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Editorial

Impulsivity: Its genetic, neurochemical and brain substrate determinants and the risks it entails for aberrant motivated behavior and psychopathology

This special issue of PBB on impulsivity frontal lobe function and mental disorders is in its major part the result of the Pharmacology Biochemistry & Behavior conference with the same theme held in Morzine, France in January 2008. In this issue many of the world's leading researchers in aspects of impulsivity are brought together from several disciplines to provide a state of the art analysis of impulsivity as a risk factor for several pathologies, but also to present new discoveries with regard to genetic, neurochemical and brain structure factors associated with the impulsive behavior. There has been a gradually emerging consensus that reduced inhibitory control of behaviors driven by strong motivations or habits is possibly even the main factor leading to compulsive drug use (Jentsch and Taylor, 1999; Jentsch et al., 1999; Volkow et al., 2003). The recognition of impulsivity as a major risk factor in vulnerability to drug abuse has developed in parallel. While a degree of risk taking may be important in adolescent development, and in healthy transitions from adolescence to adulthood, adolescence is an impulsive heightened risk period for the development of psychopathology and pathological behaviors. Within the context of motivated behaviors, elevated levels of impulsivity are associated with heavy drinking, drug use, obesity and pathological gambling (for a review see Verdejo-Garcia et al., 2008). Violence and sociopathy as well as many other aspects of mental disease and problematic behavior have also been associated with the impulsive trait (Huddy et al., 2009). The paper by *Duvvuri* et al. in the current issue proposes a translational approach to the study of a mental disorder (Anorexia Nervosa) based on inhibition of behavior in association with changes of serotonin function.

Impulsivity has been defined as a personality characteristic that can lead to a wide variety of conscious and unconscious actions that are poorly conceived, unnecessarily risky and often inappropriate in the given context (Evenden, 1999). It represents a major behavioral construct of which the most recognised components include hypersensitivity to immediate reward (delay discounting), the inability to inhibit pre-potent responses (response disinhibition), and risk taking (de Wit and Richards, 2004).

Impulsivity can be viewed on a continuum along which low levels are advantageous in certain circumstances needing quick decisions (de Wit, 2009) while high levels are often maladaptive and implicated in the etiology of psychiatric illness (Winstanley, 2007). Impulsivity is multidimensional with two aspects being difficulty in withholding a prepotent response (i.e., impaired response inhibition) and the inability to efficiently adapt behavior in response to changes in delay to reward and/or reward magnitude (i.e., impulsive choice) (Robinson et al., 2008). These forms of impulsivity are measured by different behavioral tasks, and they have been suggested to be nonoverlapping and perhaps mutually exclusive at both a behavioral and neurobiological level (e.g. de Wit and Richards, 2004; Winstanley et al., 2004). Neuroanatomical differences could underlie these two components of impulsivity. For example, performance on tasks measuring response inhibition such as the Go/No-Go and stop signal reaction time (SSRT) tasks are mediated by the anterior cingulate cortex and infralimbic cortex, while impulsive choice, as measured by the delay discounting procedure, is sensitive to orbital prefrontal cortex disruption (Winstanley et al., 2006) and correlate with performance on tasks measuring impulsive choice (Winstanley et al., 2004). Further, performance on tasks measuring impaired response inhibition does not strongly correlate with performance on tasks measuring impulsive choice (Winstanley et al., 2004). On the other hand, Robinson et al. (2008) found a correlation between impulsive performance on the 5-choice serial reaction time (5-CSRT) task and the delay-discounting task (Robinson et al., 2008) but not between delay discounting and the SSRT task (Robinson et al., 2008). Despite this apparent divergence, both forms of impulsivity are related to substance abuse symptomatology in clinical populations (e.g. Bornovalova et al., 2005; Verdejo-Garcia et al., 2008). Reward sensitivity and inhibition of pre-potent response and their importance for understanding the mechanisms underlying impulsivity are dealt with by *Boettinger* et al., and *Bornovalova* et al., in original studies and discussed within the context of the current literature in the review by *Crews & Boettinger*.

The importance of impulsivity as a complex human trait related to psychopathology is difficult to study, however both human and animals studies can address this complex behavior. Animal models of impulsivity and drug abuse provide a means to evaluate prospectively the influence of both impaired response inhibition and impulsive choice on drug abuse, and results from such studies suggest that each type of impulsive behavior may be associated with the development of aspects of drug abuse. For example, rats screened for high levels of impulsive choice on a delay-discounting task subsequently self-administered more ethanol (Poulos et al., 1995) and i.v. nicotine (Diergaarde et al., 2008), acquired cocaine self-administration faster (Perry et al., 2008), and exhibited greater reinstatement of cocaine-seeking (Perry et al., 2008) than those with low levels of impulsive choice. These studies suggest that both impaired response inhibition and impulsive choice are related to heightened drug seeking during critical phases of addiction. *Anker* et al. provide evidence for a relationship between high impulsivity rats classified on the basis of their reward sensitivity (delayed discounting) and escalation of cocaine self administration.

The genetic and neurochemical basis of impulsive traits has been the focus of extensive research and is central to this special issue. Dopamine is the neurotransmitter most commonly discussed in leading theories of

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impulsive personality trait (Everitt et al., 2008). Dopamine is also involved in the sensitization of neuronal networks an integral part to leading theories of addiction (Volkow et al., 2009). The study of Impulsive personality on the other hand consistently emphasises the high heritability of this trait. It is not surprising then that genes associated with brain dopamine activity have been the commonly studied candidates associated with impulsivity. One original report by *McGeary* et al. in the current issue gives evidence for a relationship between the DRD4 exon 3 VNTR polymorphism and urge for addictive substances whereas another one by *Esposito-Smythers* et al. suggests that the behavioral phenotype of impulsivity and problematic drug use can be moderated by A1 carrier status in the DRD2 gene. Impulsivity represents an integral part of motivated behaviors and characterizes strongly adolescent behavior. *Ernst* et al. provides a review on the evidence that will add to our understanding of the mechanisms underlying the transition in a young adult from a healthy highly motivated behavior trait to an impulsive pathology addressed in the current issue. The importance of neurodevelopment of reward and cognitive control (Chambers et al., 2003) as a means of understanding the transition from risk taking to psychopathology and drug abuse in adolescence is further examined by *Knopik* et al. whereas *Geier* et al. propose a model of reward processing in adolescents that limits their ability to inhibit impulsive behaviors. The complex cognitive mechanisms and brain substrates that govern inhibitory control are discussed within incentive theories of addiction in the papers by *Winstanley* et al., and *Wiers* et al., whereas impulsive behavior in the form of lack of inhibition as a consequence of drug or alcohol use is presented in the papers by *Hester & Garavan* for cocaine and in the papers by *Scaife & Duka* and *Nederkoorn* et al. for alcohol. The association between heavy alcohol drinking or binge drinking and impaired frontal lobe function including inhibitory control, working memory and attentional shifts was shown to be more pronounced in females (*Scaife & Duka* and *Nederkoorn* et al.). From an animal study evidence was provided of an association between oestrogen and reduction in impulsive behaviors (*Llaneza & Frye*). Furthermore, the problem of impulsivity is discussed in the context of a combined risk to develop psychopathology from an innate impulsive trait and from drugs which impair inhibitory control. Finally the case is made of impulsivity as a target for self medication with smoking (*Hamidovic* et al.) and for treatment of addiction (*Boettinger et al; Kahler* et al.) and of psychopathology (*Amitai & Markou*). The role of serotonin in inhibition of behavior (*Duvvuri* et al.) and the link between early exposure to glutamatergic antagonists and frontal damage (*Coleman* et al.) as well as the role of HPA axis and the noradrenergic system in the development of alcoholism in response to stress (*Clarke* et al.) put forward models for understanding inhibitory control and impulsivity in relation to major neurotransmitter pathways others than dopaminergic.

This special issue on impulsivity serves to integrate both human and animal studies on aspects of impulsivity. Although many studies deal with drug abuse and/or adolescence, other psychopathology and simple mechanistic studies of brain self control are included. We hope the readers of PBB enjoy this focused special issue and it broadens interest in impulsivity as a trait contributing to psychopathology.

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