Special Articles

Mechanisms of impulsivity in bipolar disorder and related illness

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SUMMARY. **Aims** – Impulsivity is a multifaceted aspect of behavior that is prominent in psychiatric disorders and has serious behavioral consequences. This paper reviews studies integrating behavioral and physiological mechanisms in impulsivity and their role in severity and course of bipolar and related disorders. **Methods** – This is a review of work that used questionnaire, human behavioral laboratory, and neurophysiological measurements of impulsivity or related aspects of behavior. Subjects included individuals with bipolar disorder, substance-use disorders, antisocial personality disorder, and healthy controls. **Results** – Models of impulsivity include rapid-response impulsivity, with inability to reflect or to evaluate a stimulus adequately before responding, and reward-based impulsivity, with inability to delay response for a reward. In normal subjects, rapid-response impulsivity is increased by yohimbine, which increases norepinephrine release. Impulsivity is increased in bipolar disorder, whether measured by questionnaire, by measures of rapid-response impulsivity, or by measures of ability to delay reward. While affective state has differential effects on impulsivity, impulsivity is increased in bipolar disorder regardless of affective state or treatment. Impulsivity, especially rapid-response, is more severe with a highly recurrent course of illness or with comorbid substance-use disorder, and with history of medically severe suicide attempt. In antisocial personality disorder, rapid-response impulsivity is increased, but reward-based impulsivity is not. In general, impulsivity is increased more in bipolar disorder than in antisocial personality disorder. In combined bipolar disorder and antisocial personality disorder, increased impulsivity is associated with substance-use disorders and suicide attempts. **Conclusions** – Impulsivity is associated with severe behavioral complications of bipolar disorder, antisocial personality disorder, and substance-use disorders.

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INTRODUCTION: IMPULSIVITY AND THE STRUCTURE OF BIPOLAR DISORDER

Bipolar disorder is diagnosed by identifying nonspecific depressive and manic syndromes. We could understand this illness better by identifying more specific and measurable behavioral and physiological mechanisms that underlie susceptibility to these mood states. Bipolar disorder entails a prominent disturbance in the initiation of action. Dysregulation of the initiation of action can predispose to behavioral disturbances, including impulsivity. We will focus on roles of impulsivity in bipolar disorder. Impulsivity provides a conceptual basis for physiological mechanisms implicated in an array of psychiatric disorders. The commonly accepted definition of impulsivity, responding to stimuli without opportunity for reflection or apparent regard for their consequences, suggests the involvement of physiological processes associated with initiation of action, as well as pre-attentional and attentional functioning. Problematic in its own right, impulsivity can be a complicating factor in almost every psychiatric disorder. Disorders for which impulsiv-

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ity is particularly salient include bipolar, cluster B personality, and substance use disorders. Impulsivity may result from common mechanisms across disorders, or could be related to specific mechanisms within disorders.

Figure 1 illustrates our multivariate formulation of impulsivity.

a) Behavioral, cognitive, and physiological aspects of early responses to stimuli include measures of stable action-oriented personality characteristics, response-inhibition including screening of stimuli and ability to delay reward, and neurophysiological mechanisms related to early responses to stimuli.
b) Clinical severity, duration and course of illness may interact with specific aspects of impulsivity. Possibilities include kindling or behavioral sensitization.
c) Context-dependent expression of impulsivity may be a function of acute activation and noradrenergic function. The sensitivity to context could be altered by severity of illness, possibly through sensitization to effects of catecholamines (Post, 2007), and could differ across subtypes of impulsivity.
4) Interactions of impulsivity with other aspects of psychopathology and individual adaptations contribute to the full clinical presentation. Clarifying the roles of these mechanisms in the onset and maintenance of problematic behavior and psychopathology is a necessary step for identifying treatment and genetic targets.

WHAT IS IMPULSIVITY?

Action-oriented traits and clinical correlates of impulsivity

Impulsivity can be defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences" (Moeller *et al*., 2001a), resulting from impaired information processing outside of conscious deliberation (Barratt, 1997). Impulsive behavior can be destructive, including impulsive aggression {Virkkunen & Linnoila, 1993), impulsive suicide attempts (Mann *et al*. 1999), and other rapid, unplanned actions with severe long-term consequences. Impulsivity involves pre-attentional and early attentional processing of information and is part of the initiation of action, which requires a balance between generation and screening of potential acts (Barratt & Patton, 1983). Impulsive behavior occurs when this balance fails, with excessive spontaneous behavior or stimulation (for example, mania (Swann *et al*., 1987; 2001) or deficient screening of potential behavior (as in frontal lobe trauma {Bechara *et al*., 1997), increasing the probability of action without conscious reflection. In addition to bipolar disorder, impulsivity is prominent in addictive disorders (Bickel *et al*., 1999; Sarramon *et al*., 1999; Swann *et al*., 2004), and in behavioral effects of abused drugs (Jentsch & Taylor, 1999; Moeller *et al*., 2002), bipolar disorder (Swann *et al*., 2001; 2004; 2007a), personality disorders (Anderson & Revelle, 1994; Steinberg *et al*., 1997), stress-related disorders (Rinne *et al*., 2000; Southwick *et al*. 1999), "high-risk" psychiatric outpatients (Crean *et al*., 2000), and intermittent explosive disorder (Virkkunen & Linnoila, 1993). Impulsivity confers increased risk for rapid behavioral responses with severe long term consequences, most notably suicide (Cremniter *et al*., 1999; Gut-Fayand *et al*., 2001; Mann *et al*., 1999; Soloff *et al*., 2000; Swann *et al*. 2005b).

Integrated, trait-like impulsivity can be measured by questionnaires. While impulsivity is often regarded in terms of "trait" and "state" characteristics, a more useful categorization may be **context-dependence vs context-independence**. High "trait" impulsivity may only alter behavior in certain contexts. The **Barratt Impulsiveness Scale (BIS-11)** identifies three components of trait impulsivity: attentional impulsivity, or lack of cognitive persistence with inability to tolerate complexity; motor impulsivity, or acting on the spur of the moment; and nonplanning impulsivity, or lack of a sense of the future (or the past) (Patton *et al*.,1995).

Models of impulsivity

Two models of impulsivity, based on failures of response inhibition, derived from studies in animals, provide the basis for laboratory measures of impulsivity: **Rapid-response** impulsivity is based on responding without 'reflection' or adequate screening of the stimulus and its context (Evenden, 1999). This model requires a filtering or screening function, possibly served by the amygdala, prefrontal cortex, and other structures, and can be assessed with continuous performance, go-no go, or stop-signal tasks (Dougherty *et al*., 2000; Halperin *et al*., 1988; Logan, 1994; Winstanley *et al*., 2006). **Reward-delay** or delay discounting impulsivity is based on preference for a small immediate reward over a larger delayed one, an exaggeration of the normal loss in value of a future reward with increased time (Evenden, 2000; Swann *et al*., 2002a). "2-choice" tests or other measures comparing preference for rapid versus delayed rewards are validated measures (Ho *et al*.,1999; Hyten *et al*., 1994).

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Behavioral and cognitive overlaps with impulsivity

Impulsivity and decision-making

Impulsivity can short-circuit conscious decision making, but impaired decision-making could be related to insensitivity to consequences of behavior in a manner related to impulsivity (Bechara *et al*., 1997). The Iowa Gambling Task (IGT) measures ability to learn to make advantageous choices relative to shifting conditions (Bechara *et al*., 1994). IGT performance is impaired in substance use disorders and with lesions of the ventromedial prefrontal cortex (Bechara *et al*., 2001). IGT performance correlates with BIS-11 impulsivity scores in minimally symptomatic subjects with bipolar disorder (Christodoulou *et al*., 2006) but is not increased during mania (Clark *et al*., 2001). Decision making, as measured by the IGT, may therefore be at least partially independent of, and possibly complementary to, impulsivity. An example is a recent report that improved decision-making predicted response to a drug that improved impulsivity in cocaine-dependence (Green *et al*., 2009). Because of its relationship to consequences of behavior, decision making may be more strongly related to reward-based impulsivity.

Impulsivity and venturesomeness

Impulsivity is an action-oriented trait, related to increased stimulus-orientation (Dickman, 1985). Venturesomeness and sensation-seeking may share this characteristic; the combination has been formulated as a "supertrait" (Zuckerman, 1991; Carrillo de la Pena, 1992) in risk for potentially destructive patterns of behavior, including aggression, suicide attempts, substance use disorders, and impulse-control disorders (Carrillo-de-la-Pena, 1992; Zuckerman, 1979; 1991). Impulsivity is related to pre-attentional responses to stimuli, however, while venturesomeness or sensation-seeking are more related to planful action (Barratt *et al*., 1997). This distinction may have clinical and physiological consequences (Magid *et al*., 2007), and may apply to other action-oriented characteristics.

Catecholamines and impulsivity: Interactions with context

Impulsive behavior has been reported with elevated dopamine (DA) (Bergh *et al*., 1997; King *et al*., 1986) or NE function (Comings *et al*., 2000; Gerra *et al*., 1999; Roy *et al*., 1988; 1989). Kindling (Anisman *et al*., 2000) or behavioral sensitization to catecholamines, whether through episodes of illness (Post, 2007), drugs of abuse (Yang *et al*., 2003), or stressors (Bremner *et al*., 1996), may increase sensitivity to acute NE effects.

Dopamine and impulsivity

Dopaminergic stimulation may increase impulsivity (Evenden, 1998; Evenden & Ryan, 1996), related to its role in motivation and the initiation of action. Serotonin (5HT) depletion in rats (Harrison *et al*., 1997; Mobini *et al*., 2000) or genetic deletion of 5HT receptors (Brunner & Hen, 1997) only increase impulsivity if DA is intact, so trait impulsivity may reflect a balance between DA and 5HT.

Norepinephrine and impulsivity

Noradrenergic activation, such as with severe stressors, impairs function in amygdala (Braga *et al*., 2004) and prefrontal cortex (Arnsten, 2000), and contributes to behavioral sensitization (Drouin *et al*., 2002), through stimulation of alpha-1 receptors. Consistent with this, sleep deprivation may increase impairment of response inhibition (Acheson *et al*., 2007). Yohimbine increases rapid-response impulsivity in normal humans, parallel to increased behavioral activation (Swann *et al*., 2005a). These findings are consistent with parallel increases in impulsivity and NE reported in manic states (Swann *et al*., 1987; 2003). Acute changes in NE may therefore underlie context-dependent changes in expression of impulsivity, especially in sensitized individuals.

Neurophysiology of impulsivity: stimulus-orientation and contextual feedback

Increased propensity for impulsive behavior may stem from relationships between NE and sensory or attention processes. Event-related potentials (ERPs) allow non-invasive study of CNS information processing on a millisecond-to-millisecond basis, including individual differences and response to experimental manipulations. After a sensory stimulus, there is a sequence of neurophysiological responses, including P50 or P1, a pre-attentional response at 50 msec, N1, is a late pre-attentional phenomenon (100 msec) reflecting an initial trigger for attention to a stimulus (Naatanen & Picton, 1987; Rinne *et al*., 2006), and P2, at 200 msec, reflecting initial conscious awareness of a stimulus (Naatanen & Picton,

1987). These components may therefore be differentially related to impulsivity, where actions occur without regard to their consequences (Moeller *et al*., 2001a), and sensation-seeking, where consequences are factored into decisions to act (Eysenck & Eyesenck, 1978).

Sensory gating

The P50 event related potential is associated with pre-attentional sensory processing, and is presumed to be related to filtering of irrelevant stimuli. Gating, or its tendency to decrease in amplitude with repeated stimuli, is impaired by different mechanisms in schizophrenia and mania (Adler *et al*., 1990). P50 gating may involve catecholamergic function. In normal subjects, yohimbine, which increases NE release, caused a transient impairment in sensory gating similar to that in manic episodes (Adler *et al*., 1994).

Clinical aspects of sensory gating

Subjects with bipolar disorder had impaired gating of P50, N100, and P200 gating compared with controls; this did not appear to be state-dependent, at least across the relatively limited range of symptom severity in this group, or to be affected by pharmacological treatments (Lijffijt *et al*., 2009d). Subjects with childhood-onset ASPD (but not subjects with adult onset antisocial behavior) had impaired P50 gating (Lijffijt *et al*., 2009c). These data show that gating is impaired in disorders of affect or impulsivity even in the absence of psychosis-proneness.

Sensory gating, impulsivity, and cognitive function

There is little information about relationships between sensory gating and demographic or other subject characteristics. In 50 healthy subjects, we found substantial relationships between sensory gating and education or intelligence (positive correlations), but weak, if any, relationship to age or gender (Lijffijt *et al*., 2009b). P50, N100, and P200 gating are differentially associated with attention and impulsivity in healthy subjects; relationships were stronger with more complex tasks (Lijffijt *et al*., 2009a). N100 gating may protect the efficiency of working memory or interference control. P200 gating is also related to attention, as well as to working memory and interference control; both N100 and P200 had more consistent correlations than P50 with impulsivity (Lijffijt *et al*., 2009d).

Response augmenting, or intensity-dependence, of event-related potentials

Impulsivity may be related to exaggerated stimulus-orientation (Dickman, 1985), potentially due to increased NE availability (Aston-Jones & Cohen, 2005; Coull, 1998). The enhanced evoked auditory response to a series of stimuli of increasing intensity (augmenting) correlates with self-reported impulsivity, disinhibition and sensation seeking (Juckel *et al*., 1995; Norra *et al*., 2003; Potts *et al*., 2006; Siegel, 1997; Zuckerman, 1979) and occurs in "high-risk" subjects who make more suicide attempts than non-augmenters, regardless of diagnosis (Aloe *et al*., 2000). The N1P2 intensity slope is commonly used as a measure of an impulsivity-venturesomeness supertrait (Carrillo de la Pena, 1992; Zuckerman, 1991).

A high N1P2 intensity slope was originally considered to be a marker for low serotonin function (Hegerl & Juckel, 1993). More recent results contradict any simple relationship to serotonin (Juckel *et al*., 2007; Laffont *et al*., 1989; O'Neill *et al*., 2008a). L-DOPA plus carbidopa increased augmenting in normal subjects (Henry *et al*., 1976), but more recent studies reported a negative correlation with dopamine metabolite levels (Bruneau *et al*., 1986). Depletion of L-tryptophan, L-tyrosine, or both had no effect on intensity slopes for N1P2 (O'Neill *et al*., 2008b).

Error-related negativity

In addition to the Iowa Gambling Task, decision-making can be measured physiologically by error-related negativity, which measures the neurophysiological response to error. The error-related negativity (ERN) is a negative deflection peaking between 50 to 250 ms following a commission error that is considered to reflect activity of the anterior cingulate cortex (Ridderinkhof *et al*., 2004a, b). The ERN reflects action monitoring and the ability to change response strategies to fit contextual demands (Ridderinkhof *et al*., 2004a), defined in our studies as the change for a commission error following trials on which a commission error was made (post-error commission errors). Previous studies showed smaller ERN amplitudes in subjects who scored higher on impulsivity and who had an impulsivity-related disorder (Dikman & Allen, 2000; Hall *et al*., 2007; Pailing & Segalowitz, 2004; Potts *et al*., 2006; Ruchsow *et al*., 2005). We have shown that ERN is related to impulsivity even in healthy subjects (Lijffijt *et al*., 2008).

Impulsivity in psychiatric disorders: severity, comorbidities, and course of illness

Impulsivity in bipolar disorder

Interactions between context-dependent and -independent impulsivity may be important in bipolar disorder (Swann *et al*., 2003; 2007b). BIS-11 scores are increased in bipolar disorder, even when patients are euthymic (Peluso *et al*., 2007; Swann *et al*., 2001; 2007a). Impulsivity may also be related differently to mania, depression, and anxiety (Apter *et al*., 1993; Barratt, 1967; Swann *et al*., 2007b). Increased impulsivity is consistent with many clinical characteristics of bipolar disorder (Najt *et al*., 2007), but there is little evidence directly linking impulsivity to specific illness-course characteristics of bipolar disorder.

Impulsivity and affective state

Relationships between impulsivity and moderate psychiatric symptoms: We investigated relationships between BIS-11 scores, symptoms, and clinical state. After correcting for effects of pharmacological treatments, BIS-11 attentional and motor scores correlated with SADS-C mania scores, while BIS-11 attentional and nonplanning scores correlated with SADS-C depression scores. In terms of relationships to specific symptoms, BIS-11 scores were not related to subjective affect but correlated with visible hyperactivity, rapid speech, increased energy, anhedonia, and hopelessness (Swann *et al*., 2008).

Relationships between impulsivity and manic symptoms during depressive episodes: In bipolar I patients experiencing major depressive episodes, there can be a wide range of manic symptoms. Manic symptoms (corrected for symptoms that might overlap with depression), trait impulsivity (BIS-11 total and motor scores), and state-related impulsivity (IMT commission errors) were correlated in bipolar I depressed subjects and were related to unstable course of illness, history of suicidal behavior, and substance-use disorders. ROC analysis revealed that mania scores of 7 or higher (note that 12 is a commonly used cut-off for hypomania) during bipolar depressive episodes were associated with more severe course of illness (Swann *et al*., 2007a).

Impulsivity and course of illness

Course of illness varies widely in bipolar disorder. Early onset and more frequent episodes are associated with susceptibility to mixed states (Swann *et al*., 2007a) and with resistance to lithium treatment (Duffy *et al*., 2002; Swann *et al*., 1997; 2002b). Impulsivity is potentially related to the long-term course of bipolar disorder, whether as a result of unstable illness or as an expression of biological factors predisposing to a severe course (Swann, 2007?). Impulsivity may worsen course of illness by contributing to substance abuse (Swann, 2004) and nonadherence to treatment (Dunayevich *et al*., 2000). Early-onset or highly recurrent bipolar disorder is associated with substance-use disorders, aggression, and suicide attempts (Cate Carter *et al*., 2003; Fergus *et al*., 2003; Grunebaum *et al*. 2006). We measured BIS-11 scores, rapid-response impulsivity, and reward-based impulsivity, in bipolar disorder relative to demographic characteristics, symptoms, and course of illness. Impulsivity was increased and response inhibition was impaired, regardless of clinical state or treatment, especially in subjects with highly recurrent illness or with complications like substance-use disorders or suicide attempts (Swann *et al*. 2009a).

Trait impulsivity and course of illness in bipolar disorder: BIS-11 scores were increased in bipolar disorder (Standardized effect size = 1.45) after correction for symptoms (intercept after regression on SADS-C depression, mania, anxiety, and psychosis) and medicine. Regardless of symptoms, treatment, or clinical state, BIS-11 impulsivity scores were related to severity of recurrence and comorbidities, with higher scores associated with early onset, many previous episodes, substance/alcohol use disorders, and histories of suicidal behavior (Swann *et al*., 2009a).

Response inhibition including rapid-response and reward-delay impulsivity and course of illness in bipolar disorder: Regardless of symptoms, treatment, or clinical state, severity of the course of illness in bipolar disorder is related to performance on tests of response inhibition (Swann *et al*., 2009b). On a test of rapid-response impulsivity, subjects with bipolar disorder had fewer correct detections, more commission errors per correct detection, slower reaction times, and lower discriminability, compared to controls. This was consistent with increased rapid-response impulsivity and with a disturbance in sustained attention. On the Single Key Impulsivity Paradigm (SKIP), which evaluates inability to withhold responding for a larger reward, subjects with bipolar disorder made more responses with shorter maximum delay. These abnormalities persisted after correction for symptoms, medicine, and clinical state. Subjects with histories of early onset, many episodes, substance/alcohol use disorders, or suicidal behavior had more commission errors,

faster reaction times to a commission error, and shorter maximal SKIP delays than other subjects with bipolar disorder, suggesting that both rapid-response and reward-delay impulsivity were associated with a more severe course of illness (Swann *et al*., 2009b).

Severe course of illness and accelerated reaction times in tests of impulsivity

Interestingly, while reaction time to a commission error was slower than controls across all subjects with bipolar disorder, those with recurrent (many episodes) or complicated (substance-use disorders, suicide attempts) course of illness had faster reaction times (Swann *et al*., 2009b), consistent with effects of increased NE release by acute yohimbine in controls (Swann *et al*., 2005a) and with faster reaction time in subjects with medically severe suicide attempts (Swann *et al*., 2005b). The slower reaction times to commission errors may reflect a compensatory mechanism in response inhibition. Faster reaction times with increasing recurrence or complications of illness would be consistent with failure of that mechanism, either because of greater inherent severity of illness or increased catecholamine-sensitivity, possibly related to behavioral sensitization or kindling.

Impulsivity in antisocial personality disorder

Trait impulsivity and response inhibition in antisocial personality disorder.

Subjects with ASPD (without bipolar disorder) had elevated BIS-11 scores (though less than in bipolar disorder; standard effect size (Cohen's d) compared to controls was about 0.75) and a pattern of impaired response inhibition that differed from that in bipolar disorder: subjects with ASPD had normal correct detections and discriminability (both were reduced compared to controls in bipolar disorder), increased commission errors, slightly prolonged reaction times, and positive response bias on IMT; they had normal performance on Two Choice Impulsivity Paradigm (TCIP, a test of ability to choose larger delayed reward over smaller immediate reward), and had slightly shorter response delays on the SKIP. Most of the effects that were similar to those with bipolar disorder were smaller than in bipolar disorder (ie, reaction time prolongation, SKIP performance). IMT commission errors correlated significantly with the number of ASPD symptoms endorsed (Swann *et al*., 2005a).

Interactions between bipolar disorder and antisocial personality disorder (ASPD) in trait impulsivity and response inhibition

Subjects with bipolar disorder, ASPD, and the combination were compared to healthy controls. Subjects with bipolar disorder (with or without ASPD) had higher BIS-11 scores than those with ASPD, regardless of symptoms or clinical state (Effect size about 0.7). Subjects with combined bipolar disorder and ASPD did not have higher BIS scores than those with bipolar disorder alone.

Subjects with both bipolar disorder and ASPD had more previous episodes and suicide attempts than those with bipolar disorder alone, and more suicide attempts and substance-use disorders than those with ASPD alone. Adverse effects of bipolar disorder in ASPD were associated with increased impulsivity, but effects of ASPD in bipolar disorder were not (Swann *et al*., 2010).

Impulsivity in substance-use disorders

Impulsivity can predispose to substance abuse, and can result from it. Impulsivity is related to increased stimulus orientation and disinhibited drive-related behavior, consistent with increased susceptibility to self-administration of cocaine and other strongly reinforcing substances. In turn, abused drugs increase impulsivity by activating catecholaminergic systems related to stimulus-orientation and action. We studied impulsivity in bipolar disorder and in substance-use disorders. Impulsivity predisposed to cocaine abuse and predicted poor retention in treatment (Moeller *et al*., 2001b). In bipolar disorder, co-existing substance-use disorder increased impulsivity and blurred the distinction between its trait- and state- aspects (Swann *et al*., 2004; 2008; 2009b). Substance- or alcohol-use disorder was associated with severe suicide attempts in bipolar disorder, but this effect was accounted for by increased rapid-response impulsivity (Swann, 2005b).

Sixty percent of patients with bipolar disorder have met lifetime criteria for an alcohol- or substance-use disorder (Regier *et al*.,1990). Substance use may worsen course of bipolar disorder, or bipolar disorder may predispose to substance-use disorders, though mechanisms like behavioral sensitization or kindling (Post, 2007).

Demographic characteristics and impulsivity: gender, education and age

Gender is not strongly related to impulsivity in bipolar disorder (Swann *et al*., 2009b). Education and age may

confound the interpretation of impulsivity relative to illness course; for example, either severe bipolar disorder or impulsive behavior could prevent completion of education, while education could provide tools for adapting to impulsivity (Barratt *et al*., 1999; Glahn *et al*., 2006). Psychiatric disorders could interrupt the educational career through behavioral or cognitive disturbances. Intelligence, though certainly not free of bias from socioeconomic characteristics, may be affected less by consequences of illness than education is (Nusslock *et al*., 2008). Intelligence is related to efficiency of cognitive function in a manner that may interact with impulsivity, and it is often advisable to control for intelligence in group comparisons involving impulsivity (Barratt & Patton, 1983).

CONCLUSIONS

Table 1 summarizes evidence about relationships between the impulsivity domains in Figure 1 and bipolar disorder and related conditions. Impulsivity is a strategic aspect of psychiatry, because of its relationship to severe psychiatric disorders and to its potentially severe behavioral consequences.

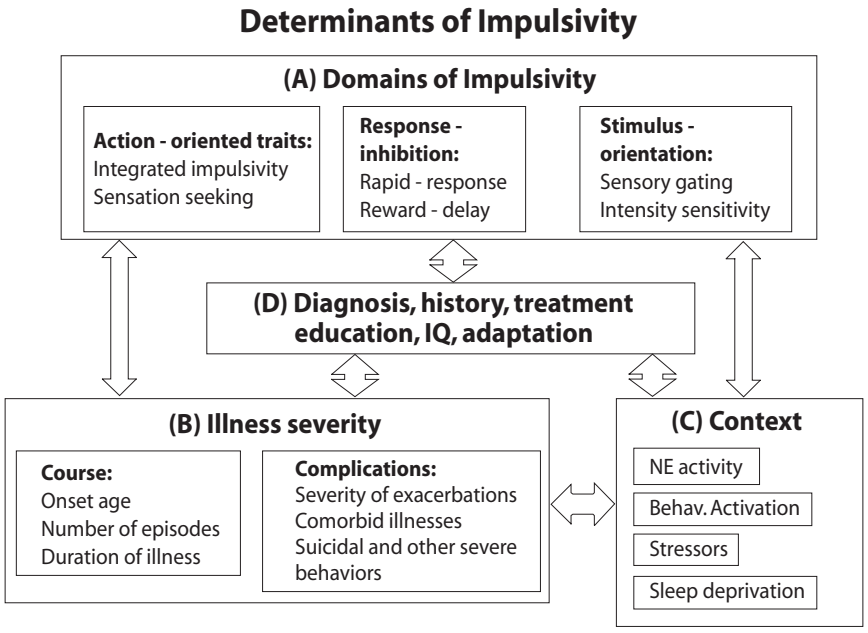

Figure 1 - Determinants of Impulsivity. The Figure shows the manner in wich physiological substrates (domains) of impulsivity interact with psychiatric illness, the immediate context, and individual characteristics to determine the risk for impulsive behavior.

The data presented here show that:

A. Impulsivity is an important dimension of behavior, with cognitive, behavioral, and neurophysiological aspects and severe consequences. It is complex and heterogeneous.
B. Impulsivity is related to stimulus-orientation, attention, response inhibition, and reward-sensitivity.
C. Neurophysiology of impulsivity involves pre-attentional and early attentional responses to stimuli.
D. Impulsivity is increased in psychiatric disorders that involve affective or behavioral instability, or abnormal sensitivity to rewards, including bipolar disorder, cluster B personality disorders like antisocial personality disorder, and substance-use disorders. Increased impulsivity is associated with worse course of illness, increased comorbidities, and increased risk for suicidal behavior.

Given the physiological interest and severe behavioral consequences of impulsivity, and its prominence in major psychiatric illnesses, impulsivity is a target for research at all levels. Further studies will increase our understanding of the physiology of impulsivity, and its clinical and treatment implications.

Table I – *Domains of Impulsivity.*

Domain	Interaction	Findings	References
Action-oriented trait	Diagnosis	BIS-11: Bipolar>ASPD>Control;	(Swann *et al*., 2004;
Barratt Impulsiveness Scale and related measures		Bipolar+substance-use>bipolar disorder or substance abuse>control	Swann *et al*., 2009c; Swann *et al*., 2010)
(Barratt & Patton, 1983;	Course severity	BIS-11: Increased with severe course of bipolar disorder	(Swann *et al*., 2009a)
Stanford *et al*., 2009)	State-trait	Differential relationships between depressive or manic symptoms and motor, attentional, or nonplanning impulsivity	(Swann *et al*., 2008)
Response inhibition	Diagnosis	Bipolar>ASPD>control	(Swann *et al*., 2009b); Swann *et al*., 2009c)
(Rapid-response, reward-delay (Dougherty et al., 2003;	Course severity	Rapid response more strongly related than reward delay to course of bipolar and ASPD	(Swann et al., 2009b; Swann *et al*., 2009c)
Evenden, 2000)	State-trait	Acute NE increases rapid-response impulsivity in controls	(Swann *et al*., 2005a)
Neurophysiology	Diagnosis	Gatin: bipolar=ASPD>control	(Lijffijt et al., 2009c; Lijffijt *et al*., 2009e)
(Sensory	Course severity	Demographics: small age and gender effects	(Lijffijt *et al*., 2009b)
	State-trait	N100, P200 related to response inhibition and working memory	(Lijffijt *et al*., 2009a)

REFERENCES

Acheson A., Richards J.B. & de Wit W.H. (2007). Effects of sleep deprivation on impulsive behaviors in men and women. *Physiology and Behavior* 91, 579-587.

Adler L.E., Gerhardt G.A., Franks R., Baker N., Nagamoto H., Drebing C. & Freedman R. (1990). Sensory physiology and catecholamines in schizophrenia and mania. *Psychiatry Research* 31, 297-309.

Adler L.E., Hoffer L., Nagamoto H.T., Waldo M.C., Kisley M.A. & Giffith J.M. (1994). Yohimbine impairs P50 auditory sensory gating in normal subjects. *Neuropsychopharmacology* 10, 249-257.

Aloe L., Iannitelli A., Angelucci F., Bersani G. & Fiore M. (2000). Studies in animal models and humans suggesting a role of nerve growth factor in schizophrenia-like disorders. *Behavioural Pharmacology* 11, 235-242.

Anderson K.J. & Revelle W. (1994). Impulsivity and time of day: is rate of change in arousal a function of impulsivity? *Journal of Personality and Social Psychology* 67, 334-344.

Anisman H., Kelly O., Hayley S., Borowski T., Merali Z. & McIntyre D.C. (2000). Acoustic startle and fear-potentiated startle in rats selectively bred for fast and slow kindling rates: relation to monoamine activity. *European Journal of Neuroscience* 12, 4405-4416.

Apter A., Plutchik R. & van Praag H.M. (1993). Anxiety, impulsivity and depressed mood in relation to suicidal and violent behavior. *Acta Psychiatrica Scandinavica* 87, 1-5.

Arnsten A.F. (2000). Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. *Progress in Brain Research* 126, 183-192.

Aston-Jones G. & Cohen J.D. (2005). Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *Journal of Comparative Neurology* 493, 99-110.

Barratt E.S. (1967). Perceptual-motor performance related to impulsiveness and anxiety. *Perceptual Motor Skills* 25, 485-492.

Barratt E.S. & Patton J.H. (1983). Impulsivity: Cognitive, behavioral, and psychophysiological correlates. In *Biological Basis of Sensation-seeking, Impulsivity, and Anxiety* (ed. M. Zuckerman), pp. 77-116. Lawrence Erlbaum Associates: Hillsdale, New Jersey.

Barratt E.S., Stanford M.S., Felthous A.R. & Kent T.A. (1997). The effects of phenytoin on impulsive and premeditated aggression: a controlled study. *Journal of Clinical Psychopharmacology* 17, 341-349.

Barratt E.S., Stanford M.S., Dowdy L., Liebman M.J. & Kent T.A. (1999). Impulsive and premeditated aggression: a factor analysis of self- reported acts. *Psychiatry Research* 86, 163-173.

Bechara A., Damasio A.R., Damasio H. & Anderson S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7-15.

Bechara A., Damasio H., Tranel D. & Damasio A.R. (1997). Deciding advantageously before knowing the advantageous strategy [see comments]. *Science* 275, (5304) 1293-1295.

Bechara A., Dolan S., Denburg N., Hindes A., Anderson S.W. & Nathan P.E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia* 39, 376-389.

Bergh C., Eklund T., Sodersten P. & Nordin C. (1997). Altered dopamine function in pathological gambling. *Psychological Medicine* 27, 473-475.

Bickel W.K., Odum A.L. & Madden G.J. (1999). Impulsivity and cigarette smoking: Delay discounting in current, never, and ex-smokers. *Psychopharmacology* 146, 447-454.

Braga M.F., Aroniadou-Anderjaska V., Manion S.T., Hough C.J. & Li H. (2004). Stress impairs alpha(1A) adrenoceptor-mediated noradrenergic facilitation of GABAergic transmission in the basolateral amygdala. *Neuropsychopharmacology* 29, 45-58.

Bremner J.D., Krystal J.H., Southwick S.M. & Charney D.S. (1996). Noradrenergic mechanisms in stress and anxiety: I. Preclinical studies. *Synapse* 23, 28-38.

Bruneau N., Barthelemy C., Jouve J. & Lelord G. (1986). Frontal auditory-evoked potential augmenting-reducing and urinary homovanillic acid. *Neuropsychobiology* 16, 78-84.

Brunner D. & Hen R. (1997). Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. *Annals of New York Academy of Science* 836, 81-105.

Carrillo-de-la-Pena M.T. (1992). ERP augmenting/reducing and sensation seeking: a critical review. *International Journal of Psychophysiology* 12, 211-220.

Cate Carter T.D., Mundo E., Parikh S.V. & Kennedy J.L. (2003). Early age at onset as a risk factor for poor outcome of bipolar disorder. *Journal of Psychiatric Research* 37, 297-303.

Christodoulou T., Lewis M., Ploubidis G.B. & Frangou S. (2006). The relationship of impulsivity to response inhibition and decision-making in remitted patients with bipolar disorder. *European Psychiatry* 21, 270-273.

Clark L., Iversen S.D. & Goodwin G.M. (2001). A neuropsychological investigation of prefrontal cortex involvement in acute mania. *American Journal of Psychiatry* 158, 1605-1611.

Comings D.E., Johnson J.P., Gonzalez N.S., Huss M., Saucier G., McGue M. & MacMurray J. (2000). Association between the adrenergic alpha 2A receptor gene (ADRA2A) and measures of irritability, hostility, impulsivity and memory in normal subjects. *Psychiatric Genetics* 10, 39-42.

Coull J.T. (1998). Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology* 55, 343-361.

Crean J.P., de Wit H. & Richards J.B. (2000). Reward discounting as a measure of impulsive behavior in a psychiatric outpatient population. *Experimental and Clinical Psychopharmacology* 8, 155-162.

Cremniter D., Jamain S., Kollenbach K., Alvarez J.C., Lecrubier Y., Gilton A., Jullien P., Lesieur P., Bonnet F. & Spreux-Varoquaux O. (1999). CSF 5-HIAA levels are lower in impulsive as compared to nonimpulsive violent suicide attempters and control subjects. *Biological Psychiatry* 45, 1572-1579.

Dickman S. (1985). Impulsivity and perception: individual differences in the processing of the local and global dimensions of stimuli. *Journal of Personality and Social Psychology* 48, 133-149.

Dikman Z.V. & Allen J.J. (2000). Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology* 37, 43-54.

Dougherty D.M., Bjork J.M., Marsh D.M. & Moeller F.G. (2000). A comparison between adults with conduct disorder and normal controls on a continuous performance test: Differences in impulsive response characteristics. *Psychological Record* 50, 203-219.

Dougherty D.M., Bjork J.M., Harper R.A., Marsh D.M., Moeller F.G., Mathias C.W. & Swann A.C. (2003). Behavioral impulsivity paradigms: A comparison in hospitalized adolescents with disruptive behavior disorders. *Journal of Child Psychology and Psychiatry* 44, 1145-1157.

Drouin C., Blanc G., Villegier A.S., Glowinski J. & Tassin J.P. (2002). Critical role of alpha1-adrenergic receptors in acute and sensitized locomotor effects of D-amphetamine, cocaine, and GBR 12783: influence of preexposure conditions and pharmacological characteristics. *Synapse* 43, 51-61.

Duffy A., Alda M., Kutcher S., Cavazzoni P., Robertson C., Grof E. & Grof P. (2002). A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. *Journal of Clinical Psychiatry* 63, 1171-1178.

Dunayevich E., Sax K.W., Keck P.E., Jr., McElroy S.L., Sorter M.T., McConville B.J. & Strakowski S.M. (2000). Twelve-month outcome in bipolar patients with and without personality disorders. *Journal of Clinical Psychiatry* 61, 134-139.

Evenden J.L. (1998). The pharmacology of impulsive behaviour in rats II: the effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and other drugs on fixed consecutive number schedules (FCN 8 and FCN 32). *Psychopharmacology* (Berl) 138, 283-294.

Evenden J.L. (1999). Varieties of impulsivity. *Psychopharmacology* (Berl) 146, 348-361.

Evenden J.L. (2000). Varieties of impulsivity. *Psychopharmacology* 146, 348-361.

Evenden J.L. & Ryan C.N. (1996). The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. *Psychopharmacology* (Berl) 128, 161-170.

Eysenck S.B. & Eysenck H.J. (1978). Impulsiveness and venturesomeness: their position in a dimensional system of personality description. *Psychological Reports* 43, 1247-1255.

Fergus E.L., Miller R.B., Luckenbaugh D.A., Leverich G.S., Findling R.L., Speer A.M. & Post R.M. (2003). Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. *Journal of AffectiveDisorders* 77, 71-78.

Gerra G., Avanzini P., Zaimovic A., Sartori R., Bocchi C., Timpano M., Zambelli U., Delsignore R., Gardini F., Talarico E. & Brambilla F. (1999). Neurotransmitters, neuroendocrine correlates of sensation-seeking temperament in normal humans. *Neuropsychobiology* 39, 207-213.

Glahn D.C., Bearden C.E., Bowden C.L. & Soares J.C. (2006). Reduced educational attainment in bipolar disorder. *Journal of Affective Disorders* 92, 309-312.

Green C.E., Moeller F.G., Schmitz J.M., Lucke J.F., Lane S.D., Swann A.C., Lasky R.E. & Carbonari J.P. (2009). Evaluation of heterogeneity in pharmacotherapy trials for drug dependence: a Bayesian approach. *American Journal of Drug and Alcohol Abuse* 35, 95-102.

Grunebaum M.F., Galfalvy H.C., Nichols C.M., Caldeira N.A., Sher L., Dervic K., Burke A.K., Mann J.J. & Oquendo M.A. (2006). Aggression and substance abuse in bipolar disorder. *Bipolar Disorders* 8, 496-502.

Gut-Fayand A., Dervaux A., Olie J.P., Loo H., Poirier M.F. & Krebs M.O. (2001). Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. *Psychiatry Research* 102, 65-72.

Hall J.R., Bernat E.M. & Patrick C.J. (2007). Externalizing psychopathology and the error-related negativity. *Psychological Science* 18, 326-333.

Halperin J.M., Wolf L.E., Pascualvaca D.M., Newcorn J.H., Healey J.M., O'Brien J.D., Morganstein A. & Young J.G. (1988). Differential assessment of attention and impulsivity in children. *Journal of the American Academy of Child and Adolescent Psychiatry* 27, 326-329.

Harrison A.A., Everitt B.J. & Robbins T.W. (1997). Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology* (Berl) 133, 329-342.

Hegerl U. & Juckel G. (1993). Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. *Biological Psychiatry* 33, 173-187.

Henry G.M., Buchsbaum M. & Murphy D.L. (1976). Intravenous l-DOPA plus carbidopa in depressed patients: average evoked response, learning, and behavioral changes. *Psychosomatic Medicine* 38, 95-105.

Ho M.Y., Mobini S., Chiang T.-J., Bradshaw C.M. & Szabadi E. (1999). Theory and method in the quatntitative analysis of "impulsive choice" behaviour: implications for psychopharmacology. *Psychopharmacology* 146, 362-372.

Hyten C., Madden G.J. & Field D.P. (1994). Exchange delays and impulsive choice in humans. *Journal of the Experimental Analysis of Behavior* 62, 225-233.

Jentsch J.D. & Taylor J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* (Berl) 146, 373-390.

Juckel G., Schmidt L.G., Rommelspacher H. & Hegerl U. (1995). The Tridimensional Personality Questionnaire and the intensity dependence of auditory evoked dipole source activity. *Biological Psychiatry* 37, 311-317.

Juckel G., Hegerl U., Giegling I., Mavrogiorgou P., Gallinat J., Augustin H., Mulert C., Pogarell O., & Rujescu D. (2007). Loudness dependence of auditory evoked potentials is not associated with polymorphisms or haplotypes in the serotonin transporter gene in a community-based sample of German healthy volunteers. *Psychiatry Research* 153, 183-187.

King R.J., Mefford I.N., Wang C., Murchison A., Caligari E.J. & Berger P.A. (1986). CSF dopamine levels correlate with extraversion in depressed patients. *Psychiatry Research* 19, 305-310.

Laffont F., Bruneau N., Roux S., Agar N., Minz M. & Cathala H.P. (1989). Effect of age on auditory evoked responses (AER) and augmenting-reducing. *Neurophysiologie Clinique* 19, 15-23.

Lijffijt M., Swann A.C. & Moeller F.G. (2008). Biological substrate of personality traits associated with aggression. In *Personality Theories and Models*, vol. 1 (ed. G.J. Boyle, G. Matthews and D.H. Saklofske), pp. 334-356. Sage: London.

Lijffijt M., Lane S.D., Meier S.L., Boutros N.N., Burroughs S., Steinberg J.L., Moeller F.G. & Swann A.C. (2009a). P50, N100, and P200 sensory gating: Relationships with behavioral inhibition, attention, and working memory. *Psychophysiology* 46, 1059-1068.

Lijffijt M., Moeller F.G., Boutros N.N., Burroughs S., Lane S.D. Steinberg J.L. & Swann A.C. (2009b). The role of age, gender, education, and intelligence in P50, N100, and P200 auditory sensory gating. *Journal of Psychophysiology* 23, 52-62.

Lijffijt M., Moeller F.G., Boutros N.N., Burroughs S., Steinberg J.L., Lane S.D. & Swann A.C. (2009c). A pilot study revealing impaired P50 gating in antisocial personality disorder. *Journal of Neuropsychiatry & Clinical Neurosciences* 21, 328-331.

Lijffijt M., Moeller F.G., Boutros N.N., Steinberg J.L., Meier S.L., Lane S.D., & Swann A.C.(2009d). Diminished P50, N100 and P200 auditory sensory gating in bipolar I disorder. *Psychiatry Research* 167, 191-201.

Logan G.D. (1994). On the ability to inhibit thought and action: A user's guide to to stop signal paradigm. In *Inhibitory Processes in Attention, Memory, and Language* (ed. D. Dagenbach and T.H. Carr), pp. 189-239. Academic Press; San Diego.

Magid V., Maclean M.G. & Colder C.R. (2007). Differentiating between sensation seeking and impulsivity through their mediated relations with alcohol use and problems. *Addictive Behaviors* 32, 2046-2061.

Mann J.J., Waternaux C., Haas G.L. & Malone K.M. (1999). Toward a clinical model of suicidal behavior in psychiatric patients. *American Journal of Psychiatry* 156, 181-189.

Mobini S., Chiang T.J., Al Ruwaitea A.S., Ho M.Y., Bradshaw C.M. & Szabadi E. (2000). Effect of central 5-hydroxytryptamine depletion on inter-temporal choice: a quantitative analysis. *Psychopharmacology* (Berl) 149, 313-318.

Moeller F.G., Barratt E.S., Dougherty D.M., Schmitz J.M. & Swann A.C. (2001a). Psychiatric aspects of impulsivity. *American Journal of Psychiatry* 158, 1783-1793.

Moeller F.G., Dougherty D.M., Barratt E.S., Schmitz J.M., Swann A.C. & Grabowski J. (2001b). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment* 21, 193-198.

Moeller F.G., Dougherty D.M., Barratt E.S., Oderinde V., Mathias C.W., Harper R.A. & Swann A.C. (2002). Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. Drug and Alcohol Dependence 68, 105-111.

Naatanen R. & Picton T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 24, 375-425.

Najt P., Perez J., Sanches M., Peluso M.A., Glahn D. & Soares J.C. (2007). Impulsivity and bipolar disorder. *European Neuropsychopharmacology* 17, 313-320.

Norra C., Mrazek M., Tuchtenhagen F., Gobbele R., Buchner H., Sass H. & Herpertz S.C. (2003). Enhanced intensity dependence as a marker of low serotonergic neurotransmission in borderline personality disorder. *Journal of Psychiatric Research* 37, 23-33.

Nusslock R., Alloy L.B., Abramson L.Y., Harmon-Jones E. & Hogan M.E. (2008). Impairment in the achievement domain in bipolar spectrum disorders: role of behavioral approach system hypersensitivity and impulsivity. *Minerva Pediatrica* 60, 41-50.

O'Neill B.V., Croft R.J. & Nathan P.J. (2008a). The loudness dependence of the auditory evoked potential (LDAEP) as an in vivo biomarker of central serotonergic function in humans: rationale, evaluation and review of findings. *Human Psychopharmacology* 23, 355-370.

O'Neill B.V., Guille V., Croft R.J., Leung S., Scholes K.E., Phan K.L. & Nathan P.J. (2008b). Effects of selective and combined serotonin and dopamine depletion on the loudness dependence of the auditory evoked potential (LDAEP) in humans. Human *Psychopharmacology* 23, 301-312.

Pailing P.E. & Segalowitz S.J. (2004). The error-related negativity as a state and trait measure: motivation, personality, and ERPs in response to errors. *Psychophysiology* 41, .

Patton J.H., Stanford M.S. & Barratt E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology* 51, 768-774.

Peluso M.A., Hatch J.P., Glahn D.C., Monkul E.S., Sanches M., Najt P., Bowden C.L., Barratt E.S., & Soares J.C. (2007). Trait impulsivity in patients with mood disorders. *Journal of Affective Disorders* 100, 227-231.

Post R.M. (2007). Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neuroscience and Biobehavioral Reviews* 31, 858-873.

Potts G.F., George M.R., Martin L.E. & Barratt E.S. (2006). Reduced punishment sensitivity in neural systems of behavior monitoring in impulsive individuals. *Neuroscience Letters* 397, 130-134.

Regier D.A., Farm M.E. & Rae D.S. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 264, 2511-2518.

Ridderinkhof K.R., Ullsperger M., Crone E.A. & Nieuwenhuis S. (2004a). The role of the medial frontal cortex in cognitive control. *Science* 306, (5695) 443-447.

Ridderinkhof K.R., van den Wildenberg W.P., Segalowitz S.J. & Carter C.S. (2004b). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition* 56, 129-140.

Rinne T., Westenberg H.G., den Boer J.A. & van den Brink W. (2000). Serotonergic blunting to meta-chlorophenylpiperazine (m-CPP) highly correlates with sustained childhood abuse in impulsive and autoaggressive female borderline patients. *Biological Psychiatry* 47, 548-556.

Rinne T., Sarkka A., Degerman A., Schroger E. & Alho K. (2006). Two separate mechanisms underlie auditory change detection and involuntary control of attention. *Brain Research* 1077, 135-143.

Roy A., Adinoff B., Roehrich L., Lamparski D., Custer R., Lorenz V., Barbaccia M., Guidotti A., Costa E. & Linnoila M. (1988). Pathological gambling. A psychobiological study. *Archives of General Psychiatry* 45, 369-373.

Roy A., De Jong J. & Linnoila M. (1989). Extraversion in pathological gamblers: Correlates with indexes of noradrenergic function. *Archives of General Psychiatry* 46, 679-681.

Ruchsow M., Spitzer M., Gron G., Grothe J. & Kiefer M. (2005). Error processing and impulsiveness in normals: evidence from event-related potentials. Brain Research. *Cognitive Brain Research* 24, 317-325.

Sarramon C., Verdoux H., Schmitt L. & Bourgeois M. (1999). Addiction et traits de personnalite: recherche de sensations, anhedonie, impulsivite. *Encephale* 25, 569-575.

Siegel J. (1997). Augmenting and reducing of visual evoked potentials in high- and low-sensation seeking humans, cats, and rats. *Behavior Genetics* 27, 557-563.

Soloff P.H., Lynch K.G., Kelly T.M., Malone K.M. & Mann J.J. (2000). Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. *American Journal of Psychiatry* 157, 601-608.

Southwick S.M., Paige S., Morgan C.A., III, Bremner J.D., Krystal J.H. & Charney D.S. (1999). Neurotransmitter alterations in PTSD: catecholamines and serotonin. S*eminars in Clinic Neuropsychiatry* 4, 242-248.

Stanford M.S., Mathias C.W., Dougherty D.M., Lake S.L., Anderson N.E. & Patton J.H. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences* 47, 385-395.

Steinberg B.J., Trestman R., Mitropoulou V., Serby M., Silverman J., Coccaro E., Weston S., de Vegvar M. & Siever L.J. (1997).

Depressive response to physostigmine challenge in borderline personality disorder patients. *Neuropsychopharmacology* 17, 264-273.
Swann A.C., Koslow S.H., Katz M.M., Maas J.W., Javaid J., Secunda S.K. & Robins E. (1987). Lithium carbonate treatment of mania. Cerebrospinal fluid and urinary monoamine metabolites and treatment outcome. *Archives of General Psychiatry* 44, 345-354.
Swann A.C., Bowden C.L., Morris D., Calabrese J.R., Petty F., Small J.G., Dilsaver S.C. & Davis J.M. (1997). Depression during mania: Treatment response to lithium or divalproex. *Archives of General Psychiatry* 54, 37-42.
Swann A.C., Anderson J.C., Dougherty D.M. & Moeller F.G. (2001). Measurement of inter-episode impulsivity in bipolar disorder. *Psychiatry Research* 101, 195-197.
Swann A.C., Bjork J.M., Moeller F.G. & Dougherty D.M. (2002a). Two models of impulsivity: Relationship to personality traits and psychopathology. *Biological Psychiatry* 51, 988-994.
Swann A.C., Bowden C.L., Calabrese J.R., Dilsaver S.C. & Morris D.D. (2002b). Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. *Neuropsychopharmacology* 26, 530-536.
Swann A.C., Pazzaglia P., Nicholls A., Dougherty D.M. & Moeller F.G. (2003). Impulsivity and phase of illness in bipolar disorder. *Journal of Affective Disorders* 73, 105-111.
Swann A.C., Dougherty D.M., Pazzaglia P.J., Pham M. & Moeller F.G. (2004). Impulsivity: A link between bipolar disorder and substance abuse. *Bipolar Disorders* 6, 204-212.
Swann A.C., Birnbaum D., Jagar A.A., Dougherty D.M. & Moeller F.G. (2005a). Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biological Psychiatry* 57, 1209-1211.
Swann A.C., Dougherty D.M., Pazzaglia P.J., Pham M., Steinberg J.L. & Moeller F.G. (2005b). Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *American Journal of Psychiatry* 162, 1680-1687.
Swann A.C., Gerard M.F., Steinberg J.L., Schneider L., Barratt E.S. & Dougherty D.M. (2007a). Manic symptoms and impulsivity during bipolar depressive episodes. *Bipolar Disorders* 9, 206-212.
Swann A.C., Steinberg J.L., Lijffijt M. & Moeller F.G. (2007b). Impulsivity: Differential relationship to depression and mania in bipolar disorder. *Journal of Affective Disorders* 106, 241-248.
Swann A.C., Steinberg J.L., Lijffijt M. & Moeller F.G. (2008). Impulsivity: differential relationship to depression and mania in bipolar disorder. *Journal of Affective Disorders* 106, 241-248.
Swann A.C., Lijffijt M., Lane S.D., Steinberg J.L. & Moeller F.G. (2009a). Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disorders* 11, 280-288.
Swann A.C., Lijffijt M., Lane S.D., Steinberg J.L. & Moeller F.G. (2009b). Severity of bipolar disorder is associated with impairment of response inhibition. *Journal of Affective Disorders* 116, 30-36.
Swann A.C., Lijffijt M., Lane S.D., Steinberg J.L. & Moeller F.G. (2009c). Trait impulsivity and response inhibition in antisocial personality disorder. *Journal of Psychiatric Research* 43, 1057-1063.
Swann A.C., Lijffijt M., Lane S.D., Steinberg J.L. & Moeller F.G. (2010). Interactions between bipolar disorder and antisocial personality disorder in trait impulsivity and severity of illness. *Acta Psychiatrica Scandinavica* Jan 7. [Epub ahead of print]
Virkkunen M. & Linnoila M. (1993). Brain serotonin, type II alcoholism and impulsive violence. *Journal of Studies on Alcohol*. Supplement 11, 163-169.
Winstanley C.A., Eagle D.M. & Robbins T.W. (2006). Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. *Clinical Psychology Review* 26, 379-395.
Yang P.B., Swann A.C. & Dafny N. (2003). Chronic pretreatment with methylphenidate induces cross-sensitization with amphetamine. *Life Sciences* 73, 2899-2911.
Zuckerman M. (1979). *Sensation Seeking: Beyond the Optimal Level of Arousal*. Erlbaum: Hillsdale, N.J..
Zuckerman M. (1991). *Psychobiology of Personality*. Cambridge University Press: Cambridge, UK.