq 14 \) score. This score was the one with the best sensitivity and specificity for retrospective screening of hypomanic episodes in patients with depression and mood disorders in various phases of disease (79, 81, 88). Among the patients with anxiety disorder a high percentage, 63.8\%, reached a \( \geq 14 \) score, the percentage decreased to 31.1\% in the control group with a significant difference between the two groups (chi-square = 9.86, \( p = .002 \)).

Anxiety disorder patients obtained a mean score on the Clinical Global Impression Severity (CGI-S) of 3.32 (sd = 1.0), indicating a global severity of the disease between mild and moderate. As regards the assessment of temperamental characteristics, anxiety disorder individuals had significantly higher scores in four subscales, out of five, of the TEMPS-M (depressive temperament, cyclothymic and anxious, \( p < .001 \), irritable temperament, \( p = .018 \)). Instead, we did not find any significant differences between the two groups regarding the hyperthymic temperament subscale; in this latter case, moreover, the average scores were slightly higher in the controls (\( t = -1.466, p = .146 \)), but the difference was not significant. As expected, individuals with anxiety disorder had significantly higher scores than controls on the Separation Anxiety Sensitivity Index (SASI) (\( p < .001 \)), for the assessment of the separation anxiety in youth. Regarding the Interpersonal Sensitivity Symptoms Inventory (ISSI), in which high scores are indicating an increased sensitivity to rejection in interpersonal context, the average scores were significantly lower in patients than in controls (\( p < .001 \)).
5.1.6 Impulsivity assessment

Table A6 shows the scores obtained on the Barratt Impulsiveness Scale (BIS) by the subjects suffering from anxiety disorder and healthy controls. Interestingly, it was possible to identify significant differences between the two groups in the total score, statistically higher (p < .001) in anxious subjects if compared to controls as well as in the subscales of the "attentional" and "motor" impulsivity that were also significantly higher in anxious subjects (respectively, p <.001 and p = .004). The score on the "non-planning" subscale was also higher in anxious subjects, reaching however a weak statistical significance (p = .047).

Table A7 shows the performance to the immediate (IMT) and Delayed (DMT) Memory Task of anxious subjects and controls. In the first task, the IMT, anxious subjects and controls did not differ in the percentage of correct answers (correct detections, p = .745), but significantly differed in the percentage of impulsive responses (commission errors, p < .001), much more represented in anxious subjects compared to controls. It was not possible to differentiate the two groups taking into account the response latencies, both in terms of the average response times to targets (which generate correct answers) both in terms of the average response time to "false alarms "(which generate the impulsive type answers or commission errors). The value of the A’ parameter (discriminability), a measure of the ability to distinguish the correct stimulus from other stimuli that are like the correct stimulus, was significantly higher in controls (p = .006) indicating, for the last ones, a better ability of differentiation. The controls also demonstrated a greater tendency to provide conservative type answers, as indicated by the presence of a significant difference (p = .016) compared to the cases, in the B” parameter (response bias).
In the second task, the DMT, generally recognized as more challenging than IMT (Dougherty, Marsh et al. 2002), patients with anxiety disorder and controls differed in the percentage of correct answers (correct detections, p = .018), more represented in controls than in cases, as well as in the percentage of impulsive type responses (commission errors, p < .018), and in this case more represented in anxious subjects, but with a weak significance (p = .046). Similarly to the IMT, even in the DMT it was not possible to distinguish between the two groups taking into account responses latencies. The value of the A' parameter (discriminability) remained significantly higher in controls (p = .004). Cases and controls, finally, manifested the same tendency to provide conservative type answers in the DMT, as indicated by the lack of a significant difference between the two groups in the B'' parameter.

5.1.7. Discussion

The aim of the initial part of our research was to obtain a complete profile of impulsivity in a mixed sample of patients suffering from anxiety disorder and to compare it with that of healthy control subjects. To the best of our knowledge, this is the first study using different paradigms (both trait and state measure) largely applied to patients with mood disorders, conduct disorders and substance use disorders to evaluate impulsivity in patients with anxiety disorders.

Concerning the symptomatological features, the subjects suffering from anxiety disorders reported, as expected, higher STAI scores than controls (Kabacoff, Segal et al. 1997) as well as BRMS and BRDS scores. According to some authors, the presence of affective symptoms in subjects suffering from anxiety disorder can not be classified as simple secondary reactions to the
disorder (Bieling, Antony et al. 1998; Rickels and M. 2001). Moreover, using the HCL-32, we performed a retrospective screening of hypomaniac symptoms highlighting how, in our sample, subjects suffering from anxiety disorders reported scores significantly higher than controls. Additionally, the first ones (in a high percentage 63.8% vs 31.1%) reached a score above 14, resulted with a good specificity (0.51) and sensitivity (0.80) for the screening of previous hypomania in patients with depression and mood disorders in various phases of disease (Meyer, Hammelstein et al. 2007; Vieta, Sánchez-Moreno et al. 2007). Even if we take account of unavoidable false positives of a screening tool, the data obtained appear congruent with the structured diagnostic assessment. Within our sample, there are 9 subjects (19.1%) suffering from anxiety disorder who satisfy the diagnostic criteria, according to DSM-IV-TR, for at least one spontaneous hypomaniac episode and 10 subjects (21.3%) with hypomania induced by antidepressant treatment. In 5 subjects (10.6%) it was also possible to perform diagnosis of cyclothymic disorder according to the DSM-IV-TR criteria, while in a much greater number, 26 subjects (55.3%), it was possible to perform diagnosis of cyclothymic disorder using the modified criteria based on Akiskal et al. (Akiskal, Djenderedjian et al. 1977; Angst and Marneros 2001). In our sample, therefore, the primary diagnosis of anxiety disorder is associated with some conditions of the spectrum of mood disorders, represented mainly by attenuated forms not included in the official taxonomy (Savino, Perugi et al. 1993; Perugi and Akiskal 2002; Hantouche, Angst et al. 2003). Should be noted that the validity of the shortened threshold of two days for hypomania has been confirmed in several studies examining the family history and longitudinal course of a large clinical and control group population as shown in the International Exchange on Bipolar Disorders (Akiskal, Djenderedjian et al. 1977). In a final consideration, we propose the important theoretical question of
the relationship and nature of the phenomena of comorbidity between anxiety disorders and bipolar spectrum disorders, previously reported in literature (Savino, Perugi et al. 1993; Perugi and Akiskal 2002). Not surprisingly, concerning the temperamental profile on the TEMPS-M, our patients suffering from anxiety disorders achieved significantly higher scores in four out of five subscales (depressive cyclothymic, irritable and anxious temperament). This temperamental profile is associated to a particular sensitivity to the separation anxiety. Moreover, the relationship between cyclothymic affective instability, separation anxiety as well as increased sensitivity to rejection in interpersonal context (closely related to mood reactivity) has been clearly confirmed by different research group (Perugi, Toni et al. 2003; Pini, Abelli et al. 2005).

With regard to the psychometric assessment of impulsivity, in our sample of patients with anxiety disorders the levels of trait impulsivity, at least as it has been conceptualized by Barratt (Barratt 1965), appear considerably higher than those presented by controls. Although anxiety and impulsivity have been traditionally considered orthogonal dimensions (Barratt 1965; Askenazy, Caci et al. 2000), our results are in line with data obtained from Summerfeldt et al. (Summerfeldt, Hood et al. 2004) on a large clinical sample of patients with anxiety disorders (40 patients with obsessive-compulsive disorder, 37 with panic disorder and 24 with social anxiety disorder) compared with a control group. The authors administered to both cases and healthy controls several self-assessment questionnaires, including the BIS. Among the various results obtained, the higher scores reported on the BIS ('total', but also 'attentional' and 'non planning' subscales) in anxious subjects compared to controls confirm our finding. Both clinical samples have, in fact, a level of a total and attentional impulsivity statistically higher than the control groups. The 'non planning'
subscale made possible to differentiate between cases and controls in the sample of Summerfeldt et al. (Summerfeldt, Hood et al. 2004), but not in ours, while for the 'motor' subscale the two clinical records seem to have an opposite trend. These results clash with the widespread tendency to consider anxiety and impulsivity orthogonal and tend to support the extended literature documenting a close association between these two dimensions in some specific disorders. As previously described, anxiety and impulsivity frequently co-occur in disorders characterized by behavioural dyscontrol such as pathological gambling (Roy, Adinoff et al. 1988; Barrault and Varescon 2013), eating disorders (Waxman 2009), personality disorders characterized by self-injuring (Simeon, Stanley et al. 1992). Moreover there are several works documenting how anxiety disorders co-occur in conditions characterized by high levels of impulsivity, such as attention deficit disorder and hyperactivity (Baldwin and Dadds 2008) and conduct disorders in adolescents and young adults (Askenazy, Sorci et al. 2003). Thus, the evidence of a coexistence of anxiety and impulsivity, both in a dimensional as well as in a categorical perspective, in specific populations has been consolidated. More recently, some clinicians have focused on atypical forms of anxiety disorders leading to the recognition of non-prototypical forms, that are not primarily characterized by behavioural inhibition and risk aversion (Erwin, Heimberg et al. 2003; Leary, Twenge et al. 2006; Kashdan and Hofmann 2008; Kashdan, McKnight et al. 2009). For example, at least in a subgroup of patients, social anxiety appears to be correlated with a particular disposition towards risk-taking behaviours, impulsivity, affective and relational instability (Erwin, Heimberg et al. 2003; Leary, Twenge et al. 2006; Kashdan and Hofmann 2008; Kashdan, McKnight et al. 2009). Similarly, several authors have documented in these patients the occurrence of impulsive/aggressive reactions to real or perceived rejection.
(Leary, Twenge et al. 2006) as well as the predisposition toward risk-prone and impulsive behaviour, resulting in a growing evidence for the heterogeneity of the disorder (Kashdan and Hofmann 2008; Kashdan, McKnight et al. 2009). More in detail, Kashdan et al. (Kashdan and Hofmann 2008) have identified an association with impulsive type behaviours (risk-prone and disinhibited behaviour) as well as a high comorbidity with substance use, in a subgroup of social phobic patients characterized by high levels of novelty-seeking tendencies. The same authors (Kashdan, McKnight et al. 2009) have drawn, from the database of the National Comorbidity Survey-Replication (NCS-R) dataset, the clinical features of similar patients suffering from not prototypical social anxiety, selected on the basis of NCS-R risk-prone items. They were compared with patients suffering from the prototypical inhibited form (with a classical pattern of behavioural inhibition and risk aversion) and resulted younger, with higher rates of concomitant psychopathology (obsessive symptoms, anger, aggression, hyper sexuality) and, in an interesting way, with high comorbidity with impulse control disorders, substance use disorders, other anxiety disorders and mood disorders. The authors, among the various possible interpretations summoned a biological-hereditary substratum, which can prepare those patients to these impulsive-uninhibited manifestations. It is interesting to underline how the psychopathological features and the course of these syndromes are superimposable on those of recent descriptions of some forms of soft bipolar spectrum, such as cyclothymia and bipolar II disorder (Perugi and Akiskal 2002).

Concerning state impulsivity, in our clinical records, patients with anxiety disorders and controls do not differ in the correct answers but they significantly differ in the impulsive responses, more represented in the former ones, while it
is not possible to differentiate the two groups taking into account the response latency. Therefore, patients with anxiety disorder do not have a particular mnemonic or attentional impairment as demonstrated by the number of correct answer (representing an indicator of cognitive integrity), but they show higher impulsivity of the disinhibitional/disattentional type as highlighted by the tendency to respond to a stimulus before fully evaluating its features. In DMT, patients with anxiety disorder provided a lower number of correct answers when compared to healthy controls, while it is confirmed the greater tendency to give impulsive answers. With regard to IMT, the differences in the anxious subject performance are, for the most part, considered as primarily determined from the different type of task in question, which includes more latencies and a distractor stimulus, which is generally recognized as more challenging than the previous one (Dougherty, Bjork et al. 2000). As for IMT, even in DMT it is not possible to discriminate the two groups taking into account the latency time, while the discriminative ability significantly remains higher in controls. These results tend to confirm that anxious subjects could be prone to subtypes of state impulsivity, in particular to its disinhibitional/disattentional forms. Supporting this assumption, there are some recent evidences that suggest a possible relationship between anxiety and disturbances in specific executive functions, such as attention, inhibitory control and task shifting (see Ansari et al. (Ansari and Derakshan 2011) and Eysenck et al. (Eysenck, Derakshan et al. 2007) for reviews) as well as a possible relationship between anxiety and complex decision-making (Miu, Heilman et al. 2008; de Visser, van der Knaap et al. 2010).

In conclusion, the presence of not just trait but also state impulsivity in our anxiety disorders patients provides a better foundation the clinical evidences
for a subset of people with anxiety disorder who are aggressive, impulsive and novelty seekers (Kashdan, McKnight et al. 2009; Jakuszkowiak-Wojten, Gałuszko-Wegielnik et al. 2013) and deviate from that prototype characterized by high levels of harm avoidance, behavioural inhibition and hypercontrol (Brown 1996; Zinbarg and Barlow 1996).
5.2 RESULTS AND DISCUSSION FOR HYPOTHESIS B

“Impulsivity may not be connected to Anxiety Disorder diagnosis in itself (Panic Attacks, Social Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder), but it is mediated by comorbidity with attenuated mood disorders, in particular with cyclothymia”.

5.2.1 Clinical sample and control subjects

During the first part of the research we have compared impulsivity, measured by different rating tools, in 47 patients with anxiety disorders and 45 healthy controls. In the same sample we now explore the influence of comorbid soft bipolar spectrum disorders on the relationship between anxiety disorders and impulsivity.

For this purpose, the initial sample of 47 patients has been divided into two subgroups according to the presence, or absence, of comorbidity for cyclothymic disorder. The first subgroup (Cyclo+) was composed of 26 patients, 5 of them met the criteria for cyclothymic disorder according to the DSM-IV TR and 21 of them met the modified criteria according to Akiskal et al. (Akiskal, Djenderedjian et al. 1977; Angst and Marneros 2001). The second (Cyclo-) subgroup was composed of the remaining 21 patients with anxiety disorder who met neither the criteria for cyclothymic disorder according to DSM-IV-TR, nor those modified by Akiskal et al. (Akiskal, Djenderedjian et al. 1977).

5.2.2 Statistical analysis

We compared familial, epidemiologic and clinical features of Cyclo+ (n = 26), Cyclo- (n = 21) and control subjects (n = 45). Comparative analysis was
performed using one-way ANOVA for dimensional variables and contingency tables for categorical ones. Due to the number of enrolled subjects and the confirmatory nature of our study, we considered, conservatively, a two-tailed significance level of \( p < 0.05 \).

5.2.3 Demographic Characteristics

As shown in Table B1, a comparison between the 3 groups, Cyclo +, Cyclo- and controls, showed no significant differences regarding gender distribution and the average age.

5.2.4 Symptomatological and personological evaluation

Table B2 shows the scores on the clinical scales obtained by the subjects belonging to the three groups. As regards the symptomatological aspects, the three groups showed no significant differences in BRMS scores. In the BRDS Cyclo+ obtained higher scores than the Cyclo-, which in turn obtained higher scores than controls \( (F = 19.490, p < .001) \). The three groups behaved in the same way as regards the STAI, both in the state component both for the trait one \( \text{STAI-S: } F = 15.293 \text{ p < .001}; \text{STAI-T: } F = 28.362 \text{ p < .001} \), as well as the HCL-32 \( (F = 12.379, p < .001) \). All three scales kept the same type of trend: the Cyclo+ subjects obtained average scores greater than the Cyclo- ones, which, in turn, obtained higher scores than the controls. In addition to the average score on the HCL-32, we calculated, for each group, the percentage of subjects who achieved a score \( \geq 14 \). Even in this parameter, as expected, the Cyclo+ showed the highest rate and the controls the lowest one, with Cyclo- setting in the intermediate position (chi-square = 13.86, p = .001)
The Cyclo+ subjects obtained an average score of 3.54 (sd = 0.989) on the CGI-Severity, higher than the Cyclo- subjects who achieved a 5.3 score (sd = 0.921). With regard to the assessment of temperamental characteristics, quantitatively explored through the TEMPS, Cyclo+ subjects had higher scores than the Cyclo- ones in four out of five subscales (depressive, cyclothymic, anxious, irritable temperament). The Cyclo- anxious subjects, in turn, had higher average scores than the controls in the same subscales. For each of the four subscales, the differences among the three groups reached statistical significance (depressive temperament: F = 37.794, p < .001; cyclothymic: F = 25.833, p < .001; anxious: F = 14.932, p < .001, irritable temperament: F = 4.934, p = .009). Instead, we did not find any significant differences among the three groups as regards the subscales used to estimate the presence of hyperthymic temperamental elements (F = 1.196, p = .307); in the last case, moreover, the average scores were slightly higher in controls compared to the Cyclo- and the latter ones reached average scores higher than the Cyclo+. Finally, the three groups differed in the SASI scores and in the ISSI ones. In the first case the Cyclo+ subjects showed higher scores than Cyclo-, which in turn had higher scores than controls (F = 7.217, p = .001). In the second case the highest scores, indicators of lower sensitivity to judgment and criticism, were the prerogative of the controls, followed by Cyclo-, while Cyclo+ subjects obtained the lowest scores (F = 7.275, p = .001).

5.2.5 Impulsivity assessment

Table B3 shows the scores obtained on the BIS by subjects of the three groups. The total score obtained by the Cyclo+ was higher than that obtained by the Cyclo- subjects; the last ones, in turn, obtained total scores higher than those by the controls. The differences among the three groups reached a
statistical significance ($F = 9.553$, $p < .001$). The scores on the "attentional" and "motor" subscales were also higher in Cyclo+ subjects than in Cyclo– ones and in the controls (respectively, $F = 11.153$, $p < .001$ and $F = 5.928$, $p = .004$). On the other hand it was not possible to differentiate the three groups taking into account the scores obtained in the "non-planning " subscale ($F = 2.010$, $p = .14$).

Finally, table B4 shows the Immediate and Delayed Memory Task performances. In the first task, the IMT, the three groups did not differ in the correct answer percentage (correct detections, $F = 0.091$, $p = .913$), but they significantly differed in the impulsive response percentage (commission errors, $F = 17.237$, $p < .001$), more significantly represented in the Cyclo+ subjects than in Cyclo – ones and in the controls. But it was not possible to differentiate the three groups taking into account the response latencies, both in terms of the response average time to correct stimuli both in terms of the average response time to "false alarms" (respectively $F = 2.512$, $p = .087$, $F = 0.773$, $p = .465$). The A’ parameter value (discriminability), a measure of the ability to discriminate the correct stimulus from other types of stimuli that resemble the correct one, was greater in the controls, followed by the Cyclo- subjects. On the contrary the A’ parameter value in the Cyclo+ subjects was low indicating, for the last ones, lower discrimination ability ($F = 6.887$, $p = .002$). In the second task, the DMT, the three groups differed, even though for a weak significance, in the correct answers percentage (correct detections, $F = 3.240$, $p = .044$), as well as in the impulsive type response percentage (commission errors, $F = 12.621$, $p < .001$), the last ones were more represented in Cyclo+ subjects followed, in this case, by the controls. The lower percentage of impulsive response was obtained by Cyclo-. Unlike the IMT, in the second task the three groups differed in the response latencies to the target stimulus (which causes correct responses): the
average latency of response in the Cyclo+ subjects appeared to be the shortest, followed by that of the controls, in turn faster than Cyclo- subjects (F = 3.932 P = .023). On the contrary, the response latencies of the catch stimulus (which produces impulsive responses) did not allow to discriminate the three groups (F = 0.815 P = .446). The A’ parameter value (discriminability) was, even in the DMT, greater in the controls, followed by the Cyclo- subjects, while in the Cyclo+ subjects appeared low, confirming, also for this task, the lower discrimination ability in the cyclothymic (F = 6.933 P = .002).

5.2.6 Discussion

With regard to the symptomatological evaluation, cyclothymic patients obtained scores higher than the not cyclothymic ones in the anxiety as well as in the depression and mania scales. Also, the global severity of symptoms was higher in the cyclothymic ones. Anxious not cyclothymic patients obtained scores of an intermediate severity between the cyclothymic and controls. In conclusion, and as expected, the cyclothymic subjects were burdened with more symptoms of anxiety and depression, and had a greater global severity of psychopathology (Akiskal, Djenderedjian et al. 1977). In the retrospective evaluation, they most frequently show hypomania and hypomanic symptoms if compared to the not cyclothymic and to controls. Regarding the temperamental and personological features cyclothymic subjects showed high scores in four out of five of the TEMPS subscales (depressive, cyclothymic, anxious, irritable temperament), while they did not differ with regard to the subscale of hyperthymic temperamental elements: in the latter case, moreover, the average scores were slightly higher in controls than in the cyclothymic. Therefore, also in our sample, it is confirmed that subjects with anxiety disorders and cyclothymia are characterized by a temperamental disposition of a cyclothymic-
depressive-anxious and irritable type associated with separation anxiety and interpersonal sensitivity (Perugi and Akiskal 2002; Signoretta, Maremmani et al. 2005; Hantouche and Perugi 2012).

Regarding the psychometric evaluation of impulsivity, cyclothymic patients showed higher levels of trait impulsivity than not cyclothymic and controls. It was the same trend for the attentional and motor subscales while it was not possible to discriminate between the three groups taking into account the scores obtained in the non-planning subscale. Also, the neurocognitive evaluation showed higher levels of inattentive/uninhibited impulsivity in subjects suffering from anxiety disorders and able to satisfy the cyclothymic disorder criteria. In particular, on the IMT, the three groups did not differ in the correct answer percentage, but significantly differed in the impulsive responses, which were more represented in cyclothymic subjects. It was not possible to differentiate the three groups taking into account the response latencies. The ability to discriminate the correct stimulus from other types of stimuli similar to the correct one was low in cyclothymic subjects, indicating a shorter ability of discrimination. The same trend is re-proposed on the DMT, where the three groups substantially did not differ in the correct answer percentage but in the impulsive responses, more represented in cyclothymic subjects and then followed by the controls, in this case. Unlike the IMT, in the second task the three groups differed in the response latency time: the average latency of response to the target stimulus (but not that to the catch stimulus) resulted the shortest in cyclothymic subjects followed by that of the controls, in turn faster than the not cyclothymic ones. Even in the DMT, the stimulus discriminative ability was greater in controls and lower in the cyclothymic. In conclusion both trait and state impulsivity, measured by psychometric instruments and
neurocognitive paradigms, appear higher in subjects who also met the criteria for cyclothymic disorder, independently from anxiety disorder diagnosis. It is also interesting that people suffering from anxiety disorder, but not able to meet the criteria for cyclothymic disorder, appear to be more impulsive than controls in trait retrospective measurements, but not in the neurocognitive testing, at least in DMT performances (Summerfeldt, Hood et al. 2004; Kashdan and Hofmann 2008; Kashdan, McKnight et al. 2009).

Summarizing and consistently with our original hypothesis, the patient subgroup with anxiety and cyclothymic disorder seems to be characterized by affective instability, separation anxiety and interpersonal sensitivity, and, ultimately, impulsivity.

Impulsivity, evaluated according to a psychometric and neurocognitive perspective, has been clearly associated with bipolarity (for a review, see (Najt, Perez et al. 2007). High levels of impulsivity have been highlighted in the various affective phases of bipolar disorder as well as in euthymic phases (Swann, Anderson et al. 2001; Swann, Steinberg et al. 2008; Swann 2010). Moreover, the presence of a concomitant anxiety disorder does not prevented and/or reduced impulsivity in bipolar disorder patients. In this regard, Taylor et al. (Taylor, Hirshfeld-Becker et al. 2008) evaluated a sample of 114 subjects (62% of whom have been diagnosed with I type bipolar disorder, 25.5% with II type bipolar disorder, and the remaining with NOS bipolar disorder) having one, or more, comorbidities for anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder). The presence of an anxiety disorder in patients with bipolar disorder resulted peculiarly associated to the presence of higher levels of impulsivity. Since the coexistence of anxiety and impulsivity is
frequent in subjects suffering from attention deficit and hyperactivity disorder (Schatz and Rostain 2006), the authors extrapolated from the initial group the subjects with such comorbidity, getting the same result: bipolar subjects with comorbidity for anxiety disorders were more impulsive than those without such comorbidity and this effect was not mediated by the ADHD presence. A 9-month follow-up data have been also available for 84 patients, showing that the baseline presence of high scores on the scales used for the assessment of anxiety predicted high impulsivity levels at the follow-up. As pointed out by the authors, a main limit for their research the only use of a psychometric assessment of impulsivity. However, the research clearly demonstrated that in bipolar disorder the presence of high levels of anxiety did not seem to constitute per se a protective factor for trait impulsivity.

On the other hand, moving from a dimensional perspective, Ashkenazy et al. (Askenazy, Sorci et al. 2003) realized a research with the aim of evaluate, psychometrically, the anxiety and impulsivity levels in a sample of adolescents acutely hospitalized for various types of behavioural dyscontrol (suicide attempts, self-injuring, substance intoxication, eating disorder, aggression, delinquent acts) independently from the subsequent structured diagnostic classification. The subjects characterized by high levels of anxiety and impulsivity interestingly resulted positive for affective episodes in their clinical history (62% had at least one hypomanic episode and 48% had at least one important depressive episode). The commonest behaviour observed was recurrent suicide attempts, presented in the 87% of the subjects. Notably, out of the six behavioural disturbances explored (first and recurrent suicide attempt, self-mutilation, violence and assault, delinquency, substance abuse, and eating disorders), three were present in 95% of the subjects of this group. The clinical
presentation and the high predominance of hypomanic and depressive episodes in clinical history of these adolescents suggested their belonging to the bipolar spectrum, as well as redefined by Akiskal and Pinto (Akiskal and Mallya 1987; Akiskal and Pinto 1999). The authors emphasized the need to pay attention to early detection of possible forms of bipolar disorder in young subjects, which reveal themselves mainly with behavioural expressions. Moreover, the authors specifically underlined how higher anxiety levels did not represent a protective factor against behavioural impulsivity. Like in our sample, as well as in that of Taylor et al. (Taylor, Hirshfeld-Becker et al. 2008), also in this population the presence of high levels of anxiety did not seem a protective factor for impulsive behaviours. Moreover anxiety and impulsivity in this population seem associated to a bipolar predisposition.
5.3 RESULTS AND DISCUSSION FOR HYPOTHESIS C

“There may be variability in the impulsivity levels, both lifetime that at the time of evaluation, related to specific affective temperamental traits or to affective symptoms”

5.3.1 Clinical sample

In the context of our ongoing research program specifically focused on impulsivity, anxiety disorders (ADs) and bipolar spectrum disorders, this further analysis deeper investigate the role of comorbid cyclothymia, affective temperaments and current mood symptoms on the relationship between ADs and impulsivity in an extended case series. The sample for this examination consisted in 78 outpatients, referred to the facilities of the “Unità Operativa di Psichiatria 1 dell’Azienda Ospedaliero-Universitaria Pisana”, consecutively enrolled in a period of 2 years. As better described above, all patients met DSM-IV-TR criteria for at least one Anxiety Disorder (Panic Disorder; Obsessive-Compulsive Disorder; Social Phobia; Generalized Anxiety Disorder). In addition, also in this analysis the sample was then subdivided into two subgroups on the basis of comorbid Cyclothymic Disorder.

5.3.2 Statistical analysis

Comparative analysis for familial, epidemiologic and clinical features of different subgroups was performed using t-test for dimensional variables and chi-square for categorical ones. Bivariate Pearson correlation analyses among Brief-TEMPS-35 subscales, BRDMS scores and BIS total score and IMT/DMT performances were conducted. Due to the number of enrolled subjects and the
confirmatory nature of our study, we considered, conservatively, a two-tailed significance levels of $p < 0.05$.

5.3.3 Diagnostic distribution and comorbidity of the entire sample

Among our 78 anxiety disorder patients the most frequent diagnosis was Panic Disorder with (41, 52.5%) and without (22, 28.2%) Agoraphobia; 13 patients (16.6%) met diagnostic criteria for Obsessive-Compulsive Disorder; 27 (34.6%) for Generalized Anxiety Disorder and 10 (12.8%) for Social Anxiety Disorder. Forty-eight (61.5%) patients met diagnostic criteria for 1 anxiety disorder, 25 (32.1%) for 2 and 5 (6.4%) for 3 anxiety disorders. Comorbid Cyclothymic Disorder according to DSM-IV-TR criteria was diagnosed in 5 (6.4%) patients; using the 2-day-hypomania modified criteria based on Akiskal et al. (Akiskal, Djenderedjian et al. 1977) (Angst and Marneros 2001) Cyclothymic Disorder was diagnosed in further 21 (26.9%) patients; so Cyclo+ group comprised 26 (33.3%) and Cyclo- 52 (66.7%) patients.

5.3.4 Comparison between patients with anxiety disorders with and without cyclothymia

No significant differences concerning age and gender distribution were observed by the comparison of Cyclo+ and Cyclo- as shown in Table C1. The two groups did not show significant differences in STAI scores, both for the state and trait components. Cyclo+ and Cyclo- also reported a similar BRDS mean score, while Cyclo+ obtained higher mean BRMS total score than Cyclo-. As regard HCL-32 mean score, the two groups did not show significant differences, as well as in the percentage of subjects reaching a HCL-32 score >14. Cyclo+ and Cyclo- also reported similar CGI-Severity mean scores. As
expected, the Cyclo+ subjects reported statistically significant higher scores than Cyclo- in 2 (depressive and cyclothymic temperaments) out of 5 Brief-TEMPS-35 subscales. As concerns the impulsivity evaluation, Cyclo+ showed a total BIS score higher than Cyclo-. The “motor” subscale score was also higher in Cyclo+ than Cyclo-, while the two groups did not report statistical differences in the “attentional” and “non-planning” subscale scores. In the IMT the two groups did not differ in the percentage of correct detections, but the percentage of impulsive answers was significantly higher in Cyclo+ than in Cyclo-. Similarly in the DMT the two groups did not differ in the number of right answers, but a higher percentage of impulsive answers was observed in Cyclo+ than in Cyclo-.

5.3.5 Correlations between affective temperaments, mood symptoms and impulsivity

Pearson correlations between affective temperaments and impulsivity measured by BIS and the IMT/DMT behavioural task are reported in Table C2. Depressive temperament showed a statistically significant positive correlation with BIS total score. No significant correlations were found between depressive temperament and IMT or DMT commission errors. Also the cyclothymic temperaments showed a positive correlation with BIS total score but not with IMT or DMT commission errors. The same pattern was detectable for irritable temperament. The hyperthymic temperament and anxious temperament did not show significant correlations with any of the impulsivity measures examined. Table C2 also shows correlations between mood symptoms and impulsivity. A statistically significant positive correlation between the BRMS average scores and IMT commission errors was found. On the other hand no
correlations were observed between BRDS average scores and any of the measures of impulsivity.

5.3.6 Discussion

The aim of the initial part of our research was to obtain a complete profile of impulsivity in a mixed sample of patients suffering from anxiety disorder and to compare it with that of healthy control subjects. We now deeper investigate the role of comorbid cyclothymia, affective temperaments and current mood symptoms on the relationship between anxiety disorders and impulsivity in an extended case series. To the best of our knowledge, this is the first analysis using different paradigms (both trait and state measure) to evaluate the role of affective temperaments in impulsivity in a group of patients with anxiety disorders.

In our sample of patients with anxiety disorders, cyclothymic subjects were not characterized by a greater global severity of psychopathology, as measured by the CGI. As expected, cyclothymic subjects reported more frequently hypomanic symptoms and higher scores in depressive and cyclothymic temperament subscales than non cyclothymic patients (Perugi, Maremmani et al. 2001). Also in this extended case series, interestingly, cyclothymic patients presented higher levels of trait impulsivity, measured by BIS total score, compared to non-cyclothymic subjects. The same trend was observed in the BIS “motor” subscale, while the “attentional” and “not planning” subscale did not differentiate cyclothymic and not cyclothymic anxious patients. The neurocognitive evaluation also showed higher levels of disinhibitional/disattentional impulsivity in cyclothymic-anxious patients. In fact, the two groups significantly differed in the percentage of impulsive
answers, which were most common in cyclothymic than in not cyclothymic patients. The same trend was observed in the DMT. We therefore confirm in an extended sample that, both trait and state impulsivity, measured respectively by psychometric instruments and a neurocognitive paradigm, resulted to be higher in patients with cyclothymia, independently from the presence of the anxiety disorder.

As main result of this further investigation the correlational analyses seem to differentiate the contribution of affective temperaments from current mood symptomatology. Indeed, TEMPS cyclothymic, depressive and irritable temperaments are significantly related to trait impulsivity, as measured by the BIS total score. It is important to notice that many previous studies have demonstrated that cyclothymic temperamental instability seems to represent a matrix that aggregates different psychopathological dimensions. For example, interpersonal sensitivity and separation anxiety are an essential part of the cyclothymic instability (Perugi, Toni et al. 2003). On the other hand, cyclothymic temperament disposition seems a fundamental state that could predispose subjects also to impulsive/disinhibited behaviours. Consequently, “trait” impulsivity has been classically included among the numerous clinical features of cyclothymic instability (Signoretta, Maremmani et al. 2005; Maremmani, Perugi et al. 2006)(Akiskal et al, 2005; Akiskal et al, 1987; Maremmani et al, 2005; Perugi et al, 2002). Moreover, the evidence that both the cyclothymic temperament, the depressive and irritable show a positive correlation to trait impulsivity as measured on the Barratt Impulsiveness Scale tends to confirm this conceptualization, although deserving more discussion. In particular, it should be considered that, in different case series (both clinical population and healthy subjects), several authors have verified how, at least
from a psychometric point of view, the affective temperamental dispositions seem to be essentially 2 instead of 4 (or 5): the depressive–cyclothymic–anxious (cyclothymic) and the hyperthymic (Pompili, Girardi et al. 2008; Perugi, Toni et al. 2012; Pompili, Innamorati et al. 2012; Lin, Xu et al. 2013). This finding has been drawn by correlation analyses that indicated that depressive, cyclothymic, and anxious temperaments are not independent but strongly interrelated each other and inversely related with hyperthymic traits. This temperamental aggregation has been confirmed in clinical samples (Perugi, Toni et al. 2012), as well as in general population (Pompili, Girardi et al. 2008; Lin, Xu et al. 2013). The depressive–cyclothymic–Anxious (cyclothymic) disposition seems to be primarily characterized by emotional instability while the hyperthymic by emotional intensity. On the other hand, the irritable temperament would seem to belong, in various sample, to a partial overlap both of the cyclothymic-anxious-depressive dimension and of a hyperthymic one (Perugi, Toni et al. 2012). Some authors have therefore suggested that irritability, more than an independent temperament, could connote a shade that can be associated to the two fundamental dispositions (Pompili, Innamorati et al. 2012), in line with what has been noticed in general population (Pompili, Girardi et al. 2008). However the strong correlation found between the BIS and the cyclothymic-depressive (but also irritable) disposition in our sample legitimates the hypothesis that impulsivity, at least as a trait component, may be mediated by the presence of affective temperaments. The observation of a correlation between impulsivity and cyclothymic traits in subjects affected by anxiety disorders agrees with the hypothesis that the last ones can mediate trait impulsivity independently from the diagnosis of anxiety disorder.
It is noteworthy that in our sample the hyperthymic temperament does not seem to be positively correlated to trait impulsivity as measured by the Barratt Impulsiveness Scale scores. However, some studies have assessed the “pathoplastic” effect of hyperthymia on the clinical expression of impulsivity. For example, Walsh et al. (Walsh, Royal et al. 2012) showed, in a recent study focused on association of affective temperaments with impairment and psychopathology in a sample of young adults, that the hyperthymic temperament was correlated with subclinical bipolar psychopathology, including a history of hypomania or interview-rated hyperthymia. Moreover, hyperthymic temperament was positively associated with lack of premeditation and sensation seeking, suggesting that individuals with hyperthymic temperament could engage in risky behaviours for the sake of thrill-seeking, rather than to alleviate negative affect (as in cyclothymic/irritable temperament and probably in anxious temperament), and fail to reflect on the potential consequences of their actions. As a current development of this line of research, similar results were reported by Perugi et al. (Perugi, Toni et al. 2012) in a manuscript that investigates the major impact of affective temperament (cyclothymic vs hyperthymic) on clinical features of a sample of bipolar disorder type I patients. Similarly, in that sample, factorial analyses indicated that depressive, cyclothymic and anxious temperaments are strongly and inversely related with hyperthymic traits: in particular, dominant cyclothymic patients (n=49) were more frequently females, reported higher separation anxiety and interpersonal sensitivity, presented more anxious comorbidity, borderline features and suicide behaviours when compared to the dominant hyperthymic patients (n=40). These latter, on the contrary, were characterized by male dominance, later onset, higher number of manic episodes and hospitalizations, drug abuse and antisocial behaviours than cyclothymic ones.
Summarizing, although several findings have confirmed that the hyperthymic temperament is independent and, in some ways, antithetical to cyclothymia and to the psychopathological dimensions related to it (Perugi, Toni et al. 2012; Pompili, Innamorati et al. 2012), different studies have been demonstrated an association between hyperthymia and some behavioural expression of impulsivity, at least in its externalizing features, thus this topic should be studied in deep in future research.

As additional main finding of this part of our investigation, severity of (hypo)manic symptomatology (BRMS) resulted significantly related to state impulsivity as measured by the IMT/DMT paradigm. This finding confirms as the IMT/DMT commission errors are related to the excitatory symptoms, as already reported in the literature (Swann, Pazzaglia et al. 2003; Swann A. C., Moeller F.G. et al. 2007). For example, Swann et al. (Swann, Pazzaglia et al. 2003) measured state impulsivity in patients who had not met episode criteria for at least 6 months (euthymic) as well as in patients who were manic and healthy control showing how commission errors (impulsive responses) on the IMT/DMT were elevated in manic subjects but were identical to controls in euthymic subjects. Moreover, the same research group (Swann A. C., Moeller F.G. et al. 2007) showed how in bipolar I patients experiencing major depressive episodes even modest manic symptoms were associated with greater state impulsivity as measured by IMT commission errors. The presence of manic symptoms in a depressive phase resulted also associated with an unstable course of illness as well as history of suicidal behaviour and substance-use disorders (Swann A. C., Moeller F.G. et al. 2007). Finally, it is worth mentioning that independent research groups have demonstrated how bipolar disorder patients display high rates of impulsive responses on different laboratory tests.
(both reward direct and response dis-inhibition paradigms) when manic or mixed, as compared to healthy subjects, that largely normalize with recovery and switching into depression (Swann, Pazzaglia et al. 2003; Strakowski, Fleck et al. 2010). On the other hand, elevated BIS-11 scores tend to persist across phases of illness (Swann, Pazzaglia et al. 2003; Strakowski, Fleck et al. 2010). These findings have been interpreted as the confirmation that impulsivity has both an affective-state dependent and a trait component in bipolar disorder.

Together, these findings also provide face validity that the BIS-11 offers a measurement of ‘real-life’ trait impulsiveness, despite the limitations of a self-report instrument, evaluating a baseline impulsive personality-style (Strakowski, Fleck et al. 2010). In contrast to the indirect BIS-11 assessment, the behavioural tasks directly measure aspects of impulsive responding that are limited to a specific time and a limited type of behaviour (i.e. state impulsivity). As a main trend, performances on the behavioural tasks tend to normalize as manic bipolar subjects switched to depression or achieved euthymia, although there were some important exceptions. We have already discussed how Swann et al. (Swann A. C., Moeller F.G. et al. 2007) founded how even modest manic symptoms were associated with greater state impulsivity as measured by IMT commission errors in depressed bipolar patients (Swann A. C., Moeller F.G. et al. 2007). Similarly, a more severe course of illness (Swann et al., 2009b) with an history of suicidal behaviours and substance-use disorders tends to prevent the normalization of the levels of “state impulsivity” described above (Swann A. C., Moeller F.G. et al. 2007; Swann 2010).

Overall, despite the rapid accumulation of knowledge related to the various aspects of impulsivity in bipolar disorder, some controversies regarding the results of different studies should be taken into account. As concern
behavioural tasks, in particular, further efforts are necessary to determine their validity, stability, mutual relations as well as their relationship with trait measure. As expected, different research groups have demonstrated an absence of correlation between self report measure and behavioural measure, in line with the hypothesis that instruments such as the BIS and the IMT/DMT measure different aspects of impulsivity. Moreover, recent findings suggest that even among the behavioural measures, different tasks measure different, perhaps unrelated, components of impulsive behaviour (Reynolds, Ortengren et al. 2006; Fineberg, Chamberlain et al. 2014).

Summarizing, regardless of the unresolved methodological questions, the strong correlation found between the BIS and the cyclothymic-anxious-depressive (but also irritable) disposition in our sample of patients with anxiety disorder legitimates the hypothesis that impulsivity, at least as a trait component, may be mediated by the presence of affective temperaments. Historically, several authors have suggested that the persistence of high levels of impulsivity in patients with bipolar disorder may be mediated by temperament traits. Nonetheless, in the light of our knowledge, this is the first study which correlates the affective temperaments with paradigms aimed to specifically evaluate impulsivity. Finally, the co-occurrence of a comorbid cyclothymic disorder seems to provoke the presence of excitatory-like symptoms that directly correlated with the state component of impulsivity. Therefore, we can speculate that in cyclothymic disorder impulsivity is an enduring characteristic, with its highly variable expression depending on the situation and affective state. In a dimensional perspective, even modest manic symptoms could increase levels of state impulsivity enough to be detectable by
behavioural task, in line with the data previously reported in the literature (Swann A. C., Moeller F.G. et al. 2007; Swann 2009).
5.4 RESULTS AND DISCUSSION FOR HYPOTHESIS D

“We tried to verify the preceding hypotheses, other than in a mixed case sample of subjects belonging to different diagnostic anxiety subtypes, in specific anxiety disorders, beginning with panic disorder.”

5.4.1 Clinical sample and control subjects

For this latter analysis we selected 64 outpatients who met the DSM-IV criteria for Panic Disorder (PD) with or without Agoraphobia: the sample included 38 (60.3%) females and 26 (39.7%) males with a mean age of 36.6 years (sd=12.3, range 19-63). As discussed above, patients presenting lifetime comorbidity for major mood episodes, schizophrenia or other psychotic disorders, organic psychiatric syndromes and severe somatic disorders were excluded. Control group included 44 healthy subjects matched for gender, age, education, job and marital status; 26 (59.1%) were females and 18 (40.9%) males, with a mean age of 34.8 years (sd=10.3, range 19-63).

5.4.2 Statistical analysis

Comparative analysis for familial, epidemiologic, clinical features of patients with PD and controls was performed using the t-student test for dimensional variables (Mann-Whitney U-test, when appropriate) and the chi-square test for categorical variables (Fisher exact-test, when appropriated). Comparative analysis for familial, epidemiologic, clinical features and course of Cyclo+, Cyclo- and controls was performed using one-way ANOVA for dimensional variables and contingency tables for categorical ones. Due to the
number of subjects and the confirmatory nature of our study, we considered, in a conservative way, two-tailed significance levels with threshold at p < 0.05.

**5.4.3 Demographic Characteristics and Diagnostic distribution**

Table D1 summarizes demographic features of subjects affected by PD (n=64) and healthy controls (n=44): there were no significant differences for gender distribution, mean age, education, work and marital status. Among the PD patients (n=64) the most frequent diagnosis was PD with (41, 64.1%) and without (22, 34.4%) Agoraphobia; only 1 subject (1.5%) presented Agoraphobia without PD. Concerning the comorbidity with other anxiety disorders, 8 patients (12.5%) also met diagnostic criteria for Obsessive-compulsive Disorder, 18 (28.1%) for Generalized Anxiety Disorder and 8 (12.5%) for Social Anxiety Disorder. Twenty-four (37.5%) patients met diagnostic criteria for another anxiety disorder, 5 (7.8%) for 2. Lifetime comorbidity with Cyclothymic Disorder (Cyclo+) was diagnosed in 20 (31.2%) PD patients; 16 (25.0 %) met only Akiskal et al. (Akiskal, Djenderedjian et al. 1977; Akiskal and Mallya 1987; Angst and Marneros 2001) modified criteria and 4 (6.2%) met also DSM-IV diagnostic criteria. Control subjects (n=44) did not meet any diagnostic criteria for any DSM-IV mental disorder.

As reported in table D2, no significant differences concerning gender and average age distribution were observed by the comparison of the 3 groups Cyclo+ (20 subjects), Cyclo- (44) and controls (n=44).
5.4.4 Symptomatological, temperamental and personality traits evaluation

As expected (table D2), PD patients differed from controls showing higher scores on STAI, both in the state (STAI-S) and trait components (STAI-T) (both with p < .001). In the same questionnaire Cyclo+ and Cyclo- subjects obtained higher scores compared to healthy controls (both with p < .001) while no significant differences were found between Cyclo+ and Cyclo- subjects. A similar trend was observed in BRDS scores. Although no significant differences between the entire sample of PD patients and healthy controls were observed in BRMS scores, Cyclo+ subjects differed significantly when compared to controls (p < .001). Cyclo+ subjects also scored higher than Cyclo- (p = 0.05).

PD patients exhibited significantly greater HCL-32 scores (p < .001) compared to healthy controls. Both Cyclo+ and Cyclo- subjects obtained higher scores compared to healthy controls (respectively p < .001 and p = .001) while no significant differences were found between Cyclo+ and Cyclo- subjects. For this latter scale, we calculated, for each group, the percentage of subjects reaching a score >14. This cut-off has been shown to be the one having the best specificity and sensitivity for the retrospective screening of hypomania in patients with depression across various phases of the illness (Angst, Adolfsson et al. 2005; Meyer, Hammelstein et al. 2007). A higher percentage of PD patients obtained a score >14 compared to healthy controls (56.3%, vs. 4, 9.1%; chi-square = 24.867; p < .001). As expected, the highest percentage of subjects who reached a score >14 was found in Cyclo+ subjects and the lowest in healthy controls, with Cyclo- setting in the intermediate position.
PD patients reported a CGI-S score of 3.4 (sd = 1.0), indicating a global severity of the disorder between mild and moderate. There were not significant differences in CGI scores between Cyclo+ and Cyclo- subjects.

Concerning the evaluation of the temperamental characteristics, PD patients recorded significantly higher in 4 out of 5 subscales of the TEMPS-M: depressive, cyclothymic, anxious and irritable temperament. No significant differences between the two groups were observed in hyperthymic temperament subscale; in this latter, the average scores were slightly higher in controls than in PD patients, but the difference was not statistically significant. As expected, Cyclo+ subjects exhibited significantly higher scores in cyclothymic temperament subscale compared to Cyclo- (p=0.01). SASI scores appeared significantly higher in PD patients (p= 0.006), as well as in Cyclo+ (p= 0.024) and Cyclo- (p=0.006) subjects compared to healthy controls. Regarding the ISSI, in which low scores indicate an increased sensitivity to rejection in interpersonal context, the mean scores were significantly lower in PD patients than in healthy controls (p< .001). Cyclo- subjects exhibited the lowest scores with a significant difference compared to healthy controls (p < .001) indicating an elevated interpersonal sensitivity.

5.4.5 Impulsivity evaluation

Significant differences between PD patients and healthy controls were observed in BIS total score (p < .001, table D3). Both Cyclo+ and Cyclo- subjects obtained higher scores compared to healthy controls (respectively p < .001 and p = .002). Nonetheless, Cyclo+ subjects obtained the highest scores with a significant difference also in comparison with Cyclo- (p = .044). As concern BIS subscales, PD patients exhibited significantly higher scores than healthy
controls (respectively in “attentional” subscale $p < .001$, “motor” $p = .001$, “non-planning” $p = .027$). All the average scores were also higher in Cyclo+ subjects compared to Cyclo- but the difference reached statistical significance only for “motor subscale” ($p = .010$).

In table D3 were also reported the performances in the IMT/DMT. In the first task, the IMT, no significant differences were found in the percentage of correct answers between PD patients and healthy controls. Similarly, no subgroups differences were found between Cyclo+, Cyclo- and controls subjects. As concern impulsive responses, PD patients reported significantly more commission errors ($p < .001$) when compared to healthy controls. Similarly, both Cyclo+ ($p < .001$) and Cyclo- patients ($p = .030$) exhibited significant differences from healthy subjects in impulsive responses. Finally, the highest percentage of commission errors was exhibited by Cyclo+ subjects, with a significant difference in comparison with Cyclo- ($p < .001$). The value represented by the parameter $A'$ (discriminability), a measure of the ability of discriminating the proper stimulus from the other similar stimuli, was significantly lower in PD patients than in healthy controls ($p=.002$). Both Cyclo+ and Cyclo- subjects scored significantly lower compared to healthy controls (respectively $p < .001$ and $p = .036$). Nonetheless, Cyclo+ subjects obtained the lowest scores with a significant difference also in comparison with Cyclo- ($p = .003$) indicating the poorest discriminability.

As described before, the second task, the DMT, is generally considered more challenging compared to the IMT as it also reflects working memory (Marsh, Dougherty et al. 2002; Meyer, Hammelstein et al. 2007). In DMT, PD patients reported less correct detections ($p = .003$) than healthy controls.
However, no significant differences were found between Cyclo+ and healthy subjects or Cyclo+ and Cyclo- subjects. In the latter group, correct answers were significantly reduced in comparison to controls (p = .022). In DMT, PD patients also reported a greater number of impulsive responses compared to healthy controls (p = .005). However, in this task, Cyclo+ subjects reported the greatest number of commission errors with a significant difference in comparison to both healthy controls and Cyclo- subjects (both p < .001). The lowest percentage of impulsive answers was observed in control subjects followed by Cyclo- with no significant differences between these two subgroups. Finally, as far as the DMT discriminability is concerned, there were significant differences in the same trend observed with the IMT: the value of the parameter remained significantly higher in controls than in anxious patients (p = .000) with the lowest discriminability exhibited by Cyclo+ subjects.

5.4.6 Discussion

The present analysis has been performed for evaluating the stability of the results previously described and obtained in a mixed sample of subjects belonging to different diagnostic subtypes. This sample of PD patients was characterized by a mild/moderate severity, as measured by the CGI, and showed a high rate of lifetime comorbidity with CD (31.2%). One quarter of the sample met Akiskal et al. (Akiskal, Djenderedjian et al. 1977; Akiskal and Mallya 1987; Angst and Marneros 2001) modified criteria and 4 patients (6.2%) met also DSM-IV diagnostic criteria for CD. These findings are consistent with previous report that found a high prevalence of bipolar spectrum disorders (BSDs) amongst patients referred to a health care provider with a principal diagnosis of PD (i.e., BPDI, 2.1%; BPDII, 5%; CD, 6.4%) (Savino, Perugi et al. 1993).
As expected, our PD patients showed state and trait anxiety scores higher than controls (Kabacoff, Segal et al. 1997); also manic, but not depressive, symptomatology was more represented in PD patients than in controls. Interestingly, the retrospective evaluation by the HCL-32 indicated that PD patients reported more past hypomanic symptoms than controls and more than half (56.3%) of them reached a score of 14 or more which indicated a high probability of previous hypomania (Angst, Adolfsson et al. 2005; Meyer, Hammelstein et al. 2007; Vieta, Sánchez-Moreno et al. 2007). This findings confirm the high prevalence of current and past bipolar spectrum features in patients with PD (Savino, Perugi et al. 1993).

Concerning temperamental traits, PD patients showed significantly higher scores than healthy controls in depressive, cyclothymic, anxious and irritable TEMPS-M subscales, as well as higher levels of separation anxiety and interpersonal sensitivity. As expected, cyclothymic subjects presented the highest scores in cyclothymic temperament. Previous studies observed that separation anxiety (Pini, Abelli et al. 2005) and interpersonal rejection sensitivity are strongly related to cyclothymic mood reactivity (Perugi and Akiskal 2002; Perugi, Toni et al. 2003; Signoretta, Maremmani et al. 2005). In a study of patients who met DSM-IV criteria for Major Depressive Disorder (MDD) with atypical features, Akiskal et al. (Akiskal, Akiskal et al. 2006) reported that the ones with a comorbidity with panic attacks exhibited a markedly significant cyclothymic temperamental disposition, as well as a higher number of past hypomanic episodes and stressors. Others authors (Forty, Smith et al. 2009) suggested that the lifetime comorbidity between recurrent panic attacks and BD may represent a particular subtype of mood disorder. This latter seems characterized by rapid mood switching (resembling
cyclothymic mood instability) and specific clinical (Savino, Perugi et al. 1993; Simon, Smoller et al. 2003), psycho-physiologic (Simon, Otto et al. 2005; MacKinnon and Zamoiski 2006), and familial-genetic backgrounds (MacKinnon, McMahon et al. 1997; Logue, Durner et al. 2009).

Interestingly, our patients presented higher levels of trait impulsivity, measured by the BIS total and subscales scores, compared to healthy controls and trait impulsivity was particularly elevated in cyclothymic subjects. Moreover, patients with PD also exhibited more dis-inhibitional/dis-attentional impulsivity compared to healthy controls as measured by the elevate percentage of commission errors both in the IMT and in the DMT; additionally the levels of inattentive and dis-inhibited impulsivity were particularly elevated in cyclothymic subjects than in not cyclothymic ones. These results are in line with our preliminary data in the mixed sample of ADs (section 5.1 and 5.2). The differences between IMT and DMT in the percentage of correct detections of PD patients in comparison to healthy controls could be probably due to the different degree of difficulties, including greater latency and distracting stimulus in the DMT (Dougherty, Marsh et al. 2002).

As better described above, the occurrence of impulsivity in the contest of primary panic disorder is not adequately explored. The studies conducted so far lead to conflicting and mixed data mainly on some behavioural aspects of impulsivity such as suicidality and aggression (George, Anderson et al. 1989; Weissman, Klerman et al. 1989; Beck, Steer et al. 1991; Lepine, Chignon et al. 1993; Korn, Plutchik et al. 1997; Pilowsky, Wu et al. 1999). The finding that, at least in some patients, PD might be associated with Cyclothymia as well as with trait and state impulsivity has relevant clinical implications. On one hand, our
data tend to confirm the results obtained by MacKinnon at al. (MacKinnon, McMahon et al. 1997; MacKinnon, Zandi et al. 2003; MacKinnon and Pies 2006; MacKinnon and Zamoiski 2006) in bipolar subjects with rapid switches, whose characteristics resulted similar to those of cyclothymic patients, suggesting that panic attacks and rapid mood switching could be considered as a specific subtype of familial bipolarity. On the other hand, our data are also in line with a recent study of Jakuszkowiak-Wojten et al. (Jakuszkowiak-Wojten, Gałuszko-Wegielnik et al. 2013) in which trait impulsivity, measured with the BIS, resulted higher in a small sample of panic disorder patients compared to healthy controls disconfirming the hypothesis that PD should be invariably characterized by high levels of harm-avoidance, behavioural inhibition and hyper-control (Summerfeldt, Hood et al. 2004; Kashdan and Hofmann 2008).

Taken as a whole, the findings tend to suggest that cyclothymic instability could be reasonably considered the basic state for both anxious/inhibited as well as impulsive/disinhibited manifestations of these patients (Perugi and Akiskal 2002; Akiskal, Akiskal et al. 2006; van Valkenburg, Kluznik et al. 2006). This matrix, which makes the same individual susceptible to anxiety, impulse-control, eating and substance-use disorders, seems to represent a substantial challenge pertaining to a large number of patients.

Our results should be considered preliminary and should be replicated in larger samples. Future research is necessary to evaluate experimental group of subjects affected by other primary anxiety disorder compared to control group and to evaluate the stability of the results obtained with neuro-cognitive tasks in longitudinal studies.
6. LIMITS, STRENGTHS AND CONCLUSION

Our study is correlational and cross-sectional and presents some methodological limitations that should be taken into account before discussing the concluding remarks. The evaluations have been performed, under the supervision of a senior psychiatrist, in a setting of routine clinical practice by a resident in psychiatry, who was taking care of patients and was informed about their diagnosis. The employ of standardized instruments should minimize eventual biases due to the lack of blind evaluation.

In our research we evaluated the presence and severity of impulsivity in a sample of patients with anxiety disorders using survey instruments that reflect different models of interpretation. We compared anxious patients with a control group coupled for demographic characteristics. Finally, we explored the role of comorbidities with cyclothymic disorder and the relationships with affective temperaments.

Our results seem to confirm our initial hypotheses:

A. Trait and state impulsivity resulted greater in patients with anxiety disorders than in matched controls. This finding, apparently in contrast with the traditional conceptualization, suggests that anxiety might display positive association with different type of impulsivity. Our further hypothesis is that, at least in a subgroup of patient, impulsivity could be associated with coexisting soft bipolar spectrum conditions.

B. Impulsivity is not connected to Anxiety Disorder diagnosis in itself, but it seems to be mediated by comorbidity with mood spectrum conditions, in particular with cyclothymic disorders. In our sample of patients with anxiety disorder the presence of broadly defined cyclothymia appears to be associated
not only with affective instability but also with separation anxiety, interpersonal sensitivity and, finally, both state and trait impulsivity.

C. Trait and/or state impulsivity levels resulted variable and seem to be associated with specific affective temperamental traits or with affective symptoms. In our sample of patients with anxiety disorder, we found a strong correlation between the BIS and the cyclothymic-anxious-depressive (but also irritable) disposition. This finding legitimates the hypothesis that impulsivity, at least as a trait component, may be mediated by the presence of affective temperaments. Moreover, the co-occurrence of a comorbid cyclothymic disorder seems to provoke the presence of excitatory-like symptoms that directly correlated with the state component of impulsivity. We can speculate that in cyclothymic disorder impulsivity is an enduring characteristic, with its highly variable expression depending on the situation and affective state. In a dimensional perspective, even modest manic symptoms could increase levels of state impulsivity enough to be detectable by behavioural tasks.

D. We replicated the results obtained in a mixed case sample of subjects belonging to different diagnostic anxiety disorder subtypes, in a sample of patients with a specific anxiety disorder: panic disorder.

Taken as a whole, our findings tend to suggest that cyclothymic instability could be reasonably considered the basic state for both anxious/inhibited as well as impulsive/disinhibited manifestations (Perugi and Akiskal 2002; Akiskal, Akiskal et al. 2006; van Valkenburg, Kluznik et al. 2006).

Our results should be considered preliminary and should be replicated in larger samples. Future research is necessary to compare different anxiety disorders and to evaluate the stability of the results obtained with trait measure
of impulsivity as well as with different neurocognitive tasks in longitudinal studies. Furthermore, it is not clear from the data obtained so far if impulsivity should be directly associated to the cyclothymic syndrome per se or to the temperamental cyclothymic diathesis or to the coexisting mood symptomatology or to a combination of these elements.
7. TABLES

Tables for hypothesis A:

“Impulsivity, in its trait and/or state component, may be greater in patients with anxiety disorders if compared to controls”

**Table A1. Demographic features in anxious and control subjects**

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=47)</th>
<th>Controls (n=45)</th>
<th>t or χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, average (sd)</td>
<td>34.5 ± 10.3</td>
<td>34.8 ± 10.2</td>
<td>-0.14</td>
<td>0.886</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>30 (63.8%)</td>
<td>28 (62.2%)</td>
<td>0.143</td>
<td>0.705</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td>1.82</td>
<td>0.400</td>
</tr>
<tr>
<td>≤ 8 years</td>
<td>10 (21.3%)</td>
<td>6 (13.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>20 (42.6%)</td>
<td>17 (37.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University or &gt;</td>
<td>17 (36.2%)</td>
<td>22 (48.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation, n (%)</td>
<td></td>
<td></td>
<td>7.7</td>
<td>0.103</td>
</tr>
<tr>
<td>Student</td>
<td>9 (19.1%)</td>
<td>10 (22.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House keeper/blue collar</td>
<td>10 (21.3%)</td>
<td>8 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office worker/teacher</td>
<td>16 (34.04%)</td>
<td>8 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manager/white collar</td>
<td>10 (21.3%)</td>
<td>8 (42.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 (4.3%)</td>
<td>1 (2.1%)</td>
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<td></td>
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<tr>
<td>Civil status</td>
<td></td>
<td></td>
<td>3.85</td>
<td>0.150</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>18 (38.3%)</td>
<td>24 (53.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>24 (51.1%)</td>
<td>20 (44.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widow/divorced</td>
<td>5 (10.6%)</td>
<td>1 (2.2%)</td>
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</tbody>
</table>
### Table A2. Diagnostic distribution, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=47)</th>
<th>Controls (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic Disorder with Agoraphobia</td>
<td>26 (55.3%)</td>
<td>--</td>
</tr>
<tr>
<td>Panic Disorder without Agoraphobia</td>
<td>11 (23.4%)</td>
<td>--</td>
</tr>
<tr>
<td>Agoraphobia without Panic Disorder</td>
<td>1 (2.1%)</td>
<td>--</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>12 (25.5%)</td>
<td>--</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>9 (19.1%)</td>
<td>--</td>
</tr>
<tr>
<td>Social Anxiety Disorder</td>
<td>7 (14.9%)</td>
<td>--</td>
</tr>
</tbody>
</table>

### Table A3. Lifetime Comorbidity for Mood Disorders, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=47)</th>
<th>Controls (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomanic episode</td>
<td>9 (19.1%)</td>
<td>--</td>
</tr>
<tr>
<td>Hypomanic episode (pharmacological)</td>
<td>10 (21.3%)</td>
<td>--</td>
</tr>
<tr>
<td>Cyclothymic Disorder (DSM-IV criteria)</td>
<td>5 (10.6%)</td>
<td>--</td>
</tr>
<tr>
<td>Cyclothymic Disorder (modified criteria)</td>
<td>26 (55.3%)</td>
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</tr>
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</table>
### Table A4. Pharmacological treatment

<table>
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<th>Controls (n=45)</th>
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<tbody>
<tr>
<td>Antiepileptics</td>
<td>12 (25.5%)</td>
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</tr>
<tr>
<td>SSRIs</td>
<td>23 (48.9%)</td>
<td>--</td>
</tr>
<tr>
<td>SNRIs</td>
<td>3 (6.5%)</td>
<td>--</td>
</tr>
<tr>
<td>TCAs</td>
<td>7 (15.2%)</td>
<td>--</td>
</tr>
<tr>
<td>Other Antidepressants</td>
<td>8 (17.4%)</td>
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</tr>
<tr>
<td>Typical Antipsychotics</td>
<td>1 (2.2%)</td>
<td>--</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>2 (4.4%)</td>
<td>--</td>
</tr>
<tr>
<td>Anxiolytics and/or Hypnotics</td>
<td>5 (10.6%)</td>
<td>--</td>
</tr>
</tbody>
</table>

### Table A5. Clinical scales scores (average score ± sd) of anxious and control subjects

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cases (n=47)</th>
<th>Controls (n=45)</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRMS</td>
<td>3.7 ± 3.9</td>
<td>2.0 ± 3.9</td>
<td>670.0</td>
<td>0.001</td>
</tr>
<tr>
<td>BRDS</td>
<td>3.8 ± 4.1</td>
<td>0.1 ± 0.5</td>
<td>222.5</td>
<td>0.004</td>
</tr>
<tr>
<td>STAI State</td>
<td>44.2 ± 12.2</td>
<td>33.0 ± 9.4</td>
<td>4.9</td>
<td>0.000</td>
</tr>
<tr>
<td>STAI Trait</td>
<td>48.3 ± 9.7</td>
<td>36.1 ± 7.3</td>
<td>6.8</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL32 Total</td>
<td>13.4 ± 5.2</td>
<td>9.1 ± 3.8</td>
<td>4.6</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL32 &gt;14 n (%)</td>
<td>30 (63.8%)</td>
<td>14 (31.1%)</td>
<td>9.86</td>
<td>0.002</td>
</tr>
<tr>
<td>CGI</td>
<td>3.32 ± 1.0</td>
<td>1.00 ± 0.0</td>
<td>15.8</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS depressive</td>
<td>21.7 ± 5.4</td>
<td>13.1 ± 4.0</td>
<td>8.635</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS cyclothymic</td>
<td>20.7 ± 6.7</td>
<td>12.4 ± 4.2</td>
<td>7.062</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS hyperthymic</td>
<td>20.4 ± 5.3</td>
<td>22.7 ± 9.2</td>
<td>-1.466</td>
<td>0.146</td>
</tr>
<tr>
<td>TEMPS irritable</td>
<td>15.1 ± 4.8</td>
<td>12.6 ± 5.1</td>
<td>2.408</td>
<td>0.018</td>
</tr>
<tr>
<td>TEMPS anxious</td>
<td>17.6 ± 5.2</td>
<td>11.9 ± 4.8</td>
<td>5.440</td>
<td>0.000</td>
</tr>
<tr>
<td>SASI Total</td>
<td>12.2 ± 7.3</td>
<td>7.0 ± 5.9</td>
<td>3.7</td>
<td>0.000</td>
</tr>
<tr>
<td>ISSI Total</td>
<td>91.4 ± 16.7</td>
<td>103.61 ± 13.3</td>
<td>-3.8</td>
<td>0.000</td>
</tr>
</tbody>
</table>

For the BRMS and BRDS scales, Mann-Whitney U-test; for the SASI, ISSI, HCL-32, STAI and CGI, T-test. BRMS, Bach-Raphaelsen mania scale; BRDS Bach-Raphaelsen depression scale; SASI, separation anxiety symptoms inventory; ISSI interpersonal sensitivity symptoms inventory; HCL-32, hypomania check list; STAI, state-trait anxiety inventory; CGI, clinical global impression.
Table A6. BIS-11 scores (average scores ± sd) in anxious and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Casi (n=47)</th>
<th>Gruppo di controllo (n=45)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attentional</td>
<td>16.3 ± 4.0</td>
<td>13.2 ± 2.5</td>
<td>4.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Motor</td>
<td>21.4 ± 3.8</td>
<td>19.1 ± 3.7</td>
<td>3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Non Planning</td>
<td>26.7 ± 3.7</td>
<td>25.1 ± 4.1</td>
<td>2.0</td>
<td>0.047</td>
</tr>
<tr>
<td>Total</td>
<td>64.4 ± 8.7</td>
<td>57.4 ± 7.6</td>
<td>4.2</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table A7. Performances at Immediate and Delayed Memory Task in anxious and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Casi (n=47)</th>
<th>Controlli (n=45)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate Memory Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections (CD)</td>
<td>81.1 ± 10.9</td>
<td>80.3 ± 13.0</td>
<td>0.326</td>
<td>0.745</td>
</tr>
<tr>
<td>Commission errors (CE)</td>
<td>30.8 ± 14.1</td>
<td>19.1 ± 11.7</td>
<td>4.313</td>
<td>0.000</td>
</tr>
<tr>
<td>CD reaction time</td>
<td>479 ± 66</td>
<td>488 ± 79</td>
<td>-0.562</td>
<td>0.576</td>
</tr>
<tr>
<td>CE reaction time</td>
<td>472 ± 78.6</td>
<td>472 ± 90</td>
<td>0.014</td>
<td>0.988</td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.51 ± 0.658</td>
<td>1.89 ± 0.613</td>
<td>-2.805</td>
<td>0.006</td>
</tr>
<tr>
<td>Response Bias</td>
<td>0.83 ± 0.381</td>
<td>1.11 ± 0.655</td>
<td>-2.457</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Delayed Memory Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections (CD)</td>
<td>83.3 ± 15.6</td>
<td>89.6 ± 8.1</td>
<td>-2.408</td>
<td>0.018</td>
</tr>
<tr>
<td>Commission errors (CE)</td>
<td>30.5 ± 16.9</td>
<td>23.5 ± 16.1</td>
<td>2.027</td>
<td>0.046</td>
</tr>
<tr>
<td>CD reaction time</td>
<td>519 ± 79</td>
<td>507 ± 87</td>
<td>0.744</td>
<td>0.459</td>
</tr>
<tr>
<td>CE reaction time</td>
<td>478 ± 69</td>
<td>489 ± 129</td>
<td>-0.506</td>
<td>0.614</td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.7 ± 0.800</td>
<td>2.2 ± 0.894</td>
<td>-2.942</td>
<td>0.004</td>
</tr>
<tr>
<td>Response Bias</td>
<td>0.83 ± 0.381</td>
<td>1.51 ± 0.658</td>
<td>0.964</td>
<td>0.337</td>
</tr>
</tbody>
</table>
Tables for hypothesis B:

“Impulsivity may not be connected to Anxiety Disorder diagnosis in itself (Panic Attacks, Social Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder), but it is mediated by comorbidity with attenuated mood disorders, in particular with cyclothymia”.

Table B1. Demographic features of the cyclothymic (Cyclo+) vs non-cyclothymic (Cyclo−) anxious patients vs. controls

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ Cases</th>
<th>Cyclo- Cases</th>
<th>Controls</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=26)</td>
<td>(n=21)</td>
<td>(n=45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, average (sd)</td>
<td>35.6 ± 11.7</td>
<td>33.1 ± 8.5</td>
<td>34.8 ± 10.2</td>
<td>0.361</td>
<td>0.698</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>18 (69.2%)</td>
<td>12 (57.1%)</td>
<td>27 (60%)</td>
<td>0.863</td>
<td>0.649</td>
</tr>
<tr>
<td></td>
<td>Cyclo+ Cases (n=26)</td>
<td>Cyclo- Cases (n=21)</td>
<td>Controls (n=45)</td>
<td>F</td>
<td>p</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>BRMS</td>
<td>4.3 ± 3.8</td>
<td>2.8 ± 4.1</td>
<td>2.0 ± 4.0</td>
<td>2.841</td>
<td>0.064</td>
</tr>
<tr>
<td>BRDS(^a)</td>
<td>4.4 ± 4.4</td>
<td>3.0 ± 3.7</td>
<td>2.0 ± 3.9</td>
<td>19.490</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL32 Total(^a)</td>
<td>17.1 ± 5.5</td>
<td>14.4 ± 6.5</td>
<td>10.6 ± 4.7</td>
<td>12.379</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL 32 &gt; 14, n (%)</td>
<td>20 (76.9%)</td>
<td>10 (47.6%)</td>
<td>14 (31.1%)</td>
<td>13.86</td>
<td>0.001</td>
</tr>
<tr>
<td>STAI State(^a)</td>
<td>47.4 ± 12.7</td>
<td>40.3 ± 10.5</td>
<td>33.0 ± 9.4</td>
<td>15.293</td>
<td>0.000</td>
</tr>
<tr>
<td>STAI Trait(^b)</td>
<td>51.2 ± 1.0</td>
<td>44.7 ± 8.1</td>
<td>36.1 ± 7.3</td>
<td>28.362</td>
<td>0.000</td>
</tr>
<tr>
<td>CGI(^a)</td>
<td>3.54 ± 0.989</td>
<td>3.05 ± 0.921</td>
<td>1.00 ± 0.0</td>
<td>135.8</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS depressive(^a)</td>
<td>22.3 ± 3.8</td>
<td>20.9 ± 6.9</td>
<td>13.1 ± 4.0</td>
<td>37.794</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS cyclothymic(^a)</td>
<td>21.6 ± 6.5</td>
<td>19.6 ± 7.0</td>
<td>12.4 ± 4.2</td>
<td>25.833</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS hyperthymic</td>
<td>19.9 ± 5.3</td>
<td>21.4 ± 5.3</td>
<td>22.7 ± 9.2</td>
<td>1.196</td>
<td>0.307</td>
</tr>
<tr>
<td>TEMPS irritable(^c)</td>
<td>16.4 ± 5.3</td>
<td>13.6 ± 3.6</td>
<td>12.6 ± 5.1</td>
<td>4.934</td>
<td>0.009</td>
</tr>
<tr>
<td>TEMPS anxious(^a)</td>
<td>18.1 ± 4.0</td>
<td>17.1 ± 6.3</td>
<td>12.0 ± 4.8</td>
<td>14.932</td>
<td>0.000</td>
</tr>
<tr>
<td>SASI Total(^a)</td>
<td>12.8 ± 7.2</td>
<td>11.4 ± 7.5</td>
<td>7.0 ± 5.9</td>
<td>7.217</td>
<td>0.001</td>
</tr>
<tr>
<td>ISSI Total</td>
<td>90.8 ± 20.0</td>
<td>92.2 ± 12.1</td>
<td>103.5 ± 13.3</td>
<td>7.275</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BRMS, Bach-Rapahelsen Mania Scale; BRDS Bach-Rapahelsen Depression Scale; HCL32, Hypomania Check List; STAI, State–Trait Anxiety Inventory; CGI, Clinical Global Impression; TEMPS, Questionnaire for the Affective and Anxious Temperaments; SASI, Separation Anxiety Symptoms Inventory; ISSI, Interpersonal Sensitivity Symptoms Inventory.

Scheffe F test:
\(^a\) = Cyclo+ and Cyclo- > Controls
\(^b\) = Cyclo+ > Cyclo- > Controls
\(^c\) = Cyclo+ > Controls
Table B3. BIS-11 scores (average scores±sd) in non-cyclothymic–anxious patients vs. cyclothymic–anxious vs. controls.

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ cases (n=26)</th>
<th>Cyclo- cases (n=21)</th>
<th>Controls (n=45)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attentional a</td>
<td>16.9 ± 4.0</td>
<td>15.5 ± 4.0</td>
<td>13.2 ± 2.5</td>
<td>11.153</td>
<td>0.000</td>
</tr>
<tr>
<td>Motor b</td>
<td>22.2 ± 4.1</td>
<td>20.4 ± 3.2</td>
<td>19.1 ± 3.7</td>
<td>5.928</td>
<td>0.004</td>
</tr>
<tr>
<td>Non Planning</td>
<td>26.7 ± 3.8</td>
<td>26.8 ± 3.5</td>
<td>25.1 ± 4.0</td>
<td>2.010</td>
<td>0.140</td>
</tr>
<tr>
<td>Total a</td>
<td>65.8 ± 9.1</td>
<td>62.7 ± 8.0</td>
<td>57.3 ± 7.6</td>
<td>9.553</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Scheffe F test: a = Cyclo+ e Cyclo- > Controlli  
b = Cyclo+ > Controlli

Table B4. Performances at Immediate and Delayed Memory Task: non-cyclothymic–anxious patients vs. cyclothymic–anxious vs. controls.

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ cases (n=26)</th>
<th>Cyclo- cases (n=21)</th>
<th>Controls (n=45)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate Memory Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections (CD)</td>
<td>80.7 ± 11.3</td>
<td>81.7 ± 10.6</td>
<td>80.3 ± 13.0</td>
<td>0.091</td>
<td>0.913</td>
</tr>
<tr>
<td>Commission errors (CE)c</td>
<td>36.6 ± 14.4</td>
<td>23.6 ± 9.9</td>
<td>19.1 ± 11.7</td>
<td>17.237</td>
<td>0.000</td>
</tr>
<tr>
<td>CD reaction time</td>
<td>459 ± 64</td>
<td>504 ± 62</td>
<td>487 ± 72</td>
<td>2.512</td>
<td>0.087</td>
</tr>
<tr>
<td>CE reaction time</td>
<td>462 ± 65</td>
<td>498 ± 70</td>
<td>483 ± 102</td>
<td>0.773</td>
<td>0.465</td>
</tr>
<tr>
<td>Discriminability d</td>
<td>1.32 ± 0.627</td>
<td>1.75 ± 0.631</td>
<td>1.89 ± 0.613</td>
<td>6.887</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ cases (n=26)</th>
<th>Cyclo- cases (n=21)</th>
<th>Controls (n=45)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed Memory Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections (CD)</td>
<td>84.7 ± 10.4</td>
<td>81.6 ± 20.4</td>
<td>89.6 ± 8.1</td>
<td>3.240</td>
<td>0.044</td>
</tr>
<tr>
<td>Commission errors (CE)c</td>
<td>39.3 ± 16.1</td>
<td>19.5 ± 10.2</td>
<td>23.5 ± 16.1</td>
<td>12.621</td>
<td>0.000</td>
</tr>
<tr>
<td>CD reaction time d</td>
<td>491 ± 68</td>
<td>554 ± 78</td>
<td>507 ± 82</td>
<td>3.932</td>
<td>0.023</td>
</tr>
<tr>
<td>CE reaction time</td>
<td>462 ± 65</td>
<td>498 ± 70</td>
<td>483 ± 102</td>
<td>0.815</td>
<td>0.446</td>
</tr>
<tr>
<td>Discriminability d</td>
<td>1.46 ± 0.752</td>
<td>2.00 ± 0.773</td>
<td>2.22 ± 0.894</td>
<td>6.933</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Scheffe F test: c = Ciclo+ > Controlli, Ciclo- d = Ciclo+ < Ciclo-
Tables for hypothesis C:

“There may be variability in the impulsivity levels, in its trait and/or state components, related to specific affective temperamental traits or to affective symptoms, related to specific affective temperamental traits or to affective symptoms”

Table C1. Demographic features, Clinical Scales Scores (average score ± sd), BIS-11 scores (average scores ± sd) and Immediate and Delayed Memory Task Performances in non-cyclothymic (Cyclo-) vs cyclothymic (Cyclo+) subjects

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ (n=26)</th>
<th>Cyclo- (n=52)</th>
<th>t or Chi square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, average (sd)</td>
<td>36.0 ± 11.9</td>
<td>35.1 ± 12.1</td>
<td>0.306</td>
<td>0.760</td>
</tr>
<tr>
<td>Female gender, n. (%)</td>
<td>17 (68.0%)</td>
<td>31 (59.6%)</td>
<td>0.506</td>
<td>0.477</td>
</tr>
<tr>
<td>BRMS</td>
<td>4.1 ± 3.9</td>
<td>2.0 ± 2.6</td>
<td>2.867</td>
<td>0.005</td>
</tr>
<tr>
<td>BRDS</td>
<td>3.8 ± 4.0</td>
<td>3.8 ± 3.5</td>
<td>-0.026</td>
<td>0.980</td>
</tr>
<tr>
<td>HCL-32 Total</td>
<td>14.8 ± 4.4</td>
<td>12.8 ± 5.1</td>
<td>1.695</td>
<td>0.094</td>
</tr>
<tr>
<td>HCL-32 &gt; 14, n (%)</td>
<td>18 (69.2%)</td>
<td>25 (48.1%)</td>
<td>3.136</td>
<td>0.077</td>
</tr>
<tr>
<td>STAI State</td>
<td>45.4 ± 11.8</td>
<td>45.4 ± 11.6</td>
<td>-0.021</td>
<td>0.984</td>
</tr>
<tr>
<td>STAI Trait</td>
<td>50.3 ± 9.2</td>
<td>47.9 ± 9.6</td>
<td>1.077</td>
<td>0.285</td>
</tr>
<tr>
<td>CGI</td>
<td>3.3 ± 0.9</td>
<td>3.2 ± 0.9</td>
<td>0.267</td>
<td>0.790</td>
</tr>
<tr>
<td>TEMPS depressive</td>
<td>22.8 ± 3.7</td>
<td>20.5 ± 4.9</td>
<td>2.129</td>
<td>0.037</td>
</tr>
<tr>
<td>TEMPS cyclothymic</td>
<td>24.1 ± 7.2</td>
<td>20.4 ± 6.5</td>
<td>2.342</td>
<td>0.022</td>
</tr>
<tr>
<td>TEMPS hyperthymic</td>
<td>19.8 ± 5.5</td>
<td>20.4 ± 5.7</td>
<td>-0.439</td>
<td>0.662</td>
</tr>
<tr>
<td>TEMPS irritable</td>
<td>16.3 ± 5.8</td>
<td>14.2 ± 4.3</td>
<td>1.881</td>
<td>0.064</td>
</tr>
<tr>
<td>TEMPS anxious</td>
<td>18.8 ± 5.7</td>
<td>18 ± 5.5</td>
<td>0.631</td>
<td>0.370</td>
</tr>
<tr>
<td>BIS Attentional</td>
<td>17.4 ± 3.8</td>
<td>16.5 ± 3.9</td>
<td>0.912</td>
<td>0.365</td>
</tr>
<tr>
<td>BIS Motor</td>
<td>23.2 ± 3.6</td>
<td>20.4 ± 3.9</td>
<td>3.042</td>
<td>0.003</td>
</tr>
<tr>
<td>BIS Non Planning</td>
<td>27.4 ± 3.4</td>
<td>26.7 ± 5.5</td>
<td>0.619</td>
<td>0.538</td>
</tr>
<tr>
<td>BIS Total Score</td>
<td>68 ± 7.4</td>
<td>63.2 ± 9.3</td>
<td>2.258</td>
<td>0.027</td>
</tr>
<tr>
<td>IMT Correct Detections</td>
<td>79.5 ± 15.4</td>
<td>81 ± 11.5</td>
<td>-0.471</td>
<td>0.639</td>
</tr>
<tr>
<td>IMT Commission Errors</td>
<td>43.3 ± 9.5</td>
<td>23.8 ± 11.3</td>
<td>7.552</td>
<td>0.000</td>
</tr>
<tr>
<td>DMT Correct Detections</td>
<td>84.5 ± 14.4</td>
<td>82.6 ± 16.7</td>
<td>0.501</td>
<td>0.618</td>
</tr>
<tr>
<td>DMT Commission Errors</td>
<td>47.9 ± 15.7</td>
<td>22.8 ± 11.1</td>
<td>8.151</td>
<td>0.000</td>
</tr>
</tbody>
</table>

BRMS, Beck-Rafaelson Mania Scale; BRDS Beck-Rafaelson Depression Scale; HCL-32, Hypomania Check List; STAI, State-Trait Anxiety Inventory; CGI, Clinical Global Impression; TEMPS, Questionnaire for the Affective and Anxious Temperaments; BIS, Barratt Impulsiveness Scale; IMT, Immediate Memory Task; DMT, Delayed Memory Task.
Table C2. Correlations between Affective Temperaments, Symptoms and Impulsivity

<table>
<thead>
<tr>
<th></th>
<th>BIS</th>
<th>IMT</th>
<th>DMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Score</td>
<td>Commission</td>
<td>Commission</td>
</tr>
<tr>
<td>TEMPS Depressive</td>
<td>0.225*</td>
<td>0.037</td>
<td>0.079</td>
</tr>
<tr>
<td>TEMPS Cyclothymic</td>
<td>0.406**</td>
<td>0.084</td>
<td>0.203</td>
</tr>
<tr>
<td>TEMPS Hypertimic</td>
<td>0.026</td>
<td>-0.077</td>
<td>-0.133</td>
</tr>
<tr>
<td>TEMPS Irritable</td>
<td>0.279*</td>
<td>0.064</td>
<td>0.173</td>
</tr>
<tr>
<td>TEMPS Anxious</td>
<td>0.070</td>
<td>0.067</td>
<td>0.285</td>
</tr>
<tr>
<td>BRMS</td>
<td>0.131</td>
<td>0.420**</td>
<td>0.226</td>
</tr>
<tr>
<td>BRDS</td>
<td>0.073</td>
<td>-0.098</td>
<td>0.207</td>
</tr>
<tr>
<td>CGI</td>
<td>0.085</td>
<td>0.086</td>
<td>0.051</td>
</tr>
</tbody>
</table>

TEMPS, Questionnaire for the Affective and Anxious Temperaments; BRMS Beck-Rafaelsen Mania Scale; BRDS Beck-Rafaelsen Depression Scale; CGI, Clinical Global Impression; BIS, Barratt Impulsiveness Scale; IMT, Immediate Memory Task; DMT, Delayed Memory Task.

*p<.05

**p<.01
Tables for hypothesis D:
“We tried to verify the preceding hypotheses, other than in a mixed case sample of subjects belonging to different diagnostic anxiety subtypes, in specific anxiety disorders, beginning with panic disorder.”

**Table D1. Demographic features of PD patients and healthy controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=64)</th>
<th>Controls (n=44)</th>
<th>t or ( \chi^2 ) (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (ds)</td>
<td>36.56 ± 12.3</td>
<td>34.8 ± 10.3</td>
<td>0.772</td>
<td>0.442</td>
</tr>
<tr>
<td>Female n(%)</td>
<td>38 (60.3%)</td>
<td>26 (59.1%)</td>
<td>0.016</td>
<td>0.899</td>
</tr>
<tr>
<td>Education, n (%) ≤ 8 years</td>
<td>18 (28.1%)</td>
<td>6 (13.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (42.2%)</td>
<td>16 (36.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University or &gt;</td>
<td>19 (29.6%)</td>
<td>22 (50%)</td>
<td>12.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Work, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>13 (20.6%)</td>
<td>10 (22.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Collar</td>
<td>27 (42.2%)</td>
<td>25 (56.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue Collar</td>
<td>16 (25.0%)</td>
<td>7 (15.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/retired</td>
<td>4 (6.4 %)</td>
<td>2 (4.5%)</td>
<td>1.009</td>
<td>0.507</td>
</tr>
<tr>
<td>Marital Status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>32 (50.8%)</td>
<td>20 (45.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>26 (41.3%)</td>
<td>23 (52.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowhood / divorce</td>
<td>5 (7.9%)</td>
<td>1 (2.3%)</td>
<td>4.147</td>
<td>0.386</td>
</tr>
<tr>
<td>Demographic and clinical features of PD patients with (Cyclo+) and without (Cyclo-) comorbid Cyclothymic Disorder and healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Ciclo+ (n=20)</td>
<td>Ciclo- (n=44)</td>
<td>Total Cases (n=64)</td>
<td>Control (n=44)</td>
</tr>
<tr>
<td>Age, mean (ds)</td>
<td>37.8 ± 11.9</td>
<td>36.0 ± 12.6</td>
<td>36.6 ± 12.3</td>
<td>34.8 ± 10.3</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (68.4%)</td>
<td>25 (56.8%)</td>
<td>38 (60.3%)</td>
<td>26 (59.1%)</td>
</tr>
<tr>
<td>BRMS</td>
<td>4.4± 3.9</td>
<td>2.1 ± 2.7</td>
<td>2.8 ± 3.3</td>
<td>1.8 ± 3.6</td>
</tr>
<tr>
<td>BRDS</td>
<td>4.1 ± 3.9</td>
<td>4.0 ± 3.6</td>
<td>4.0 ± 3.7</td>
<td>0.1± 0.5</td>
</tr>
<tr>
<td>HCL32 Total</td>
<td>15.3 ± 4.5</td>
<td>12.9 ± 5.4</td>
<td>13.7 ± 5.2</td>
<td>9.1 ± 3.8</td>
</tr>
<tr>
<td>HCL32 ≥ 14 n (%)</td>
<td>15 (75.0%)</td>
<td>21 (47.7%)</td>
<td>36 (56.3%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>STAI - State</td>
<td>47.9 ± 12.1</td>
<td>45.3± 11.1</td>
<td>46.1 ± 11.4</td>
<td>33.1 ± 9.5</td>
</tr>
<tr>
<td>STAI - Trait</td>
<td>51.6 ± 8.7</td>
<td>48.3± 9.9</td>
<td>49.3 ± 9.6</td>
<td>36.2± 7.3</td>
</tr>
<tr>
<td>CGI</td>
<td>3.3 ± 0.9</td>
<td>3.4 ± 0.9</td>
<td>3.4 ± 1.0</td>
<td>1.0± 0.0</td>
</tr>
<tr>
<td>TEMPS depressive</td>
<td>22.6 ± 3.8</td>
<td>20.3 ± 5.0</td>
<td>21 ± 4.8</td>
<td>13.2± 4.0</td>
</tr>
<tr>
<td>TEMPS cyclothymic</td>
<td>24.7± 7.4</td>
<td>20.0 ± 5.9</td>
<td>21.5 ± 6.7</td>
<td>12.5± 4.2</td>
</tr>
<tr>
<td>TEMPS hypertimic</td>
<td>20.2± 5.5</td>
<td>20.4± 5.8</td>
<td>20.3 ± 5.7</td>
<td>22.5± 9.2</td>
</tr>
<tr>
<td>TEMPS irritable</td>
<td>17 ± 4.9</td>
<td>14.1± 4.2</td>
<td>15 ± 4.6</td>
<td>12.3± 4.6</td>
</tr>
<tr>
<td>TEMPS anxious</td>
<td>18.9 ± 6.2</td>
<td>18.3± 5.5</td>
<td>18.5 ± 5.7</td>
<td>12.0± 4.9</td>
</tr>
<tr>
<td>SASI Total</td>
<td>12.2 ±7.2</td>
<td>11 ± 7.3</td>
<td>11.4 ± 7.3</td>
<td>7.1 ± 5.9</td>
</tr>
<tr>
<td>ISSI Total</td>
<td>94.6 ± 20.2</td>
<td>86.5 ± 16.4</td>
<td>89.0 ± 17.9</td>
<td>103.1± 13.1</td>
</tr>
</tbody>
</table>

BRMS, Bech-Rafaelsen Mania Scale; BRDS, Bech-Rafaelsen Depression Scale; HCL32, Hypomania Check List; STAI, State-Trait Anxiety Inventory; CGI, Clinical Global Impression; TEMPS, Questionnaire for the Affective and Anxious Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified; SASI, Separation Anxiety Symptoms Inventory; ISSI Interpersonal Sensitivity Symptoms Inventory.
### Table D3. BIS scores and IMT/DMT performances of PD patients with (Cyclo+) and without (Cyclo-) comorbid Cyclothymic Disorder and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ (n=20)</th>
<th>Cyclo- (n=44)</th>
<th>Total Cases (n=64)</th>
<th>Controls (n=44)</th>
<th>Total Cases Vs Controls</th>
<th>Cyclo+ Vs Controls</th>
<th>Cyclo- Vs Controls</th>
<th>Cyclo+ Vs Cyclo-</th>
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<tbody>
<tr>
<td><strong>BIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentional</td>
<td>17.8 ± 3.5</td>
<td>16.34 ± 3.49</td>
<td>16.8 ± 3.5</td>
<td>13.1 ± 2.5</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>ns</td>
</tr>
<tr>
<td>Motor</td>
<td>23.7 ± 3.3</td>
<td>20.63 ± 3.89</td>
<td>21.6 ± 4</td>
<td>18.9 ± 3.6</td>
<td>0.001</td>
<td>0.000</td>
<td>ns</td>
<td>0.010</td>
</tr>
<tr>
<td>Non Planning</td>
<td>27.6 ± 3.8</td>
<td>27.0 ± 5.8</td>
<td>27.2 ± 5.2</td>
<td>25.0 ± 4.1</td>
<td>0.027</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Total</td>
<td>69.0 ± 7.1</td>
<td>63.5 ± 8.9</td>
<td>65.2 ± 8.7</td>
<td>57.1 ± 7.5</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>0.044</td>
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<tr>
<td><strong>IMT</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Correct</td>
<td>78.2 ± 16.9</td>
<td>79.9 ± 11.8</td>
<td>79.4 ± 13.5</td>
<td>79.9 ± 12.9</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>(CD)</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Commission</td>
<td>44.2 ± 9.8</td>
<td>24.7 ± 11.7</td>
<td>30.8 ± 14.3</td>
<td>18.4 ± 10.8</td>
<td>0.000</td>
<td>0.000</td>
<td>0.030</td>
<td>0.000</td>
</tr>
<tr>
<td>errors (CE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.05 ± 0.56</td>
<td>1.66 ± 0.71</td>
<td>1.47 ± 0.72</td>
<td>1.88 ± 0.62</td>
<td>0.002</td>
<td>0.000</td>
<td>0.036</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>DMT</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>84.5 ± 14.6</td>
<td>81.2 ± 17.4</td>
<td>82.2 ± 16.5</td>
<td>89.5 ± 8.2</td>
<td>0.003</td>
<td>ns</td>
<td>0.022</td>
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<tr>
<td>detections</td>
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<td>(CD)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commission</td>
<td>49.8 ± 16.5</td>
<td>24.5 ± 10.9</td>
<td>32.4 ± 17.4</td>
<td>23.0 ± 16.0</td>
<td>0.005</td>
<td>0.000</td>
<td>ns</td>
<td>0.000</td>
</tr>
<tr>
<td>errors (CE)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.21 ± 0.67</td>
<td>1.77 ± 1.67</td>
<td>2.2 ± 0.904</td>
<td>2.2 ± 0.904</td>
<td>0.000</td>
<td>0.000</td>
<td>0.036</td>
<td>0.041</td>
</tr>
</tbody>
</table>
8. REFERENCES


within tic-related subgroups." Personality and Individual Differences 36(3): 539-553.


9. PUBLICATIONS
Different measures of impulsivity in patients with anxiety disorders: A case control study

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Barratt Impulsiveness Scale (BIS-11)

A B S T R A C T

The relationship between anxiety and impulsivity is controversial and not well explored. The present investigation aims to compare impulsivity, measured by different rating tools, in patients with anxiety disorders vs. healthy controls. Forty-seven subjects with different anxiety disorders and 45 matched controls underwent diagnostic and symptomatological evaluations by the Mini Neuropsychiatric Interview (M.I.N.I) Plus 5.0, Bech-Rafaelsen Depression and Mania Scale (BRDMS), State–Trait Anxiety Inventory (STAI), Hypomania Check List (HCL-32) and the Clinical Global Impression (CGI); temperamental evaluations by the Questionnaire for the Affective and Anxious Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified (TEMPS-M), the Separation Anxiety Sensitivity Index (SASI), the Interpersonal Sensitivity Symptoms Inventory (ISSI); and psychometric and a neurocognitive evaluations of impulsivity using the Barratt Impulsiveness Scale (BIS-11) and the Immediate and Delayed Memory Task (IMT-DMT). Subjects with anxiety disorders were more impulsive than the controls in all the explored measures, with higher scores in symptomatological and, temperamental scales. Patients with anxiety disorders but without a lifetime history of comorbid major mood episodes had greater trait and state impulsivity than controls. Further investigations are needed to assess the extent to which impulsivity might or might not be directly related to the anxiety disorder.

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1. Introduction

The relationship between anxiety and impulsivity is controversial and, traditionally, the two dimensions have been considered inversely related (Barratt, 1965; Askenazy et al., 2000a).

In an investigation of correlation between clinical variables and suicidal risk in violent and non-violent psychiatric patients, Apter et al. reported that anxiety, evaluated by the State–Trait anxiety scale (Spielberger, 1983), led to a reduced risk for violent behaviors (Apter et al., 1999). A study on a sample of violent adolescents with high impulsivity levels (Askenazy et al., 2000b) reported a lack of correlation between anxiety, measured by the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), and impulsivity, evaluated by the Impulsivity Rating Scale (IRS) (Lecrubier et al., 1995). Similarly, no correlation between anxiety and impulsivity was observed in a non-clinical sample of adolescents (Caci et al., 1998). On the other hand, although findings are mixed on the topic (Bienvenu et al., 2000; Potenza et al., 2009; Piero, 2010; Sulikowski et al., 2011), a tight association between anxiety and impulsivity has been documented at least for impulse control disorders, such as pathological gambling (Roy et al., 1988), and other conditions in which impulsivity represents a core clinical characteristic such as bipolar disorder (BD) (Najt et al., 2007), eating disorders (Askenazy et al., 1998), personality disorders with self-injuring episodes (Simeon et al., 1992), attention deficit hyperactivity disorder (ADHD) (Baldwin and Dadds, 2008) and conduct disorders (CDs) (Askenazy et al., 2003). Furthermore, norepinephrine increase due to pharmacological interventions enhances impulsive Immediate Memory Task (IMT) responses and subjective anxiety in healthy subjects (Swann et al., 2005a).

These results suggest that, at least in certain populations, anxiety is more than a simple inhibition of behavior. Barratt et al. reported that, among healthy subjects, impulsivity and anxiety were orthogonal (Barratt et al., 1987). Those with high impulsivity and low anxiety levels had antisocial characteristics, while those with high impulsivity and high anxiety were more likely to seek treatment for a psychiatric disorder. Impulsive behavior can be increased by high arousal and activation of catecholaminergic systems (Barratt and Patton, 1983) that are also involved in anxiety (Albus et al., 1992). In particular, dopaminergic stimulation may increase impulsivity related to its role in motivation.
and the initiation of action, while noradrenergic activation, such as with severe stressors, may contribute to behavioral sensitization (Swann, 2010). This raises the possibility that, in susceptible individuals, the high arousal associated with anxiety could increase the probability of impulsive behavior.

Aiming to explore the relationship between anxiety, impulsivity, risk-taking behaviors and psychiatric disorders, Askenazy et al. (Askenazy et al., 2003) evaluated anxiety and impulsivity levels in a sample of adolescents admitted to the hospital for a broad spectrum of behavioral problems (suicide attempts, aggressive behavior, delinquent behaviors, substance poisoning, eating disorders). The authors concluded that impulsivity and anxiety, when associated with mood disorders, strongly predict risk for suicidal attempts. Moreover, the presence of anxiety in an impulsive population, instead of protecting from behavioral dyscontrol, may lead to aggressiveness that can be self-directed. On the other hand, impulsivity without anxiety is related to anti-social behaviors, CD's, and “hetero-directed” behaviors (e.g. toward other people, animal, objects or other targets different from the “self”) (Askenazy et al., 2003). Finally, the association between impulsivity and anxiety tends to show a wide overlap with soft bipolar spectrum (Akiskal and Mallya, 1987b) disorders (Perugi and Akiskal, 2002; Askenazy et al., 2003).

A recent study by Taylor et al. (Taylor et al., 2008) showed that BD patients with one or more comorbid anxiety disorders present higher levels of “trait” impulsivity (intended as a “stable characteristic” in contrast to “state-dependent” impulsivity), as measured by the Barratt Impulsiveness Scale (BIS), in comparison to BD patients without such a comorbidity. The authors concluded that the presence of an anxiety disorder does not reduce the potential for impulsive behavior in bipolar patients. In an another study, social anxiety was related (Kashdan and Hofmann, 2008) to a specific predisposition toward risk taking behaviors, impulsivity, and instability of affect and interpersonal relationships. Some authors also related the chance of impulsive/aggressive reactions to a (real or perceived) rejection (Leary et al., 2006). More recently, Kashdan et al. (Kashdan and Hofmann, 2008) reported a high rate of impulsive behaviors and comorbid substance abuse in a subgroup of patients with social anxiety disorder characterized by high levels of “novelty seeking”. Higher levels of trait impulsivity among bipolar patients were also found by Ekinci et al. in euthymic subjects (Ekinci et al., 2011).

The prevalence of impulsivity in the specific context of primary anxiety disorders has not been systematically explored. In a study by Summerfeldt et al. (Summerfeldt et al., 2004) the BIS was given to subjects with a range of anxiety disorders (40 with obsessive-compulsive disorder, 37 with panic disorder and 24 with social anxiety disorder). Interestingly, anxiety disorder patients reported higher scores (both for “total”, “attentional” and “non-planning” subscales of BIS-11) than healthy controls. In particular, the authors observed that elevated rates of impulsivity may be more related to having a psychiatric disorder in general than to suggesting a unique relationship between anxiety and impulsivity.

Questionnaires such as the BIS-11 measure recalled attitudes and behavior. Predisposition to impulsivity can also be assessed using neurocognitive performance tests that measure constructs that are central to impulsive behavior, such as response inhibition. These tests provide objective measures that are not subject to recall or other biases (Dougherty et al., 2003). For example, the rate of impulsive commission errors on a modified continuous performance task (the Immediate-Delayed Memory task or IMT-DMT) was increased in children with disruptive behavior disorders and their parents, and commission error rates correlated with severity of personality disorder symptoms (Swann et al., 2002).

Therefore, aiming to shed further light on the putative relationship between anxiety and impulsivity, the present study evaluates and compares impulsivity using different assessment tools (rating scales and neurocognitive tests) in patients with anxiety disorders and control subjects, matched for demographic features, specifically testing our hypothesis that impulsivity scores, measured by different tools, might be higher in patients with anxiety disorders than in controls, finally exploring the putative presence of specific Axis I and/or temperamental features eventually associated higher levels of impulsivity.

2. Methods

2.1. Subjects

A sample of 47 outpatients, referred to the facilities of the “Unità Operativa di Psychiatria 1 dell’Azienda Ospedaliero-Universitaria Pisana”, was consecutively enrolled in a period of 1 year. The sample included 30 (63.8%) female subjects and 17 (36.2%) males with a mean age of 34.5 years (S.D. = 10.3, range 19–63). All patients met DSM-IV criteria (American Psychiatric Association, 1994) for at least one anxiety disorder (panic disorder; obsessive-compulsive disorder; social phobia; generalized anxiety disorder). Patients presenting comorbidity for lifetime schizophrenia or other psychotic disorders, organic psychiatric syndromes and severe somatic disorders were excluded from the study.

The control group included 45 healthy subjects matched for gender, age, education, job and marital status; 28 (62.2%) were females and 17 (38.8%) males, with a mean age of 34.8 years (S.D. = 10.2, range 19–63).

Each subject included in the study was extensively informed about the study procedure and gave his/her own written informed consent before starting any evaluation. The study protocol was approved by the local Ethics Committee of the “Azienda Ospedaliero-Universitaria Pisana”.

2.2. Measures and procedures

The diagnostic and clinical evaluations were performed by a resident in psychiatry, (ADC) under the supervision of a senior psychiatrist (GP). The resident in psychiatry underwent a specific training for the administration of the rating tools. The diagnostic evaluation was performed using the Italian version of the Mini Neuropsychiatric Interview (MINI) Plus 5.0 (Sheehan, 2004), a structured interview for Axis-I diagnoses, according to the DSM-IV criteria.

The symptomatological evaluation was conducted by means of the Bech-Rafaelsen Depression and Mania Scale (BRMS) – whose inter-observer reliability is considered adequate and homogenous compared with the solely melancholic assessment provided by the Hamilton Depression Rating Scale (HDRS) (Bech et al., 1979; Bech, 1988) and the Clinical Global Impression (CGI). Severity of Impairment scale (Guy, 1976).

Patients were asked to complete a set of self-report rating instruments. The assessment of the levels of anxious symptomatology was performed with the State-Trait Anxiety Inventory (STAI) (Spiegelberger, 1983) – a widely adopted and multi-culturally validated tool whose original (1970) test–retest correlations were calculated to be 0.54 for the State section and 0.86 for the trait section (Spiegelberger et al., 1970) – although it has been recently questioned whether the scales strictly evaluate anxiety rather than negative affect (Baños et al., 2010). The Barratt Impulsiveness Scale (BIS-11) has been employed for the evaluation of impulsivity (Patton et al., 1995). The BIS-11 is made up of 30 items, assesses the frequency of impulsivity-related behavior or cognitions. Each item is measured on a 4-point scale, ranging from rarely/never through to almost always, with no available neutral response. Item 4 indicates the most impulsive response; therefore, the higher the subscale score, the higher the level of impulsiveness. The scale is based on a tri-dimensional model of impulsivity, which distinguishes between ‘Motor Impulsiveness’ (11 items, e.g. Doing things without thinking), ‘Cognitive Impulsiveness’ (8 items, e.g. I don’t pay attention) and ‘Non-planning Impulsiveness’ (11 items, e.g. I plan tasks carefully). There are no filler items. Patton et al. (1995) reported acceptable internal reliability across their groups of undergraduates, psychiatric inpatients and male inmates, while Miller et al. (2004) reported the following internal reliability coefficients: alpha 0.70 (mean 22.4; ±4.46), 0.72 (mean 24.23; ±4.49), 0.61 (mean 16.53 ± 3.30) for “motor impulsiveness”, “non-planning impulsiveness” and “cognitive impulsiveness” (Miller et al., 2004). The Hypomania Check List (HCL-32) (Angst et al., 2005) was utilized for the retrospective evaluation of hypomanic symptoms. The Check List was developed as a screening instrument for hypomania (Angst et al., 2005); a total score of 14 or above has been associated with high sensitivity (0.8) and fair specificity (0.51) in differentiating BD depression from recurrent major depressive disorder (Angst et al., 2005; Vietta et al., 2007). The sensitivity and specificity of the HCL-32 seem to be independent from the mood state at the moment of the evaluation (Angst et al., 2005).

The temperamental traits evaluation was performed by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified (TEMPS-M) (Erfurth et al., 2005), a 35-items self-rating scale allowing the detection of a affective and anxious temperamental features according to the criteria proposed by Asiksal and Mallya (Akiskal and Mallya, 1987a). The questionnaire comprises five subscales, each one assessing, in a quantitative way, the presence of temperamental elements of a depressive, cyclothymic, hyperthymic, irritable or anxious nature. Separation anxiety and interpersonal sensitivity were explored using the Separation Anxiety Symptoms Inventory (SASI) (Silove et al., 1996), a 36-item self-report instrument evaluating interpersonal and rejection sensitivity.
Neurocognitive evaluation of impulsivity was conducted by a clinical psychologist (MB), blind to the diagnosis of the patient, using the Immediate and Delayed Memory Task (IMT/DMT), derived from the Continuous Performance Test (Dougherty et al., 2000). Subjects were shown five-digit numbers on a computer screen, for 0.5 s, at 0.5-s intervals. For the immediate memory task, subjects were instructed to respond if a set of numbers matched the previous set. There are three outcomes: correct detections (matching sets are identified accurately), commission errors (sometimes called false alarms, where the subject responds to a set with four of the five digits correct), and random errors (subject responds to a set of five completely different numbers). The delayed memory task was similar except that, between sets of numbers to be matched, three distracters consisting of ve-digit numbers on a computer screen, for 0.5 s at 0.5- intervals. High rates of commission errors were reported in impulsive populations (Dougherty et al., 1999, 2000; Moeller et al., 2001; Marsh et al., 2002). Commission errors were also increased in manic patients, were correlated with mania rating scores (Swann et al., 2001, 2003) and were increased in subjects with a history of severe and life-threatening suicidal attempts (Swann et al., 2005b). In the present study we report only correct detections and commission errors; random errors, in fact, never exceeded 5% and did not vary across experimental groups.

2.3. Data analysis

Comparative analysis for familial, epidemiological, clinical features and course of different subgroups was performed using the Student t-test for dimensional variables (Mann-Whitney U-test, when appropriate) and the chi-square test for categorical variables (Fisher exact-test, when appropriate). Due to the number of subjects and the confirmatory nature of our study, we considered, in a conservative way, two-tailed significance levels with threshold at $p < 0.05$.

3. Results

3.1. Demographic features

Table 1 summarizes demographic features of subjects affected by anxiety disorder (n = 47) and controls (n = 45) are reported. There are no significant differences for gender distribution, mean age, education, work and marital status. The investigator team specifically focused on the selection of the control group matched for age, education and social level, since all of these could influence measures of impulsivity (Marsh et al., 2002).

3.2. Diagnostic distribution, co-morbidities and actual treatment

Among the anxiety disorder patients (n = 45) the most frequent diag-is was panic disorder with (26, 55.3%) and without (11, 23.4%) agoraphobia; only one subject (1.8%) presented agoraphobia without panic disorder. Concerning the other anxiety disorders, 12 patients (25.5%) met diagnostic criteria for obsessive-compulsive disorder, nine (19.1%) for generalized anxiety disorder and seven (14.9%) for social anxiety disorder. Thirty (66.6%) patients met diagnostic criteria for one anxiety disorder, eleven (24.4%) for two and four (8.8%) for three anxiety disorders.

Regarding lifetime co-morbidities with mood disorders, nine patients with anxiety disorder (19.1%) reported a spontaneous hypomanic episode while 10 (21.3%) reported hypomaniac episodes induced by treatment with antidepressants. In five patients (10.6%), it was possible to diagnose comorbid cyclothymic disorder according to DSM-IV criteria. Control subjects (n = 42) did not meet any diagnostic criteria for any DSM-IV mental disorder.

Concerning psychopharmacological treatment, 12 patients (25.5%) were taking pregabaline, 23 (48.9%) were on selective serotonin reuptake inhibitors (SSRIs), three (6.5%) were on selective serotonin norepinephrine reuptake inhibitors (SNRIs), seven (15.2%) were taking tricyclic antidepressants (TCAs) and eight (17.4%) were on other antidepressants (bupropion, mirtazapine, trazodone). A small percentage of patients (n = 5; 10.6%) were taking low doses (less than 1 mg/day of lorazepam equivalent) of benzodiazepines.

3.3. Symptomatological, temperamental trait evaluation

As expected, anxiety disorder patients differed from controls, with higher higher scores on the BRMS (p = 0.001), BRDS (p = 0.004), STAI, both state (STAI-S) and trait components (STAI-T) (both with p < 0.001) and Hypomania Check List (HCL-32) (p = 0.001) (Table 2). For this latter scale, we calculated, for each group, the percentage of subjects reaching a score ≥ 14. This cut-off has been shown to be the one having the best specificity and sensitivity for the retrospective screening of hypomania in patients with depression across various phases of the illness (Angst et al., 2005; Meyer et al., 2007; Vieta et al., 2007). A higher number of anxiety disorder patients obtained a score ≥ 14 in comparison with controls (respectively 30, 63.8%, vs. 14, 31.1%; chi-square = 9.86; p = 0.002). Finally, anxiety disorder patients reported a CGI-S score of 3.32 (S.D. = 1.0), indicating a global severity of the disorder between mild and moderate.

Concerning the evaluation of the temperamental characteristics, anxiety disorder patients recorded significantly higher scores in four out of five subscales of the TEMPS-M: depressive, cyclothymic and anxious temperament (p < 0.001), irritable temperament (p = 0.018). On the contrary, no significant differences between the two groups were observed in the hyperthymic temperament subscale; in this latter the average scores were slightly higher in controls than in anxious patients, but the difference was not statistically significant (t = −1.466; p = 0.150).

### Table 1

Demographic features in anxious and control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 47)</th>
<th>Controls (n = 45)</th>
<th>t or χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, average (S.D.)</td>
<td>34.5 ± 10.3</td>
<td>34.8 ± 10.2</td>
<td>−0.14</td>
<td>0.886</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>30 (63.8%)</td>
<td>28 (62.2%)</td>
<td>0.143</td>
<td>0.705</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td>1.82</td>
<td>0.400</td>
</tr>
<tr>
<td>≤8 years</td>
<td>10 (21.3%)</td>
<td>6 (13.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>20 (42.6%)</td>
<td>17 (37.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University or &gt;</td>
<td>17 (36.2%)</td>
<td>22 (48.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation, n (%)</td>
<td></td>
<td></td>
<td>7.7</td>
<td>0.103</td>
</tr>
<tr>
<td>Student</td>
<td>9 (19.1%)</td>
<td>10 (22.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House keeper/blue collar</td>
<td>10 (21.3%)</td>
<td>8 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office worker/teacher</td>
<td>16 (34.04%)</td>
<td>8 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manager/white collar</td>
<td>10 (21.3%)</td>
<td>8 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 (4.3%)</td>
<td>1 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
<td>3.85</td>
<td>0.150</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>18 (38.3%)</td>
<td>24 (53.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>24 (51.1%)</td>
<td>20 (44.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed/divorced</td>
<td>5 (10.6%)</td>
<td>1 (2.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

Clinical scale scores (average score ± sd) of anxious and control subjects.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cases (n = 47)</th>
<th>Controls (n = 45)</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRMS</td>
<td>3.7 ± 3.9</td>
<td>2.0 ± 3.9</td>
<td>670</td>
<td>0.001</td>
</tr>
<tr>
<td>BRDS</td>
<td>3.8 ± 4.1</td>
<td>0.1 ± 0.5</td>
<td>222.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

For the BRMS and BRDS scales, Mann–Whitney U-test; for the ISSI, HCL-32, STAI and CGI, TEMPS t-test or χ². BRMS, Bech-Raphaelsen Mania Scale; BRDS, Bech-Raphaelsen Depression Scale; SASI, Separation Anxiety Symptoms Inventory; ISSI Interpersonal Sensitivity Symptoms Inventory; HCL-32, Hypomania Check List; STAI State-Trait Anxiety Inventory; CGI, Clinical Global Impression.
p = .146). As expected, patients with anxiety disorders reported higher SASI scores (p < 0.001). Regarding the ISSI, in which low scores indicate an increased sensitivity to rejection in an interpersonal context, the mean scores were significantly lower in patients than in controls (p < 0.001).

3.4. Measures of impulsivity

Significant differences between the two groups were observed in the BIS total score (p < 0.001) and in “attentional” and in “motor” impulsivity subscales (p < 0.001 and p = 0.004 respectively) (Table 3). All the scores were significantly higher in the anxious subjects than in controls. The “non-planning” subscale score was also higher in anxious subjects (p = 0.047).

The performances of anxious and control subjects at the IMT-DMT are reported in Table 3. In the first task, the IMT, anxious subjects and controls did not differ in the percentage of correct answers (correct detections, p = 0.745), but the anxious subjects made significantly more impulsive responses (commission errors, p < 0.001). The value represented by the parameter A’ (discriminability), a measure of the ability of discriminating the proper stimulus corrected by other similar stimuli, was significantly higher in controls than in patients (p = 0.006). The controls also manifested a greater tendency to give conservative answers, as indicated by the presence of a significant difference (p = 0.016) in comparison to the anxious patients in the parameter B’ (response bias). The second task, the DMT, is generally considered as more difficult compared to the IMT as it also reflects working memory (Marsh et al., 2002). Anxiety disorder patients made fewer correct detections (p = 0.018), and more impulsive responses (commission errors, p = 0.046). The value of the parameter A’ (discriminability) remained significantly higher in controls than in anxious patients (p = 0.004). Finally, patients and controls showed the same trend to provide conservative answers, as indicated by the absence of a statistically significant difference in the parameter B’ of DMT.

4. Discussion

4.1. Symptomatological, temperamental evaluation

As expected, our anxiety disorder patients showed state and trait components of STAI scores that were higher than those of controls (Kabacoff et al., 1997); also depressive and manic symptomatology as recorded by BRMS and the BRDS was more represented in anxious patients than in controls. This finding confirms the high prevalence of mood symptoms in patients with anxiety disorders (Bieling et al., 1998; Rickels and Rynn, 2001). Interestingly, also the retrospective evaluation by the HCL-32 indicated that anxiety disorder patients reported more past hypomanic symptoms than controls and 63.8% of them reached a score of 14 or more which indicated a high probability of previous hypomania (Angst et al., 2005; Meyer et al., 2007; Vieta et al., 2007). Even taking into account the unavoidable false positive cases of a screening instrument, this finding seems to be congruent with the structured diagnostic evaluation, according to which nine subjects (19.1%) with anxiety disorders fulfilled the DSM-IV diagnostic criteria for a spontaneous hypomanic episode and 10 (21.3%) reported a past history of drug-induced hypomania. Additionally, for five patients (10.6%), it was possible to make diagnosis of cyclothymic disorder according to DSM-IV criteria. Consequently, in our sample the primary diagnosis of anxiety disorder is frequently associated with a sub-threshold mood disorder. It is therefore unsurprising that the TEMPS-M temperamental profile of anxiety disorder patients showed significantly higher scores than controls in four out of five subscales: depressive, cyclothymic, anxious and irritable temperaments. This temperamental profile is also associated with a marked sensitivity with separation anxiety, already associated with an affective instability of cyclothymic nature (Pini et al., 2005), as well as with interpersonal rejection sensitivity, which has been observed as strictly related to cyclothymic mood reactivity (Perugi et al., 2003) and also confirmed by a recent publication from our group indicating a preferential role of cyclothymic temperament in the presence of higher levels of impulsivity in the course of different anxiety disorders (Perugi et al., 2011).

4.2. Impulsivity evaluation

To the best of our knowledge, this is the first study using different paradigms largely applied to patients with mood disorders. CIs and substance use disorders to evaluate impulsivity in patients with anxiety disorders. Although anxiety and impulsivity have been traditionally considered as inversely related psycho(patho)logical dimensions (Barratt, 1965; Askenazy et al., 2000a), our results are consistent with data reported by Summerfeldt et al. (2004) in a large sample of anxiety disorder patients compared with a control group. In this latter study, as well as in our patients, the anxious subjects reported higher BIS mean scores than controls in “total”, “attentional” and “not planning” subscales. In contrast to the Summerfeldt et al. (2004) study, in our anxious patients the mean score of the “motor” subscale was also higher than in controls. These secondary differences might be accounted for by different sampling procedures.

The finding that, at least in some patients, anxiety disorders might be associated with impulsivity has relevant clinical implications. For example, social anxiety has been related, at least in a subgroup of patients (Kashdan et al., 2008), to a particular predisposition toward risk taking behavior, impulsivity and interpersonal and relational instability. Kashdan et al. (2008), after having separated two groups of social anxiety disorder patients on the basis of the degree of novelty seeking, identified an association with impulsive behaviors and a high comorbidity level of substance use disorder in the subgroup of patients characterized by high levels of novelty seeking. The same authors, Kashdan et al. (2009), analyzing the National Comorbidity Survey-Replication (NCS-R) dataset, focused on people with current (N = 679) or lifetime (N = 1143) social anxiety disorder (SAD). Latent class analysis on NCS-R risk-prone behavior items, found two SAD classes: (1) a pattern of behavioral inhibition and risk aversion and (2) an atypical pattern of high anger and aggression, and moderate/high sexual impulsivity and substance use problems. The pattern of risk-prone behaviors was associated with greater functional impairment, less education and income, younger age, and psychiatric comorbidities. The authors concluded that the nature, course, and treatment of SAD might be compromised by not attending to heterogeneity in such a behavioral pattern. It is interesting to underline how the psychopathological features and the course of these syndromal pictures overlap with recent descriptions of cyclothymia and Type-II BD (Perugi et al., 2002).
In our study, patients with anxiety disorders do not present a particular mnemonic or attentive impairment, as measured by the percentage of correct detections on the IMT, but they had more difficulty in inhibitory/dis-attentional impulsivity. This finding contrasts with the tendency to conceptualize anxiety disorders as characterized by high levels of harm avoidance, behavioral inhibition and hypercontrol (Brown, 1996; Zinbarg and Barlow, 1996). By contrast, the ability of discriminating the proper stimulus was greater in controls than in patients. Control subjects also showed a higher tendency to provide conservative answers. In the DMT, as in the IMT, patients with anxiety disorder provided a lower number of correct detections than healthy controls. The differences between the IMT and the DMT in the performances of the anxious subjects could be due to the different degrees of difficulty, including greater latency and distracting stimuli (Dougherty et al., 2000). The ability to discriminate in the DMT remains significantly higher in controls than in patients.

4.3. Limitations

Our study presents some methodological limitations that should be taken into account before discussing the results. The evaluations were made, under the supervision of a senior psychiatrist, in a setting of routine clinical practice by a resident in psychiatry, who was taking care of patients and was informed about their diagnosis. The employment of standardized instruments should minimize eventual biases due to the lack of blind evaluation. The patients affected by anxiety disorder belonged to different diagnostic subtypes, which could differ in terms of impulsivity or the other psychological dimensions. However, the number of subjects was not sufficient to permit comparisons among diagnostic subtypes and the low power of the study, essentially due to its small sample size, also precluded the opportunity to control for depression when comparing between impulsivity and aggressive behavior.

4.4. Conclusion

In conclusion, our patients with anxiety disorders were more impulsive than control subjects, concerning both psychometric and neurocognitive measures. Our results contrast with the assumption that harm avoidance and behavioral inhibition are invariably associated with anxiety. As major implication, this study suggests that harm avoidance and behavioral inhibition are invariably associated with anxiety. Our results contrast with the assumption that impulsivity and aggressive behavior. As major implication, this study suggests that impulsivity and aggressive behavior are not synonymous nor homogenous in anxiety disorders. In some anxious patients behavioral inhibition plus hypercontrol could be considered as secondary mechanisms to impulsivity, especially in “perceived impulsivity”, as clearly indicated by the impulsive–compulsivity overlapping (Hantouche et al., 2003).

It is not clear from our data whether the presence of impulsivity should be directly related to the anxiety disorder or could be associated with coexisting soft bipolar symptomatology. This latter seems to be frequently associated with anxiety disorders, possibly reflecting a susceptibility to over-arousal in these patients.

Our results should be considered preliminary, requiring replication in larger samples. It should also be interesting to compare impulsivity measures in different anxiety disorders and in longitudinal studies, in order to test the stability of the results obtained with neurocognitive tasks.

References

Preliminary communication

Impulsivity in anxiety disorder patients: Is it related to comorbid cyclothymia?

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Cyclothymia

Objective: The relationship between anxiety and impulsivity is controversial and not well explored. In a previous study we compared impulsivity, measured by different rating tools, in patients with anxiety disorders vs. healthy controls. In the same sample we now explore the influence of comorbid soft bipolar spectrum disorders on the relationship between anxiety disorders and impulsivity.

Method: A sample including 47 subjects with anxiety disorder(s) and 45 control subjects matched for demographic, educational and work characteristics underwent a diagnostic evaluation by the Mini Neuropsychiatric Interview (MINI); a symptomatological evaluation by the Bech–Rafaelsen Depression and Mania Scale (BRDMS), the State–Trait Anxiety Inventory (STAI), the Hypomania Check List (HCL-32) and the Clinical Global Impression (CGI); a temperamental and personological evaluation by the Questionnaire for the Affective and Anxious Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Modified (TEMPS-M), the Separation Anxiety Symptoms Inventory (SASI), the Interpersonal Sensitivity Symptoms Inventory (ISSI); and, finally, a psychometric and a neuro-cognitive evaluation of impulsivity by the Barratt Impulsiveness Scale (BIS) and the Immediate and Delayed Memory Task (IMT/DMT).

The initial sample of patients with anxiety disorders was then subdivided into two subgroups depending on the presence of comorbid cyclothymia (Cyclo+, n=26 and Cyclo−, n=21). For the diagnosis of cyclothymic disorder, we used both the DSM-IV-TR criteria and also a modified threshold for hypomania with a duration of 2 days. We compared symptomatological, temperamental, personological and impulsivity measures in Cyclo+, Cyclo− and controls.

Results: The comparison between Cyclo+, Cyclo− and controls showed that Cyclo+ are the most impulsive subjects in all the investigated measures and are characterized by greatest symptomatological impairment, highest scores in temperamental scales, and highest levels of interpersonal sensitivity and separation anxiety. Cyclo− subjects resulted to be more impulsive compared to controls concerning the retrospective trait measures, but not in the neuro-cognitive test.

Limitations: Correlational cross-sectional study.

Conclusion: In our patients with anxiety disorders, without lifetime comorbidity with major mood episodes, trait and state impulsivity resulted to be greater than in controls. In particular impulsivity was highest in patients with both anxiety disorders and cyclothymia. In anxious-cyclothymic patients also separation anxiety and interpersonal sensitivity were more severe than...
in anxious patients without cyclothymia and controls. Our findings suggest that impulsivity, rather than being directly related to the presence of the anxiety disorder, could be associated with comorbidity with cyclothymia.

1. Introduction

The relationship between anxiety and impulsivity is controversial and, traditionally, the two dimensions have been considered inversely related (Barratt, 1965; Askenazy et al., 2000). Studies conducted with different methodologies found no correlation between anxiety and impulsivity (Apter et al., 1993; Lecrubier et al., 1995; Caci et al., 1998; Askenazy et al., 2000). On the other hand, at least in subgroups of subjects, anxiety disorders may occur in atypical forms in which impulsivity may be present. In recent research, a subtype of social anxiety resulted to be related to a specific predisposition toward risk taking behaviors, impulsivity, relational and affective, interpersonal instability (Kashdan and Hofmann, 2008; Kashdan et al., 2009). In a study by Summerfeldt et al. (2004) anxiety disorder patients reported higher scores than healthy controls, both in “total”, “attentional” and “not planning” subscales of Barratt Impulsiveness Scale (BIS). A major limit of this study is the use of only a psychometric measure of impulsivity. In a previous study by our group (Del Carlo et al., submitted for publication), we observed greater state and trait impulsivity, measured with a neuro-cognitive task and the BIS, in patients with anxiety disorders than in healthy controls.

The relationship between impulsivity and mood disorders has been widely documented. High levels of impulsivity have been reported in Major Depressive Episode (MDE), particularly when associated with suicidality (Corruble et al., 1999), as well as in depressive and manic phases of Bipolar Disorder (BD) (Moeller et al., 2001a). Impulsivity is particularly elevated during the manic and mixed episodes and tends to persist during the inter-episodic phases (Swann et al., 2003, 2008; Strakowski et al., 2010).

Trait impulsivity in BD has been classically included among temperamental features (Akiskal and Mallya, 1987; Perugi and Akiskal, 2002). Affective temperament has been viewed as biological disposition, corresponding to a constitutional substrate expressed through a series of signs and features, usually manifested by a certain stability of mood, attitudes toward the environment, sensitivity to external stimuli and characteristic modes of reaction (Perugi and Akiskal, 2002; Akiskal et al., 2006). In their extreme manifestations ‘dysthymic’ and ‘cyclothymic’ dispositions have received official sanction in the contemporary psychiatric nomenclature as dysthymic and cyclothymic, while irritable and hyperthymic have not (Akiskal, 2001).

In DSM-IV-TR the essential features of cyclothymia are considered: the presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms for at least 2 years (Criterion A). The diagnosis is not commonly made in clinical practice, because it is almost always seen when a patient presents with Major Depressive Episodes, warranting the designation of ‘bipolar II’. Another source of confusion originates from the fact that some of the core characteristics of cyclothymia such as impulsivity, affective instability, mood reactivity and extreme emotionality are reported by DSM-IV as part of the criteria included in the dramatic cluster of personality disorders (Perugi and Akiskal, 2002; Perugi et al., 2003). However, in an epidemiological perspective, Angst (1998) reported lifetime prevalence rates ranging between 5 and 8% for brief episodes of hypomania associated with short-lasting depression. The average length of a hypomanic episode in general population seems to be 2 days, in many cyclothymic patients elated episodes are shorter than 1 day and often associated with environmental stimuli or substance misuse. Based on these observations, the 4-day threshold proposed by DSM-IV for the definition of hypomanic episode has been criticized (Akiskal, 2007). The proportion of patients with depressive symptoms who can be classified as cyclothymic grows significantly if the 4-day threshold for the hypomanic episode proposed by the DSM IV is reconsidered. Despite its epidemiological relevance, cyclothymia remains understudied from clinical and therapeutic points of view (Akiskal, 2001, 2007).

The clinical presentation of cyclothymia is particularly rich in terms of psychopathological manifestations (Perugi et al., 2003). Anxiety comorbidity is often the rule in these subjects (Perugi et al., 1999; Perugi and Akiskal, 2002): they report panic attacks, anxiety and varying degrees of phobic avoidance, or agoraphobia. The coexistence of cyclothymia with anxiety, impulse control and substance use disorders is well established (Perugi and Akiskal, 2002; Akiskal, 2007).

To our knowledge no studies have specifically focused on impulsivity, anxiety and bipolar spectrum. Therefore, in the present study we explore the influence of comorbid cyclothymia on the relationship between anxiety disorders and impulsivity. Moreover, we hypothesize that impulsivity, as measured by different tools, might not be directly related to the anxiety disorder rather to missed comorbid cyclothymic diathesis.

2. Method

2.1. Sample

A sample of 47 outpatients, referred to the facilities of the “Unità Operativa di Psichiatria 1 dell’Azienda Ospedaliero-Universitaria Pisana”, was consecutively enrolled in a period of 1 year. The sample included 30 (63.8%) female subjects and 17 (36.2%) males with a mean age of 34.5 years (sd = 10.3, range 19–63). All patients meet DSM-IV-TR criteria for at least one anxiety disorder (panic disorder; obsessive–compulsive disorder; social phobia; generalized anxiety disorder). Patients presenting comorbidity for lifetime schizophrenia or other psychotic disorders, organic psychiatric syndromes and severe physical illness were excluded from the study.

Control group included 45 subjects matched for age, gender, education, job, and marital status; 28 (62.2%) were
males and 17 (38.8%) females, with a mean age of 34.8 years (sd = 10.2, range 19–63).

Each subject included in the study was extensively informed about the study procedures and gave his/her own written informed consent before starting any evaluation. Finally, the study was approved by the local Ethics Committee of the “Azienda Ospedaliero-Università Pisana”.

The initial sample of the anxiety disorder patients was therefore divided into two subgroups depending on the presence (Cyclo+) or the absence (Cyclo−) of comorbid cyclothymia. Cyclo+ group comprised 26 (57.7%) patients (5 meet criteria for DSM-IV-TR cyclothymia and 21 for Akiskal-modified criteria for cyclothymia) (Akiskal et al., 1977) and Cyclo− 21 (42.3%) patients.

2.2. Evaluation procedure

The diagnostic and clinical evaluations were performed by a resident in psychiatry, (ADC) under the supervision of a senior psychiatrist (GP). The resident in psychiatry underwent a specific training for the administration of the rating tools. The diagnostic evaluation was performed using the Mini-Neuropsychiatric Interview (MINI), a structured interview for Axis-I diagnoses according to the DSM-III-R criteria. The diagnosis of cyclothymia was made according to two different sets of criteria: DSM-III-R diagnostic criteria require the presence, for at least two years, of numerous hypomanic episodes (lasting for at least 4 days or more) associated with numerous periods characterized by depressive symptoms not meeting criteria for Major Depressive Episode (MDE). We also adopted a broader approach considering criteria for hypomania based on Akiskal et al. (1977): patients must satisfy at least three of Washington University (Feighner et al., 1972) criteria for mania but at subsyndromal level, for a period not longer than two days, without having psychotic features and without presenting a significant impairment of functioning during the period of mood elevation. Specifically, the following must be absent: difficulty in maintaining an adequate conversation within the time; euphoric mood that becomes hostile; hallucinations or frank delusions about patient’s own capacities or identity; persecutory delusions, auto-referential delusions, erotomanic delusions, and absence of insight leading to a relevant social impairment. The validity of the 2-day threshold for hypomania was confirmed by same studies examining the familial history and longitudinal course of a broad clinical and control group population, as shown at the “International Exchange on Bipolar Disorders” (Akiskal et al., 2000).

The symptomatological evaluation was conducted by: the Bech–Rafaelsen Depression and Mania Scale (BRDMS) (Bech et al., 1979; Bech, 1988) and the Clinical Global Impression Severity and Improvement (CGI) (Guy, 1976).

Patients were asked to fill-out a set of self-report rating instruments. The assessment of the anxious symptomatology was performed using the State–Trait Anxiety Inventory (STAI) (Spielberger, 1983). The Barratt Impulsiveness Scale (BIS) has been employed for the evaluation of the impulsivity (Patton et al., 1995). The Hypomania Check List (HCL-32) (Angst et al., 2005) was utilized for the retrospective evaluation of hypomanic symptoms; the latter was developed as screening instrument for hypomania (Angst et al., 2005): a total score of 14 or more had showed a good sensitivity (0.8) and fair specificity (0.51) in differentiating BD depression from recurrent MDE (Angst et al., 2005). The questionnaire is not specific enough for separating Type-I from Type-II BD (Vierta et al., 2007), but its sensitivity and specificity seem independent from the mood state (Angst et al., 2005).

The temperamental and personality traits evaluation was performed by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Modified (TEMPS-M) (Erfurth et al., 2005) a 35-item self-rating scale developed to detect the affective and anxious temperamental features according to the criteria proposed by Akiskal and Mallya (1987). The questionnaire comprises 5 subscales each one assessing, in a quantitative way, the presence of temperamental elements of depressive, cyclothymic, hyperthymic, irritable or anxious nature. Separation anxiety and interpersonal sensitivity were assessed by the Separation Anxiety Symptoms Inventory (SASI) (Silove et al., 1993), a self-report tool including 15 items, and the Interpersonal Sensitivity Symptoms Inventory (ISSI) (Davidson et al., 1989), a 36-item self-report instrument evaluating the interpersonal rejection-sensitivity, the insight of the subject and the way he/she relates with others.

Neurocognitive evaluation of impulsivity was conducted by a clinical psychologist (MB), blind to the diagnosis of the patient, using Immediate and Delayed Memory Task (IMT/ DMT) derived from the Continuous Performance Test (Dougherty et al., 2000). Subjects were shown five-digit numbers on a computer screen, for 0.5 s, at 0.5-second intervals. For the immediate memory task, subjects were instructed to respond if a set of numbers matched the previous set; three responses are possible: correct detections (matching sets are identified accurately), commission errors (also called false alarms, where the subject responds to a set with 4 of the 5 digits correct), and random errors (subject responds to a set of five completely different numbers). The delayed memory task was similar but for the presence, between sets of numbers to be matched, of three “distracting factors” consisting of “12345” shown for 0.5 s at 0.5-second intervals. High rates of commission errors have been reported in impulsive populations (Dougherty et al., 1999, 2000; Moeller et al., 2001b; Marsh et al., 2002). Commission errors were also increased in manic patients and correlated with mania rating scores (Swann et al., 2001, 2003). In the present study we report only correct detections and commission errors; random errors never exceeded 5% and did not vary across any experimental groups.

2.3. Statistical analysis

Comparative analysis for familial, epidemiologic, clinical features and course of different subgroups was performed using one-way ANOVA for dimensional variables and contingency tables for categorical ones. Due to the number of enrolled subjects and the confirmatory nature of our study, we considered, conservatively, a two-tailed significance level of p < 0.05.

3. Results

3.1. Diagnostic distribution, comorbidities and actual treatment

Among the anxiety disorder patients (n = 45) the most frequent diagnosis was panic disorder with (26, 55.3%) and
without (11, 23.4%) agoraphobia; only 1 subject (1.8%) presented agoraphobia without panic disorder. Concerning the other anxiety disorders, 12 patients (25.5%) met diagnostic criteria for obsessive–compulsive disorder, 9 (19.1%) for generalized anxiety disorder and 7 (14.9%) for social anxiety disorder. Thirty (66.6%) patients met diagnostic criteria for 1 anxiety disorder, 11 (24.4%) for 2 and 4 (8.8%) for 3 anxiety disorders.

Concerning lifetime comorbidities with mood disorders, 9 patients with anxiety disorder (19.1%) reported a spontaneous hypomanic episode and 10 (21.3%) hypomanic episodes induced by pharmacological treatment with antidepressants. Comorbid cyclothymia was diagnosed in 5 (10.6%) patients according to DSM-IV-TR criteria and in 21 (46.6%) patients using the 2-day-hypomania modified criteria based on Akiskal et al. (1977). Control subjects (n = 42) did not meet any diagnostic criteria for any DSM-III-R mental disorder, but in 3 subjects (6.7%) modified criteria for cyclothymia were fulfilled.

3.2. Comparison between patients with anxiety disorders with and without cyclothymia and controls

3.2.1. Demographic features

As reported in Table 1, no significant differences concerning gender and average age distribution were observed by the comparison of the 3 groups, Cyclo+ (26 subjects), Cyclo− (21 subjects) and controls (n = 45).

3.2.2. Symptomatological, temperamental and personality traits evaluation

The 3 groups did not show significant differences in the BRMS mean score (Table 1), while in the BRDS mean score Cyclo+ obtained higher scores compared to Cyclo−, which in turn obtained higher scores than controls (F = 19.490, p < 0.001). The 3 groups reported a similar trend in STAI, both for the state and trait components (STAI-S: F = 15.293 p < 0.001; STAI-T: F = 28.362 p < 0.001), and in HCL-32 (F = 12.379, p < 0.001). For this latter we calculated for each group the percentage of subjects reaching a score ≥14. As expected, the Cyclo+ reported the highest percentage and the controls the lowest, with Cyclo− setting in the intermediate position (chi-square = 13.86; p = 0.001). Cyclo+ and Cyclo− subjects showed similar mean CGI-severity scores (respectively 3.54 ± 0.99 vs. 3.05 ± 0.92). Concerning the evaluation of the affective temperaments explored by the TEMPS, the Cyclo+ subjects reported higher scores than Cyclo− in 4 out of 5 subscales (depressive, cyclothymic, anxious and irritable temperaments). In turn, the anxious Cyclo− subjects showed higher mean scores for the same subscales when compared to controls. For each one of the 4 subscales, the differences between the three groups were statistically significant (depressive: F = 37.794, p < 0.001; cyclothymic: F = 25.833, p < 0.001; anxious: F = 14.932, p < 0.001; irritable: F = 4.934, p = 0.009). On the other side, no significant differences were observed among the 3 groups in the mean score of the hyperthymic temperament subscale (F = 1.196, p = 0.307). Finally, the 3 groups differed both for the SARI and ISSI mean scores. Cyclo+ subjects presented higher SARI mean scores than Cyclo−, which in turn reported higher scores than controls (F = 7.217, p = 0.001). The highest ISSI scores, indicating a lower interpersonal sensitivity, were reported by the controls, followed by Cyclo−, while Cyclo+ subjects reported the lowest scores (F = 7.275, p = 0.001).

3.2.3. Impulsivity evaluation

The Cyclo+ showed a total BIS score higher than Cyclo− (Table 2); nonetheless, Cyclo− scored higher than controls (F = 9.553, p < 0.001). The “attentional” and “motor” subscale scores were also higher in Cyclo+ than Cyclo− and controls (F = 11.153, p < 0.001 and F = 5.928, p = 0.004, respectively).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ cases (n = 26)</th>
<th>Cyclo− cases (n = 21)</th>
<th>Control cases (n = 45)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, average (sd)</td>
<td>35.6 ± 11.7</td>
<td>33.1 ± 8.5</td>
<td>34.8 ± 10.2</td>
<td>0.361</td>
<td>0.698</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>18 (69.2%)</td>
<td>12 (57.1%)</td>
<td>27 (60%)</td>
<td>0.863</td>
<td>0.649</td>
</tr>
<tr>
<td>BRMS</td>
<td>4.3 ± 3.8</td>
<td>2.8 ± 4.1</td>
<td>2.0 ± 4.0</td>
<td>2.841</td>
<td>0.064</td>
</tr>
<tr>
<td>BRDS^a</td>
<td>4.4 ± 4.4</td>
<td>3.0 ± 3.7</td>
<td>2.0 ± 3.9</td>
<td>19.490</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL-32 total^a</td>
<td>17.1 ± 5.5</td>
<td>14.4 ± 6.5</td>
<td>10.6 ± 4.7</td>
<td>12.379</td>
<td>0.000</td>
</tr>
<tr>
<td>HCL-32 14, n (%)</td>
<td>20 (76.9%)</td>
<td>10 (47.6%)</td>
<td>14 (31.1%)</td>
<td>13.86</td>
<td>0.001</td>
</tr>
<tr>
<td>STAI state^a</td>
<td>47.4 ± 12.7</td>
<td>40.3 ± 10.5</td>
<td>33.0 ± 9.4</td>
<td>15.293</td>
<td>0.000</td>
</tr>
<tr>
<td>STAI trait^b</td>
<td>51.2 ± 1.0</td>
<td>44.7 ± 8.1</td>
<td>36.1 ± 7.3</td>
<td>28.362</td>
<td>0.000</td>
</tr>
<tr>
<td>CGI</td>
<td>3.54 ± 0.989</td>
<td>3.05 ± 0.924</td>
<td>1.00 ± 0.0</td>
<td>135.8</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS depressive</td>
<td>22.3 ± 3.8</td>
<td>20.9 ± 6.9</td>
<td>13.1 ± 4.0</td>
<td>37.794</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS cyclothymic</td>
<td>21.6 ± 6.5</td>
<td>19.6 ± 7.0</td>
<td>12.4 ± 4.2</td>
<td>25.833</td>
<td>0.000</td>
</tr>
<tr>
<td>TEMPS hyperthymic</td>
<td>19.9 ± 5.3</td>
<td>21.4 ± 5.3</td>
<td>22.7 ± 9.2</td>
<td>1.196</td>
<td>0.307</td>
</tr>
<tr>
<td>TEMPS irritable</td>
<td>16.4 ± 5.3</td>
<td>13.6 ± 3.6</td>
<td>12.6 ± 5.1</td>
<td>4.934</td>
<td>0.009</td>
</tr>
<tr>
<td>TEMPS anxious^c</td>
<td>18.1 ± 4.0</td>
<td>17.1 ± 6.3</td>
<td>12.0 ± 4.8</td>
<td>14.932</td>
<td>0.000</td>
</tr>
<tr>
<td>SASI total^b</td>
<td>12.8 ± 7.2</td>
<td>11.4 ± 7.5</td>
<td>7.0 ± 5.9</td>
<td>7.217</td>
<td>0.001</td>
</tr>
<tr>
<td>ISSI total</td>
<td>90.8 ± 20.0</td>
<td>92.2 ± 12.1</td>
<td>103.5 ± 13.3</td>
<td>7.275</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BRMS, Bech–Rafaelsen Mania Scale; BRDS, Bech–Rafaelsen Depression Scale; HCL-32, Hypomania Check List; STAI, State–Trait Anxiety Inventory; CGI, Clinical Global Impression; TEMPS, Questionnaire for the Affective and Anxious Temperaments; SASI, Separation Anxiety Symptoms Inventory; ISSI, Interpersonal Sensitivity Symptoms Inventory.

Scheffe F test:
^a Cyclo+ and Cyclo− > controls.
^b Cyclo+ > Cyclo− > controls.
^c Cyclo+ > controls.
On the opposite side, it was not possible to differentiate the 3 groups in the “non-planning” subscale scores (F = 2.010, p = 0.14).

Comparison of IMT/DMT performances between Cyclo+, Cyclo− and controls is also reported in Table 2. In the first task, the IMT, the three groups did not differ in the percentage of right answers (correct detections, F = 0.091 p = 0.913), but they presented a statistically significant difference in the percentage of impulsive answers (commission errors, F = 17.237 p < 0.001). The latter were more represented in Cyclo+ than in Cyclo− and controls. In the second task, the DMT, the 3 groups differed in the number of right answers (correct detections, F = 3.240 p = 0.044), and in the number of impulsive answers (commission errors, F = 12.621 p < 0.001), with the latter being most represented in Cyclo+ followed by controls. On the opposite, the lowest percentage of impulsive answers was observed in Cyclo− subjects.

4. Discussion

Our study presents some methodological limitations that should be taken into account before discussing the results. The evaluations have been performed, under the supervision of a senior psychiatrist, in a setting of routine clinical practice by a resident in psychiatry, who was taking care of patients and was informed about their diagnosis. The employ of standardized instruments should minimize eventual biases due to the lack of blind evaluation.

In our sample of patients with anxiety disorders, cyclothymic ones obtained higher average scores than non-cyclothymic in anxiety and depression scales. Cyclothymic subjects were also characterized by a greater severity of psychopathology, while the scores obtained by non-cyclothymic anxious patients settled between cyclothymic and control subjects.

As expected, cyclothymic subjects reported more frequently hypomanic symptoms than non-cyclothymic patients and controls. As for the temperamental and personality features, the cyclothymic subjects presented highest scores in depressive, cyclothymic, anxious and irritable temperament subscales, as well as in separation anxiety and interpersonal sensitivity scales. On the contrary they did not differ from the other groups in the hyperthymic temperament subscale. This finding is consistent with previous reports, confirming how subjects with anxiety disorders, atypical depression and bipolar II disorder are characterized by a cyclothymic-depressive-anxious temperamental disposition, associated with separation anxiety and interpersonal rejection sensitivity (Perugi and Akiskal, 2002; Perugi et al., 2003; Signoretta et al., 2005).

Consistently with our original hypothesis, cyclothymic patients presented highest levels of trait impulsivity compared to non-cyclothymic and control subjects. The same trend was observed in the BIS “attentive” and “motor” subscales, while the “not planning” subscale did not differentiate the three groups. The neurocognitive evaluation also showed high levels of inattentive and disinhibitional impulsivity in cyclothymic–anxious patients. In fact, the three groups significantly differed in the percentage of impulsive answers, which were most common in cyclothymic patients. The same trend was observed in the DMT; interestingly, in this latter test the percentage of impulsive answers was higher in controls than in non-cyclothymic patients with anxiety disorders. In other words, both the trait and the state impulsivity, measured respectively by psychometric instruments and by neurocognitive paradigms, resulted to be highest in patients with cyclothymia, independently from the presence of the anxiety disorder. In the same line, anxious patients without cyclothymia resulted to be more impulsive than controls in the retrospective measures of trait impulsivity but not in the neurocognitive tests, indicating that state related impulsivity seems to be reduced in this population.

These findings are consistent with previous studies suggesting the existence of a subgroup of patients with anxiety disorders with an atypical pattern of anger and aggression, high novelty-seeking, risk-prone and impulsive behaviors (Summerfeldt et al., 2004; Kashdan and Hofmann, 2008; Kashdan et al., 2009). In our sample the subgroup of

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ cases (n = 26)</th>
<th>Cyclo− cases (n = 21)</th>
<th>Controls (n = 45)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentinal</td>
<td>16.9 ± 4.0</td>
<td>15.5 ± 4.0</td>
<td>13.2 ± 2.5</td>
<td>11.153</td>
<td>0.000</td>
</tr>
<tr>
<td>Motor</td>
<td>22.2 ± 4.1</td>
<td>20.4 ± 3.2</td>
<td>19.1 ± 3.7</td>
<td>5.928</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-planning</td>
<td>26.7 ± 3.8</td>
<td>26.8 ± 3.5</td>
<td>25.1 ± 4.0</td>
<td>2.010</td>
<td>0.140</td>
</tr>
<tr>
<td>Total</td>
<td>65.8 ± 9.1</td>
<td>62.7 ± 8.0</td>
<td>57.3 ± 7.6</td>
<td>9.553</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>IMT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections</td>
<td>80.7 ± 11.3</td>
<td>81.7 ± 10.6</td>
<td>80.3 ± 13.0</td>
<td>0.091</td>
<td>0.913</td>
</tr>
<tr>
<td>Commission errors</td>
<td>36.6 ± 14.4</td>
<td>23.6 ± 9.9</td>
<td>19.1 ± 11.7</td>
<td>17.237</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>DMT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct detections</td>
<td>84.7 ± 10.4</td>
<td>81.6 ± 20.4</td>
<td>89.6 ± 8.1</td>
<td>3.240</td>
<td>0.044</td>
</tr>
<tr>
<td>Commission errors</td>
<td>39.3 ± 16.1</td>
<td>19.5 ± 10.2</td>
<td>23.5 ± 16.1</td>
<td>12.621</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Schaeffer F test:
- Cyclo+ and Cyclo− > controls.
- Cyclo+ > controls.
- Cyclo+ > controls, Cyclo−.
- Cyclo+ < Cyclo−.
patients with anxiety and cyclothymia appears to be characterized by affective instability, separation anxiety and interpersonal sensitivity and high level of trait and state impulsivity.

Recently, in a sample of adolescents hospitalized for behavioral changes and impulsivity related problems (suicidal attempts, self-injuring, substance intoxication, eating disorders, anger, delinquency), Askenazy et al. (2003) observed that 62% of the subjects are characterized by high levels of anxiety and impulsivity and reported a positive personal history of hypomania and 48% reported at least a MDE, suggesting a potential attribution of the above population to the bipolar spectrum (Akiskal and Mallya, 1987; Akiskal and Pinto, 1999). Like in our sample, even in this population the presence of high levels of anxiety did not seem to constitute per se a protective factor for the impulsive behavior. This observation is consistent with a study by Taylor et al. (2008) who investigated the relationships between anxiety and impulsivity in a cohort of 114 subjects with Bipolar Disorder (62% with BP-I diagnosis, 25.5% BP-II and the remaining others being BP-NOS). The presence of a concomitant anxiety disorder (panic disorder, social anxiety, generalized anxiety, post-traumatic stress disorder, obsessive-compulsive disorder) was associated with the presence of high levels of impulsivity and this effect did not result mediated by the concomitant presence of ADHD.

In conclusion, in our sample of patients with anxiety disorder the presence of broadly defined cyclothymia appears to be associated not only with affective instability but also with separation anxiety, interpersonal sensitivity and, finally, impulsivity. This latter seems not directly related to the presence of the anxiety disorder, but to the comorbidity with cyclothymia. Our results should be considered preliminary and should be replicated in larger samples. Future research is necessary to compare different anxiety disorders and to evaluate the stability of the results obtained with neurocognitive tasks in longitudinal studies.

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Conflict of interest
All the authors assure that there are no current or past commercial or financial involvements that might present an appearance of a conflict of interest in connection with this article.

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Impulsivity in patients with panic disorder-agoraphobia: The role of cyclothymia

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Abstract

The relationship between Panic Disorder (PD) and impulsivity is not well explored. The present investigation aims to compare impulsivity, measured by different rating tools, in PD patients vs. healthy controls and to explore the influence of co-morbid Cyclothymic Disorder (CD) on the relationship between PD and impulsivity. Sixty-four subjects with PD and 44 matched controls underwent a diagnostic and symptomatological evaluations by the Mini Neuropsychiatric Interview (M.I.N.I) Plus 5.0; the Bech-Rafaelsen Depression and Mania Scale (BRDMS), the State-Trait Anxiety Inventory (STAI), the Hypomania Check List (HCL-32) and the Clinical Global Impression (CGI); the Questionnaire for the Affective and Anxious Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified (TEMPS-M), the Separation Anxiety Sensitivity Index (SASI), the Interpersonal Sensitivity Symptoms Inventory (ISSI). Finally, psychometric and neurocognitive evaluations of impulsivity was carried out using the Barratt Impulsiveness Scale (BIS-11) and the Immediate and Delayed Memory Task (IMT/DMT). Subjects with PD were more impulsive than the controls in all the explored measures, reporting higher scores in symptomatological and temperamental scales. The comparison between PD patients with (Cyclo+) and without (Cyclo−) comorbid CD and controls showed that Cyclo+ are the most impulsive subjects in all the investigated measures and are characterized by the greatest symptomatological impairment, the highest scores in temperamental scales, and the highest levels of interpersonal sensitivity and separation anxiety. In our patients with PD, without lifetime comorbidity with major mood episodes, trait and state impulsivity may be related to the presence of comorbid cyclothymic mood instability.

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1. Introduction

Impulsivity is a feature of the normal and pathological behavior, which characterizes the passage from the intent to the action and an important determinant of personality differences, psychiatric disorders, and associated risk-taking behaviours [1,2]. The relationship between Panic Disorder (PD) and impulsivity has not been adequately studied. Few data are available regarding behaviors strongly associated with impulsivity such as non premeditated suicidality and aggression [3–5], leading to discrepant findings [6–13]. For example, several studies [6,8] have reported a higher incidence of suicidal ideation and suicide attempts in subjects with panic attacks. In other reports [10] a lifetime history of PD was not related with an increased risk of suicide attempts and, similarly, people with PD that have a higher risk of suicide attempts would be only those characterized by the presence of any comorbidities. In particular, high rates of suicidal ideation and behaviour were detectable in patients with panic attacks when associated with depression, substance abuse or Borderline Personality Disorder (BPD) [11]. A recent study [12] showed that 31.7% of outpatients with PD had experienced suicidal ideation in the previous 2 weeks, associated with young age, early onset of symptoms, alcohol consumption, symptom severity, reduced social support and sensitivity to drugs. Similarly, although aggressive behaviours have been reported in people with panic attacks [7,13], the relationship between aggression and PD is unclear. However, in PD patients the
comorbidity with depression seems to increase the prevalence of property destruction and aggression, as well as homicidal ideation, other than suicidal ideation [7].

Increased trait and state impulsivity in Bipolar Disorder (BD) has been widely documented and reviewed [14–17]. Impulsivity is also considered a core characteristic of Bipolar Spectrum Disorders (BSDs) [18,19] and, as a trait, it has been classically included among hyperthymic and cyclothymic temperamental features [19,20]. The co-occurrence of BD and Cyclothymic Disorder (CD) with anxiety, impulsivity, impulse control and substance use disorders is also well established [18,19,21–24].

Interestingly, two recent studies conducted by independent research groups [21,25] showed that BD patients with one or more comorbid anxiety disorder present higher levels of “trait” impulsivity, as measured by the BIS, in comparison to BD patients without such comorbidity. We recently evaluated impulsivity, by two different rating tools, in patients with primary anxiety disorders and control subjects [26,27]. In contrast with the idea that harm avoidance and behavioural inhibition are invariably associated with anxiety disorders, anxious patients resulted more impulsive than control subjects, in both psychometric and neuropsychological measures [26]. In particular impulsivity was highest in patients with comorbid CD [27].

Among the broad range of anxiety-related symptoms and disorders, patients with BD and CD can frequently report panic attacks and varying degrees of phobic avoidance, up to extended agoraphobia [28,29]. Panic attacks can be triggered by separation events or under the influence of certain substances such as stimulants or cannabis. In some cases panic attacks start during periods of hyperactivity or excitement and sometimes mark the switch from an elated to a depressive phase [30]. Although the relationship between PD and CD could be merely viewed as an association between two separate disorders, some data suggest that panic attacks and rapid mood switching could be described as a whole, in a particular subtype of familial bipolarity. MacKinnon et al. [31–33] have carried out a series of clinical and family studies on bipolar subjects with rapid mood switches, whose characteristics in many ways resulted similar to those of cyclothymic patients. The presence of rapid mood fluctuations is associated with a high familial load for Mood and Anxiety Disorders (MDs, ADs), early onset, comorbidity with PD and substance use disorders, higher rate of violent behavior, suicidal behavior and non-suicidal self-harm. These findings are consistent with the results of the studies on the characteristics of BD in children and adolescents, pointing out high familial loading, comorbidity with multiple ADs and rapid circadian switches [34]. Comorbidity with PD and rapid switches seems to define a particular familial subtype of BD characterized by early onset and cyclothymic instability and perhaps impulsivity [33,34].

To our knowledge no studies have specifically focused on impulsivity and PD. We therefore concentrated on this topic wishing moreover to better delineate the nature of the clinical interface between PD, CD and impulsivity. In the first part of the study our aim is to evaluate and compare impulsivity using different assessment tools (rating-scale and neurocognitive test) in patients with PD and control subjects. In a second step we explore the influence of co-morbid CD on the relationship between PD and impulsivity. We hypothesize that impulsivity, as measured by different tools, might not be directly related to the presence of the PD in itself, but to the frequent co-occurrence of cyclothymic mood instability.

2. Materials and methods

2.1. Subjects

A sample of 64 outpatients, referred to the facilities of the “Unità Operativa di Psichiatria I dell’Azienda Ospedaliero-Universitaria Pisana”, was consecutively enrolled in a period of one year. The sample included 38 (60.3%) females and 26 (39.7%) males with a mean age of 36.6 years (sd = 12.3, range 19–63). All patients met DSM-IV criteria for PD with or without Agoraphobia. Patients presenting lifetime comorbidity for major mood episodes, schizophrenia or other psychotic disorders, organic psychiatric syndromes and severe somatic disorders were excluded from the study.

The control group included 44 healthy subjects matched for gender, age, education, job and marital status; 26 (59.1%) were females and 18 (40.9%) males, with a mean age of 34.8 years (sd = 10.3, range 19–63). Each subject included in the study was extensively informed about the study procedures and gave his/her own written informed consent before starting any evaluation. The study protocol was approved from the local Ethic Committee of the “Azienda Ospedaliero-Universitaria Pisana”.

2.2. Measures and procedures

This research is part of an ongoing research program specifically focused on impulsivity in primary ADs. The evaluation procedure used has been described in our previous reports [26,27] evaluating impulsivity in a sample of subject belonging to different diagnostic subtypes of anxiety disorders. The present report is focused on a sample of patients with Panic Disorder/agoraphobia as a specific diagnostic subtype.

The diagnostic evaluation was performed using the Mini-Neuropsychiatric Interview (MINI) a structured interview for Axis-I diagnoses according to the DSM-III-R criteria. The diagnosis of CD was made according to two different sets of criteria: DSM-III-R diagnostic criteria require the presence, for at least two years, of numerous hypomanic episodes (lasting for at least 4 days or more) associated with numerous periods characterized by depressive symptoms not meeting criteria for Major Depressive Episode (MDE). We also adopted a broader approach considering criteria for hypomania based on Akiskal et al. [35]; patients must satisfy at least three of Washington University [36] criteria for mania but at sub-syndromal level, for a period not longer
than two days, without having psychotic features and without presenting a significant impairment of functioning during the period of mood elevation. The initial sample of the PD patients was therefore divided into two subgroups depending on the presence (Cyclo+) or not (Cyclo−) of comorbid CD.

The symptomatic evaluation was conducted by: the Bech-Rafaelsen Depression and Mania Scale (BRMS) [37,38] and the Clinical Global Impression Severity and Improvement (CGI) [39]. Patients were asked to fill-out a set of self-report rating instruments. The assessment of the anxiomatic symptomatology was performed using the State Trait Anxiety Inventory (STAI) [40]. The Barratt Impulsiveness Scale (BIS) has been employed for the evaluation of impulsivity [41]. The Hypomania Check List (HCL-32) [42] was utilized for the retrospective evaluation of hypomanic symptoms.

The temperamental traits evaluation was performed by the Brief 35-items Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified (Brief-TEMPS-35) self-rating scale.

Neurocognitive evaluation of impulsivity was conducted by a clinical psychologist (MB), blind to the diagnosis of the patient, using the Immediate And Delayed Memory Task (IMT/DMT) derived from the Continuous Performance Test [44].

2.3. Data analysis

Comparative analysis for familial, epidemiologic, clinical features of patients with PD and controls was performed using the Student’s t-test for dimensional variables (Mann–Whitney U-test, when appropriate) and the chi-square test for categorical variables (Fisher exact-test, when appropriate). Comparative analysis for familial, epidemiologic, clinical features and course of Cyclo+, Cyclo− and controls was performed using one-way ANOVA for dimensional variables and contingency tables for categorical ones. Due to the number of subjects and the confirmatory nature of our study, we considered, in a conservative way, two-tailed significance levels with threshold at p < 0.05.

3. Results

3.1. Demographic features, diagnostic distribution and co-morbidities

Table 1 summarizes demographic features of the 3 groups Cyclo+ (20 subjects), Cyclo− [44] and controls (n = 44). There were no significant differences for gender distribution, mean age, education, work and marital status. The investigator team specifically focused on the selection of the control group matched for age, education and social level, since all of these variables could influence measures of impulsivity [45].

Among the initial sample of PD patients (all-PD patients, n = 64) the most frequent diagnosis was PD with (41, 64.1%) and without (22, 34.4%) Agoraphobia; only 1 subject (1.5%) presented Agoraphobia without PD. Concerning the comorbidity with other anxiety disorders, 8 patients (12.5%) also met diagnostic criteria for Obsessive-compulsive Disorder, 18 (28.1%) for Generalized Anxiety Disorder and 8 (12.5%) for Social Anxiety Disorder. Twenty-four (37.5%) patients met diagnostic criteria for another anxiety disorder, 5 (7.8%) for 2.

Among the initial sample of PD patients (all-PD patients, n = 64) lifetime comorbidity with CD (Cyclo+) was reported by 20 (31.2%) subjects: 16 (25.0%) met only Akiskal et al [20,35] modified criteria and 4 (6.2%) met also DSM-IV diagnostic criteria. Control subjects (n = 44) did not meet any diagnostic criteria for any DSM-IV mental disorder.

3.2. Clinical features

As expected (Table 2), all-PD patients differed from controls showing higher scores on STAI, both state (STAI-S) and trait components (STAI-T) (both with p < .001). In the
same questionnaire Cyclo+ and Cyclo− subjects obtained higher scores compared to healthy controls (both with p < .001) while no significant differences were found between Cyclo+ and Cyclo− subjects. A similar trend was observed in BRDS scores. Although no significant differences between all-PD patients and healthy controls were observed in BRMS scores, Cyclo+ subjects differed significantly when compared to controls (p < .001). Cyclo+ subjects also scored higher than Cyclo− (p = 0.05). All-PD patients exhibited significantly greater HCL-32 scores (p < .001) compared to healthy controls. Both Cyclo+ and Cyclo− subjects obtained higher scores compared to healthy controls (respectively p < .001 and p = .006) while no significant differences were found between Cyclo+ and Cyclo− subjects. For this latter scale, we calculated, for each group, the percentage of subjects reaching a score >14. This cut-off has been shown to be the one having the best specificity and sensitivity for the retrospective screening of hypomania in patients with depression across various phases of the illness [42,46,47].

A higher percentage of all-PD patients obtained a score >14 compared to healthy controls (56.3%, vs. 4, 9.1%; chi-square = 24.867; p < .001). As expected, the highest percentage of subjects who reached a score >14 was found in Cyclo+ subjects and the lowest in healthy controls, with Cyclo− setting in the intermediate position. All-PD patients reported a CGI-S score of 3.4 (sd = 1.0), indicating a global severity of the disorder between mild and moderate. There were not significant differences in CGI scores between Cyclo+ and Cyclo− subjects.

Concerning the evaluation of the temperamental characteristics, all-PD patients recorded significantly higher in 4 out of 5 subscales of the TEMPS-M: depressive, cyclothymic, anxious and irritable temperaments. No significant differences between the two subgroups (Cyclo+ and Cyclo−) were observed in hyperthymic temperament subscale; in this latter the average scores were slightly higher in controls than in all-PD patients, but the difference was not statistically significant. As expected, Cyclo+ subjects exhibited significantly higher scores in cyclothymic temperament subscale compared to Cyclo− (p = 0.01). SASI scores appeared significantly higher in all-PD patients (p = 0.006), as well as in Cyclo+ (p = 0.024) and Cyclo− (p = 0.006) subjects compared to healthy controls. Regarding the ISSI, in which low scores indicate an increased sensitivity to rejection in interpersonal context, the mean scores were significantly lower in all-PD patients than in healthy controls (p < .001).

Cyclo− subjects exhibited the lowest scores with a significant difference compared to healthy controls (p < .001) indicating an elevated interpersonal sensitivity.

### 3.3. Measures of impulsivity

Significant differences between all-PD patients and healthy controls were observed in BIS total score (p < .001, Table 3). Both Cyclo+ and Cyclo− subjects obtained higher scores compared to healthy controls (respectively p < .001 and p = .002). Nonetheless Cyclo+ subjects obtained the highest scores with a significant difference also in comparison with Cyclo− (p = .044).

As concern BIS subscales, all-PD patients exhibited significantly higher scores than healthy controls (respectively “attentional” subscale p < .001, “motor” p = .001, “non-planning” p = .027). All the average scores were also higher in Cyclo+ subjects compared to Cyclo− but the difference reached statistical significance only for “motor subscale” (p = .010).

In Table 3 were also reported the performances in the IMT/DMT. In the first task, the IMT, no significant differences were found in the percentage of correct answers
between all-PD patients and healthy controls. Similarly, no subgroups differences were found between Cyclo+ and Cyclo− and controls subjects. As concern impulsive responses, all-PD patients reported significantly more commission errors (p < .001) when compared to healthy controls. Similarly, both Cyclo+ (p < .001) and Cyclo− patients (p = .030) exhibited significant differences from healthy subjects in impulsive responses. Finally, the highest percentage of commission errors was exhibited by Cyclo+ subjects, with a significant difference in comparison with healthy controls (p = .005). However, in this task Cyclo+− subjects reported a greater number of impulsive responses compared to controls (p = .022). In DMT, all-PD patients also reported a greater number of impulsive responses compared to healthy controls (p = .005). However, in this task Cyclo+ subjects reported the greatest number of commission errors with a significant difference in comparison to both healthy controls and Cyclo− subjects (both p < .001). The lowest percentage of impulsive answers was observed in control subjects followed by Cyclo− with no significant differences between these two subgroups. Finally, as far as the DMT discriminability is concerned, there were significant differences in the same trend observed with the IMT; the value of the parameter remained significantly higher in controls than in anxious patients (p = .000) with the lowest discriminability exhibited by Cyclo+ subjects.

### 4. Discussion

The present study presents some methodological limitations that should be taken into account before discussing the results. The evaluations have been performed, under the supervision of a senior psychiatrist, in a setting of routine clinical practice by a resident in psychiatry, who was taking care of patients and was informed about their diagnosis. Nevertheless, the employ of standardized instruments should minimize eventual biases due to the lack of blind evaluation.

Our sample of PD patients was characterized by a mild/moderate severity, as measured by the CGI and showed a high rate of lifetime comorbidity with CD (31.2%). One quarter of the sample met Akiskal et al. [35] modified criteria and 4 patients (6.2%) met also DSM-IV diagnostic criteria for CD. These findings are consistent with previous report that found a high prevalence of BSDs amongst patients referred to a health care provider with a principal diagnosis of PD (i.e., BPDI, 2.1%; BPDII, 5%; CD, 6.4%) [29].

As expected, our PD patients showed state and trait anxiety scores higher than controls [48]; also manic, but not depressive, symptomatology was more represented in PD patients than in controls. Interestingly, the retrospective evaluation by the HCL-32 indicated that our patients reported more past hypomanic symptoms than controls and more than half (56.3%) of them reached a score of 14 or more, which indicated a high probability of previous hypomania [42,46,47]. This findings confirm the high prevalence of current and past bipolar spectrum features in patients with PD [29].

Concerning temperamental traits, PD patients showed significantly higher scores than healthy controls in Table 3

<table>
<thead>
<tr>
<th></th>
<th>Cyclo+ (n = 20)</th>
<th>Cyclo− (n = 44)</th>
<th>All-PD patients (n = 64)</th>
<th>Controls (n = 44)</th>
<th>All-PD patients Vs Controls</th>
<th>Cyclo+ Vs Controls</th>
<th>Cyclo− Vs Controls</th>
<th>Cyclo+ Vs Cyclo−</th>
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<tbody>
<tr>
<td><strong>Barratt Impulsiveness Scale (BIS)</strong></td>
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<td></td>
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<tr>
<td>Attentional</td>
<td>17.8 ± 3.5</td>
<td>16.34 ± 3.49</td>
<td>16.8 ± 3.5</td>
<td>13.1 ± 2.5</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>ns</td>
</tr>
<tr>
<td>Motor</td>
<td>23.7 ± 3.3</td>
<td>20.63 ± 3.89</td>
<td>21.6 ± 4</td>
<td>18.9 ± 3.6</td>
<td>0.001</td>
<td>0.000</td>
<td>ns</td>
<td>0.010</td>
</tr>
<tr>
<td>Non Planning</td>
<td>27.6 ± 3.8</td>
<td>27.0 ± 5.8</td>
<td>27.2 ± 5.2</td>
<td>25.0 ± 4.1</td>
<td>0.027</td>
<td>ns</td>
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<td>ns</td>
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<tr>
<td>Total</td>
<td>69.0 ± 7.1</td>
<td>63.5 ± 8.9</td>
<td>65.2 ± 8.7</td>
<td>57.1 ± 7.5</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>0.044</td>
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<tr>
<td><strong>Immediate Memory Task (IMT)</strong></td>
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<tr>
<td>Correct detections (CD)</td>
<td>78.2 ± 16.9</td>
<td>79.9 ± 11.8</td>
<td>79.4 ± 13.5</td>
<td>79.9 ± 12.9</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Commission errors (CE)</td>
<td>44.2 ± 9.8</td>
<td>24.7 ± 11.7</td>
<td>30.8 ± 14.3</td>
<td>18.4 ± 10.8</td>
<td>0.000</td>
<td>0.000</td>
<td>0.030</td>
<td>0.000</td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.05 ± 0.56</td>
<td>1.66 ± 0.71</td>
<td>1.47 ± 0.72</td>
<td>1.88 ± 0.62</td>
<td>0.002</td>
<td>0.000</td>
<td>0.036</td>
<td>0.003</td>
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<tr>
<td><strong>Delayed Memory Task (DMT)</strong></td>
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<td></td>
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<tr>
<td>Correct detections (CD)</td>
<td>84.5 ± 14.6</td>
<td>81.2 ± 17.4</td>
<td>82.2 ± 16.5</td>
<td>89.5 ± 8.2</td>
<td>0.003</td>
<td>ns</td>
<td>0.022</td>
<td>ns</td>
</tr>
<tr>
<td>Commission errors (CE)</td>
<td>49.8 ± 16.5</td>
<td>24.5 ± 10.9</td>
<td>32.4 ± 17.4</td>
<td>23.0 ± 16.0</td>
<td>0.005</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Discriminability</td>
<td>1.21 ± 0.67</td>
<td>1.77 ± 0.79</td>
<td>1.6 ± 0.8</td>
<td>2.2 ± 0.904</td>
<td>0.000</td>
<td>0.000</td>
<td>0.036</td>
<td>0.041</td>
</tr>
</tbody>
</table>
depressive, cyclothymic, anxious and irritable TEMPS-M subscales, as well as higher levels of separation anxiety and interpersonal sensitivity. As expected, cyclothymic subjects presented the highest scores in cyclothymic temperament. Previous studies observed that separation anxiety [49] and interpersonal rejection sensitivity are strongly related to cyclothymic mood reactivity [19,50,51]. In a study of patients who met DSM-IV criteria for Major Depressive Disorder (MDD) with atypical features, Akiskal et al. [52] reported that the ones with a comorbidity with panic attacks exhibited a markedly significant cyclothymic temperamental disposition, as well as a higher number of past hystopanic episodes and stressors. Others authors [53] suggested that the lifetime comorbidity of recurrent panic attacks and BD may represent a subtype, characterized by rapid mood switching (resembling cyclothymic mood instability) with specific clinical [29,54], psycho-physiologic [55,56], and familial-genetic backgrounds [57,58].

To the best of our knowledge this is the first study using different paradigms largely applied to patients with MDs, Conduct Disorders (CDs) and Substance Use Disorders (SUDs) to evaluate impulsivity in patients with PD. Interestingly, PD patients presented higher levels of trait impulsivity, measured by the BIS total and subscales scores, compared to healthy controls. Trait impulsivity was particularly elevated in cyclothymic subjects. These data are in line with a previous report by Summerfeldt et al. [59] in which, along with other questionnaires, it has been employed the BIS to a case series of subjects affected by anxiety disorders (40 with obsessive-compulsive disorder, 37 with panic disorder and 24 with social anxiety disorder). Interestingly, anxiety disorder patients reported higher scores (both for “total”, “attentional” and “not planning” subscales of BIS) than healthy controls. In our study, PD patients also exhibited more dis-inhibitional/dis-attentional impulsivity (“state impulsivity”) compared to healthy controls as measured by the high percentage of commission errors both in the IMT and in the DMT; moreover the levels of inattentive and dis-inhibited impulsivity were higher in cyclothymic subjects than in non cyclothymic ones. These results, taken as a whole, are in line with previous reports by our group [26,27] in patients with ADs belonging to different diagnostic subtypes. AD patients resulted more impulsive than control subjects, in both psychometric and neurocognitive measures [60,61] and impulsivity was highest in patients with both AD and CD [27].

The finding that, at least in some patients, PD might be associated not only with BSDs such as CD, but also with trait and state impulsivity, has relevant clinical implications. Taken as a whole, the findings tend to suggest a departure from the syndrome-oriented approach of DSM-IV and a validation of the Soft Bipolar Spectrum [62] with its complex features that include mood lability [19,63,64], rapid switching [31,32,52], panic attacks and impulsivity (the present study) as well as impulse control, addictive and binge-eating disorders [23,65,66]. Our results should be considered preliminary and should be replicated in larger samples. Future research is necessary to compare different anxiety disorders and to evaluate the stability of the results obtained with neurocognitive tasks in longitudinal studies.

Contributors

Drs. Perugi and Drs. Dell’Osso designed the study and wrote the protocol. Drs. Toni and Drs. Benvenuti managed the literature searches and analyses. Drs. Perugi undertook the statistical analysis, and author Drs. Del Carlo wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Drs Perugi has acted as consultant of Sanofi Aventis, Bristol Myers Squibb, Astra Zeneca, Eli Lilly, Boehringer Ingheim; received grant/research support from Eli Lilly, Astra Zeneca, Boehringer Ingheim, Glaxo-SmithKline; is on the speaker/advisory board of Sanofi Aventis, Bristol Myers Squibb, Astra Zeneca, Eli Lilly, Boehringer Ingheim, Glaxo-SmithKline, Pfizer, Wyeth, Jannsen-Cilag, Lundbeck. Drs Del Carlo, Drs Benvenuti, Drs Toni, Drs Dell’Osso have no conflicts of interest.

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