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Focusing on Symptoms Rather than Diagnoses in Brain Dysfunction: Conscious and Nonconscious Expression in Impulsiveness and Decision-Making

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Symptoms and syndromes in neuropathology, whether expressed in conscious or nonconscious behaviour, remain imbedded in often complex diagnostic categories. Symptom-based strategies for studying brain disease states are driven by assessments of presenting symptoms, signs, assay results, neuroimages and biomarkers. In the present account, symptom-based strategies are contrasted with existing diagnostic classifications. Topics include brain areas and regional circuitry underlying decision-making and impulsiveness, and motor and learned expressions of explicit and implicit processes. In three self-report studies on young adult and adolescent healthy individuals, it was observed that linear regression analyses between positive and negative affect, self-esteem, four different types of situational motivation: intrinsic, identified regulation, extrinsic regulation and amotivation, and impulsiveness predicted significant associations between impulsiveness with negative affect and lack of motivation (*i.e.*, amotivation) and internal locus of control, on the one hand, and non-impulsiveness with positive affect, self-esteem, and high motivation (*i.e.*, intrinsic motivation and identified regulation), on the other. Although presymptomatic, these cognitive-affective characterizations illustrate individuals' choice behaviour in appraisals of situations, events and proclivities essentially of distal perspective. Neuropathological expressions provide the proximal realities of symptoms and syndromes with underlying dysfunctionality of brain regions, circuits and molecular mechanisms.

Keywords: Symptom; Decision-making; Diagnosis; Substrates; Impulsiveness; Expression; Nonconscious; Conscious; Neuropathology

INTRODUCTION

Efforts to describe and understand symptom profiles over diagnostic constraints and disorder categorizations remain bedeviled by the straightjackets of existing criteria, instruments and classifications. In focussing upon a "symptom strategy", it is implicitly concluded that the presenting symptoms, signs, assay results, neuroimages and biomarkers are themselves the targets for attempts to grapple with the neuropathology of brain disease states. Thus, the contributions of conscious and noncon-

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scious processes to cognitive, affective and motor expressions of behavioural dysfunctionality and the underlying neural substrates await elucidation.

Functionality and Dysfunctionality

So-called 'everyday memory failures', *e.g.*, forgetting to put on a tie for a formal public occasion, have given rise to conceptualizations such as a breakdown of "unity of consciousness" and the "unity model of memory failure" (Gennaro *et al.*, 2006). These notions suggest that although poor encoding retention or retrieval may result in memory failure, problems of forgetting may result from disruptions of the "unity of consciousness", brought about by practical, undramatic events on a daily basis. Emotional states, stressful situations and personal cognitive appraisals may imbue the "unity of consciousness" breakdowns with more sinister, neuropsychiatric aspects, distinct from memory *per se* (Reason, 1984). Current notions of memory processes distinguish explicit memory, *e.g.*, declarative memories that support the ability to recognise and/or recall events consciously, from implicit memory, *e.g.*, non-declarative memories inaccessible to conscious report yet inferred from performance improvements due to previous experience of the task; the latter normally is preserved in amnesia (Verfaellie et al., 2006). However, recently Chun (2005) discussed evidence of an impairment in implicit memory in the transient amnesia of healthy volunteers administered midazolam (an anti-anxiety benzodiazepine producing amnesia for surgical procedures by blocking the encoding of new information despite subjects remaining alert and performing the task normally (Polster *et al.*, 1993). It was shown that midazolam impaired implicit relational memory while allowing non-relational memory to be preserved (Hirshman *et al.*, 1999). In addition, the involvement of contextual cuing variables in implicit memory under conditions of brain damage offers further complexity for implications of states of consciousness in cognition (Chun and Phelps, 1999; Manns and Squire, 2001; Chun and Jiang, 2003; see also Rosenbaum *et al.*, 2007).

From a parallel perspective, Le Moal *et al.* (2008) have addressed issues arising from the applications of animal models in behavioural pathology. They discuss the consequences of introducing medical models and the various procedures inherent to diagnosis into psychiatry, on the one hand, and collection and assembly of symptoms and syndromes, on the other. A major constraint in many cases appears to be the absence of reliable and valid laboratory data (neuroimaging may lack the status of a reliable marker) (Rutter *et al.*, 2001; 2006). Most animal models appear not to fit the clinical features and, above all, the clinical realities. Pathological traits or phenotypes characterise the co-existence of different modular components, each a symptomatic expression of dysfunction within a given functional system (Petronis, 2004). The notion, derived from animal and/or human research, that neuropathological traits present multi-symptom sets, essentially syndromes, within distinct intertwinned behavioural and biological levels or conglomerations provides plausible logic for a disease (Piazza and LeMoal, 1996).

Biological defects co-exist with pathobehavioural trait characteristics as signatures of different neurobiological systems (Rapp and Amaral, 1992). The case may be illustrated with regard to the condition labelled 'psychopath', referring to individuals showing antisocial personality disorder, characterised by inability to develop emotional involvements and recurrent infringements of the rights of others (Hare *et al.*, 1978; Veit *et al.*, 2002). These individuals lack the ability to anticipate punishment and show autonomic conditioning deficiencies (Lykken, 1957; Hare and Quinn, 1971; Lilienfeld and Andrews, 1996). Recently, Birbaumer *et al.* (2005) examined cerebral, peripheral and subjective correlates of fear conditioning in ten criminal psychopaths and ten healthy volunteers through application of an aversive differential Pavlovian delay conditioning paradigm with neutral faces as conditioned stimulus and painful pressure as unconditioned stimulus. They found that healthy volunteers showed differential activation of the limbic-prefrontal circuit, consisting of amygdala, orbitofrontal cortex, insula and anterior cingulate cortex, during acquisition of fear and successful verbal and autonomic conditioning, as assessed with functional magnetic resonance imaging. Conversely, the psychopaths (indexed with the Hare Psychopathy Checklist-Revised) showed no significant activity in this circuit and no conditioned skin conductance and

emotional valence ratings, despite contingency and arousal ratings being normal. They concluded that the lack of anticipation of aversive events by the psychopaths was due to the dissociation of emotional and cognitive processing in the brain, confirming observations that disruptions of the orbitofrontal cortex of the frontolimbic circuit result in "acquired sociopathic" manifestations (Anderson *et al.*, 1999; Damasio, 2000).

Similarly, Geyer (2008) discusses aspects of the neurobiological substrates, constructs and mechanisms underlying the development of animal models to mimic diagnostic syndromes in the search for models of specific symptoms. The development of cross-species methodolgy has offered particular utility for deriving the symptom/presymptom profiles originating from brain abnormalities (Vallee *et al.*, 1997; 1999; Lemaire *et al.*, 2000; Bateson *et al.*, 2004). Prepulse inhibition (PPI), a sensory gating procedure of established applicability in studying symptom profiles (Braff and Geyer, 1990), was shown to be reduced in schizophrenic and manic bipolar patients (Braff *et al.*, 2001; Perry *et al.*, 2001). PPI deficits interacted with strain in animal models and antipsychotic medication in humans (Olivier *et al.*, 2001; Powell and Geyer, 2002; Cilia *et al.*, 2005; Geyer, 2006; Swerdlow *et al.*, 2006; Csomor *et al.*, 2008; Young *et al.*, 2007). Illustrations of more or less valid cross-species models, specific animal paradigms that parallel pre-cognitive - cognitive expressions and development of novel human models of neuropsychiatric symptoms are outlined and discussed together with genetic predispositions (Palmer *et al.*, 2000; Geyer *et al.*, 2002).

Verhoeven and Tunier (2008) discussed the genetic underpinnings of schizophrenia from the perspective of a broad clinical phenotype regarding developmental issues, symptoms and co-morbidity (Verhoeven and Tunier, 2001; Wijers *et al.*, 2005; Cuesta *et al.*, 2007). The long-lasting debate regarding symptom categorization in order to facilitate further insights into disease etiology and neuropathology has resulted in the development of criteria for diagnosing disorders; yet, there exists a remarkable surfeit of precise symptomatical boundaries and a vagueness regarding systems that may offer validity for genetic and other biological research (Rosenman *et al.*, 2003; Matsuura *et al.*, 2004; Serretti and Olgiati, 2004). Thus, for example, the search to identify linkages between schizophrenia and one or more genes has yielded few reliable findings. Verhoeven and Tunier (2008) discuss the search for candidate genes, *e.g.*, *DISC1* (Ekelund *et al.*, 2001; Hwu *et al.*, 2003; Sachs *et al.*, 2005) and the 22q11 deletion syndrome (Shprintzen *et al.*, 1978; Shprintzen, 2000; Schaer *et al.*, 2006; Williams *et al.*, 2007). From the case of the 22q11 deletion syndrome, psychotic symptoms emerge from a context of brain anomalies, an interaction of somatic abnormalities and specific neurocognitive deficits whereas in the Prader-Willi syndrome (Verhoeven and Tunier, 2006), a hypothalamic disorder which is expressed by psychotic symptoms that may resemble schizophrenia. Children presenting the 22q11 deletion syndrome exhibited a neuropsychological profile of relative verbal strength versus visuospatial and perceptual deficits (Swillen *et al.*, 1999; Lajiness-O'Neill *et al.*, 2006) as well as an impaired short term verbal memory (Majerus *et al.*, 2007), whereas at later age significant impairments in visuoperceptual ability, problem solving and planning are present (Henry *et al.*, 2002). Verhoeven *et al.* (2007) have described a group of adults displaying 22q11syndrome and psychotic features together with verbal and performance IQ discrepancies and impairments in visuoperceptual ability and comprehension of abstract and symbolic language. They discuss too the putative existence of a susceptibility locus for schizophrenia and bipolar disorder on chromosome 15q26 (Vazza *et al.*, 2007). Finally, it was concluded, not only that schizophrenia is a highly variable disease, but that the genetic samples are even more heterogenous.

Decision-making and Impulsiveness

The notion that decision-making represents a rational and conscious process, *e.g.*, decisions of the type that are unpleasant in the short-term may offer long-term advantages, relatively removed from implicit or emotional considerations, may be questionable (*e.g.*, Bechara *et al.*, 1994; Damasio, 1998). Decision-making may be assisted by emotion-related stimuli, "somatic markers", that may occur prior to complete consciousness regarding the suitability of the choice. Confronted by the Iowa Gambling Task (IGT) (Bowman *et al.*, 2005),

healthy subjects select cards from all four decks but learn quickly to rely on the advantageous decks, displaying greater anticipatory skin conductance responses (SCRs) prior to selecting a card from the disadvantageous decks; this observation is consistent with the somatic marker hypothesis. Thus, individuals are offered choices between card decks that yield high monetary rewards but higher losses (*i.e.*, the disadvantageous decks) or decks with low rewards but lower penalties. Although each deck is linked to a specific schedule of "win-lose" ratios, it is not possible to make an exact calculation of deck payoffs with the consequence that players are confronted with conflicts between playing from decks with risky high rewards or from those associated with low rewards and low punishment. Patients with ventromedial prefrontal cortex damage choose more from the disadvantageous decks in the IGT (Bechara *et al.*, 1997; 2000; 2005; Manes *et al.*, 2002), which implies the involvement of this region in mediating a sensitivity for future consequences of current actions (Bechara *et al.*, 1996). Recently, Gutbrod *et al.* (2006) tested whether or not explicit, conscious memory was necessary for acquisition of a strategy allowing the performance of advantageous responses, using the IGT procedure and measuring skin conductance responses concomitantly. Accordingly, five amnesic patients with damage to the basal forebrain and orbitofrontal cortex and six amnesic patients with damage to the medial temporal lobe or the diencephalon were compared with eight healthy controls. They observed that the healthy controls acquired a preference for advantageous choices and generated large SCRs to high levels of punishment over 100 trials; the anticipatory SCRs to disadvantageous choices by the controls were greater than to the advantageous choices. On the other hand, nine out of the eleven amnesic patients performed the IGT at chance level and did not exhibit the differential SCRs to advantageous and disadvantageous choices, nor was anticipatory SCR magnitude linked to performance. The authors concluded that the acquisition of strategic preference in decision-making, whether regarding advantageous or disadvantageous choices, places demands upon a functioning explicit memory that remembers the outcome of previous trials in a punishment reinforcement situation. Thus, the linkage of stimuli and their particular outcomes appears a necessary prerequisite for learning in emotionally-charged decision-making situations (Ptak *et al.*, 2001; Hinson *et al.*, 2002; Tomb *et al.*, 2002; Clark *et al.*, 2004; Denburg *et al.*, 2005; Fellows and Farrah, 2005).

Several disorders, in which immediate gratification is given a higher priority than long-term goals in decision-making, are characterised by high levels of impulsiveness and poor decisions, including attention deficit hyperactivity disorder (ADHD), psychopathy, substance-abuse disorders, eating disorders and certain personality disorders (*e.g.*, Bulik *et al.*, 1997; Petry *et al.*, 1998; Bechara *et al.*, 2001; Lynskey and Hall, 2001; Mitchell *et al.*, 2002). Under the influence of alcohol, normally healthy individuals frequently make impulsive choices without regard for the future consequences of these choices; intoxication may induce gamblers to persist with higher wagers (Kyngdon and Dickerson, 1999) but may also induce less impulsiveness (Ortner *et al.*, 2003), although willingness to gamble is elevated by alcohol across all individuals (Breslin *et al.*, 1999). Furthermore, the acute effects of alcohol on executive functioning vary differentially with the descending curve linked to executive functioning impairments (Pihl *et al.*, 2003). Psychopathic individuals and substance abusers, both displaying high levels of impulsiveness (Palomo *et al.*, 2007), showed impaired performance on the IGT (Grant *et al.*, 2000; Bechara and Damasio, 2002; as well as above). Recently, Balodis *et al.* (2006) assessed the performance of 127 male undergraduate students on the IGT, the Newman Perseveration task, measuring impulsiveness, and Barratt's Impulsiveness Scale (BIS) under alcohol intoxication or not. They obtained unimpaired performance of the IGT by the intoxicated group, concluding that individual characteristics rather than the direct action of alcohol induce a greater influence on decision-making. Neverthe-less, impulsiveness is a diagnostic criterion for mania (American Psychiatric Association, 1994; Swann *et al.*, 2003; 2004; 2005); it follows therefore that this notion together with risky decision-making may be associated with bipolar disorder (Rubensztein *et al.*, 2000; Murphy *et al.*, 2001; Blumberg *et al.*, 2003; Frangou *et al.*, 2003). Christodoulou *et al.* (2006)

investigated twenty-five remitted bipolar disorder patients who completed the BIS, the Hayling Sentence Completion task and a computerized version of the IGT. They found that higher scores on the BIS attentional and non-planning subscales were associated with more errors on the Hayling Sentence Completion task and less advantageous choices in the IGT. Despite the limitations of all the patients being under medication and no healthy controls being included, they concluded that impulsiveness, response inhibition and decision-making in bipolar disorder may be manifestations of possible ventral prefrontal cortical dysfunction.

Impulsiveness Relative to Affect, Motivation, Self-esteem and Locus of Control

Individuals expressing higher levels of impulsiveness often display deficits over a variety of executive function tests (Dolan and Park, 2002; Rogers, 2003), cognitive tasks requiring response control (Potter and Newhouse, 2004) and cognitive flexibility (Mungas, 1988; Barratt *et al.*, 1997). Keilp *et al.* (2005) found that performance of executive function, verbal fluency, tasks requiring decision-making against time, reaction time to paired words and paired faces memory tasks, the Go-No Go task, the time estimation task and response bias on the continuous performance task correlated substantially with the self-reported scores on Barratt's Impulsiveness Scale. Performance on the Go-No Go task is the strongest correlate for self-rated impulsiveness whereby decision-making and response-organisation tasks under pressure of time give stringent tests of the trait. Archer *et al.* (2008) described studies assessing the influence of affective personality upon stress, motivation, self-esteem, optimism, depression and anxiety and locus of control in different populations, and the predictive relationships between positive affect, negative affect, self-esteem, intrinsic motivation and depression (Beck's BDI) within and across estimations of cognitive-emotional expressions, as assessed with regression analysis. In the present account, the findings of three self-report studies designed to investigate the predictive relations, using regression analyses, between self-rated impulsiveness, affect, motivation, self-esteem and locus of control are described.

In three studies, 167 high school students, 83 female and 84 male, with a mean age of 18.41 years (SD = 3.70; range = 16 to 19) and 194 high school students, 101 female and 93 male, with a mean age of 18.47 years (SD = 3.75; range = 16 to 19) and from the south-east (Kalmar) of Sweden and 321 middle-to-high school pupils, 241 female and 80 male (age range 12 - 18 years), from the Greater Gothenburg region (Sweden) participated. Choice of participant in studies 1 and 2 was determined by the presence of these individuals in a situation (university studies) in which high academic performance was of central importance, this particular population of individuals was thereby considered relevant due to the stress experience associated with motivational levels focused upon high achievement. Choice of participant for study 3 was determined by willingness of the participants to complete the questionnaires regarding PANAS, Stress and Energy, Dispositional optimism, Rosenberg's Self-esteem and Barratt's Impulsiveness Scale (modified to take into account the ages of the younger subjects). The students belonged to different educational programs, including social sciences, health care, vehicles, humanities, business, and pure science.

Instruments and Procedure

Positive affect and negative affect scale (PANAS). The PANAS-instrument provides a self-estimation of affect, both positive and negative. It consists of 10 adjectives for the NA dimension and 10 adjectives for the PA dimension. The test manual (Watson *et al.*, 1988a,b) postulates that the adjectives describe feelings (Affect) and mood level. Participants were instructed to estimate how they felt during the last few days. The response alternatives were presented on a five-grade scale that extended from 1 = not at all to 5 = very much. For each participant the responses to the 10 negatively-charged adjectives were summated to provide a total NA-result for NA affect, and similarly the responses to the positively-adjectives were summated to provide a total PA-result for PA affect. The PANAS instrument has been validated through studies analyzing conditions associated with general aspects of psychopathology (Huebner and Dew, 1995), as well as a multitude of other expressions of affect (Watson and Clark, 1984). Previous

studies (Norlander *et al.*, 2002; Bood *et al.*, 2004; Palomo *et al.*, 2004) have modified and developed the PANAS instrument further through a subject-response based derivation of the four types of affective personality (see Design). This procedure was implemented in the present study through dividing the results on the PA-scale into two parts thereby distributing the participants into one group with high PA and another group with low PA (*cut-off point* = 53.2%). The same procedure was implemented for the participants' responses on the NA-scale (*cut-off point* = 48.9%). Following this, the results from these two scales were combined according to the procedure that assigned each one of the participants into one of the four affective personality groups, as follows: individuals showing high PA and low NA ("Self-fulfilling"), high PA and high NA ("High affective"), low PA and low NA ("Low affective") and low PA and high NA ("Self-destructive").

Locus of Control. Locus of Control was measured using a modified version according to Millet and Sandberg (2003; Millet, 2005) using an abbreviated version of the Rotter scale (1966) as developed by, for example Andersson (1976), for use mainly in Swedish work settings. The scale has a minimum score of 8 and a maximum of 40, with a lower score representing an external locus of control orientation and a higher score representing an internal locus of control orientation. Several empirical studies have shown that perceived control is strongly correlated with rehabilitational outcomes, not least empowerment (Tseng, 1970; Levenson, 1974; Partridge and Johnston, 1989; Erbin-Roesemann and Simms, 1997). Possible considerations pertaining to cross-confounding with other constructs appear to have been rebutted by Lefcourt (1991).

Situational Motivation Scale (SIMS). The SIMS instrument was designed to provide an estimation of the constructs (factor), intrinsic motivation, identified regulation, external regulation and amotivation (*cf.*, Deci and Ryan, 1985; 1991) in both field and laboratory settings. Guay *et al.* (2000) have shown that SIMS is composed of four internally consistent values (Cronbach's α) for each factor, showing: intrinsic motivation = 0.95, identified regulation = 0.80, external regulation = 0.86 and amotivation = 0.77, with self-report internal consistency scales in the 0.70-0.80 range acceptable for research purposes. The construct validity of SIMS has been shown to be supported by correlations with other constructs, *e.g.*, perceived competence, concentration and behavioural intentions. The present version of SIMS included four items for each factor, *e.g.*, *intrinsic motivation*: "Because I think this activity is interesting", *identified regulation*: "Because I am doing it for my own good", *external regulation*: "Because I am supposed to do it", and *amotivation*: "I do this activity but I am not sure it is worth it", with seven response alternatives [1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = enough, 6 = a lot, 7 = exactly] that provided eigenvalues of 5.70, 2.63, 1.33, and 0.73, for each factor, respectively. Guay *et al.* (2000) have shown both that perceived competence, concentration and behavioural intentions of future persistence toward the activity were associated with SIMS factors according to the self-determination continuum and specific and positive interrelations between Academic Motivation Scale factors (*cf.*, Vallerand *et al.*, 1989) and the SIMS factors.

Rosenberg's Self-esteem Scale (SES). The SES instrument is a self-estimation, 10-item questionnaire which has been constructed to measure the extent to which individuals consider themselves "sufficiently functional", particularly in adolescents and young adults (Rosenberg, 1965). Self-esteem is measured using ten items (statements, each item rated on a four point Likert scale) concerned with feelings about oneself and one's attitude towards one's resources, relations to others and achievements, whereby half of the statements express positive aspects about self and half express negative aspects. The participants were required to respond with the number that they considered to fit the degree to which they agreed with the statement or disagreed with the statement, whereby 1 = "*agree* completely" and 4 = "*disagree* completely". For example, statements like "I can do things as well as anybody else", or "I wish that I had more respect for myself", or "On the whole I am satisfied with myself" were included.

Barratt's Impulsiveness Scale (BIS-11, modified and translated). The present modified, Swedish version BIS-11 instrument is a self-estimation 25-item questionnaire that assesses impulsiveness (Patton *et al.*, 1995). Participants respond to statements on a 4-point scale, "Never" - "Sometimes" - "Often" - "Always", whereby 16 out of the 25 items express impulsiveness, such as "I do things without consideration", or "I act impulsively", and, conversely, 9 out of 16 items express non-impulsiveness, such as "I have good self-control", or "I plan for the future". Nine of the twenty-five items are scored formulated to express 'non-impulsiveness' thereby providing a reverse order, avoiding response bias, and sixteen items provided direct scores of impulsiveness. According to the factor analysis study by Li and Chen (2007), BIS items may be chosen to produce three factors, inability to plan, lack of self-control and sensation/novelty seeking, that are tangental to the three subscales, nonplanning, motor and cognitive impulsiveness. BIS has been translated into several different languages with test-retest reliability ranging from 0.71 to 0.89 (Fossati *et al.*, 2001; Someya *et al.*, 2001).

Procedure. Participants (except in Study3 wherein the instruments were sent out over the internet) were assembled in groups of 5 to 6 participants (within each respective testing environment) before receiving instructions followed by the questionnaires. They were provided with an envelope containing the questionnaire with all the instruments and were instructed to complete these quietly and independently. In each study, the amount of time allocated to the participants was 20-30 minutes. All instructions and questionnaires were in Swedish and all the participants were guaranteed anonymity and assured that their collaboration was on a voluntary basis. First, the participants completed a background sheet providing information concerning age, sex, education, physical exercise, use of medicine, etc. After this, they completed all the other instruments, including PANAS, Locus of Control, SES, SIMS and BIS (as arranged within each respective Study).

RESULTS AND DISCUSSION

Regression analyses indicated that Impulsiveness was predicted by negative affect (β=0.22) and amotivation (β=0.15), and was counterpredicted by internal locus of control (-β=0.17) in Study I; it was predicted by amotivation (β=0.27) in Study II; and, it was predicted by negative affect (β=0.33) and counterpredicted by positive affect (β=-0.29) in Study III. Table I presents the standardized weights from linear regression analysis with (a) Impulsiveness in Study I [$F_{(9,157)}$=5.26, p <0.001; Adjusted R_2=0.187], (b) Study II [$F_{(6,187)}$=3.34, p <0.01; Adjusted R_2=0.069], and (c) Study III [$F_{(4,316)}$=24.69, p <0.001; Adjusted $_{R2}$=0.228], respectively, as dependent variable and Positive and Negative affect, internal and external locus of control, self-esteem, intrinsic motivation, identified regulation, external regulation and amotivation as independent variables.

Regression analyses indicated that Non-impulsiveness was predicted by positive affect (β=0.17), self-esteem (β=0.19), intrinsic motivation (β=0.20) and identified regulation (β=0.20) in Study I; it was predicted by positive affect (β=0.20), and counterpredicted by amotivation (β=-0.15) in Study II; and, it was predicted by positive affect (β=0.50) and internal locus of control (β=0.17) in Study III. Table II presents the standardized weights from linear regression analysis with (a) Non-impulsiveness in Study I [$F_{(9,157)}$=11.64, p <0.001; Adjusted R_2=0.366], (b) Study II [$F_{(6,187)}$=3.70, p <0.01; Adjusted R_2=0.078], and (c) Study III [$F_{(4,316)}$ =34.09, p <0.001; Adjusted R_2=0.293], respectively, as dependent variable and Positive and Negative affect, internal and external locus of control, self-esteem, intrinsic motivation, identified regulation, external regulation and amotivation as independent variables.

The present findings from three studies, carried out on relatively young or adolescent, relatively healthy, nonclinical individuals, implicate markedly the predictive associations between impulsiveness with negative affect and lack of motivation (*i.e.*, amotivation) and an absence of internal locus of control, on the one hand, and non-impulsiveness with positive affect, self-esteem, a high level of motivation (*i.e.*, intrinsic motivation and identified

regulation) and internal locus of control, on the other hand. One notion of 'impulsiveness versus restraint' views impulsiveness and anxiety at opposite dimensional poles with impulsiveness occurring when anxiety is low, and vice versa, whereas others conceptualize several different dimensions of impulsiveness-restraint, particularly in the context of brain function (Epstein, 1994; Sloman, 1996; Metcalfe and Mischel, 1999; Bechara, 2005; Carver, 2005). Much evidence suggests that high levels of, or unrestricted impulsiveness, are associated with adventuresome decision-making in a range of situations studying neural correlates of and brain regions associated with risk-taking behaviour (*e.g.*, Sanfey *et al.*, 2003; Hsu *et al.*, 2005; DeMartino *et al.*, 2006; Huettel *et al.*, 2006; Weller *et al.*, 2007). A variety of decisions, unexplainable solely on the basis of rational imperatives, may be influenced markedly by affective state, *e.g.*, by the emotion of 'regret' in guiding choice behaviour (Bell, 1982; Gilovich and Melvec, 1994; Byrne, 2002; Coricelli *et al.*, 2005) with the involvement of orbitofrontal cortex-amygdala circuits seeming to characterise anticipation of regret (Mellers *et al.*, 1999;

Table I Standardized weights from linear regression analysis with Impulsiveness in (a) ***Study I*** [$F_{(9,157)}$=5.26, p <0.001; Adjusted R_2=0.187], (b) ***Study II*** [$F_{(6,187)}$=3.34, p <0.01; Adjusted R_2=0.069], and (c) ***Study III*** [$F_{(4,316)}$= 24.69, p <0.001; Adjusted R_2=0.228], respectively, as dependent variable and Positive and Negative affect, internal and external locus of control, self-esteem, intrinsic motivation, identified regulation, external regulation and amotivation as independent variables.

(a) **Impulsiveness: Study I**

Predictor variable	Standardized Beta (β)
Amotivation	0.22**
Negative affect	0.15*
Internal locus of control	-0.17*

*p<0.05, **p<0.01. Predictor variables: Positive affect, intrinsic motivation, identified regulation, external regulation, external locus of control and self-esteem were non-significant.

(b) **Impulsiveness: Study II**

Predictor variable	Standardized Beta (β)
Amotivation	0.27**

**p <0.01, ***p <0.001. Predictor variables: Positive and negative affect, intrinsic motivation, identified regulation, external regulation, internal and external locus of control and self-esteem were non-significant.

(c) **Impulsiveness**: **Study III**

Predictor variable	Standardized Beta (β)
Negative affect	0.33***
Positive affect	-0.29***

*p <0.05, **p <0.01, ***p <0.001. Predictor variables: External locus of control almost reached significance, β = 0.11, p=0.6, but internal locus of control was non-significant.

Coricelli *et al.*, 2005). Additionally, affective appraisals and their eventual consequences may modulate particular mechanisms of cognitive-emotional control of choice processes, involving reinforcement or avoidance of the experienced behaviour, with selective activations of their underlying neural circuits (Bechara *et al.*, 1999; Peters and Slovic, 2000; Rustichini, 2005; Frank and Claus, 2006; LaBar and Cabeza, 2006; Steidl *et al.*, 2006; Coricelli *et al.*, 2007; Koenigs and Tranel, 2007). Against this conceptual and neuropathological context, it appears remarkable, that in three different analyses of reasonably healthy and normal individuals, to observe significant associations between high expressions of impulsiveness with negative emotions, almost nonexistent motivation (amotivation) and lack of ability to explain/expect events from one's own ability and efforts, which ought to provide a frighteningly disadvantageous prognosis for this substantial portion of the young population studied. Conversely, expressions of non-impulsiveness enjoyed strong causal links with positive affect, high levels of quality motivation, personal self-esteem and the expectancy of internal locus of

Table II Standardized weights from linear regression analysis with Non-impulsiveness in (a) ***Study I*** [$F_{(9,157)}$= 11.64, p <0.001; Adjusted R_2=0.366], (b) ***Study II*** [$F_{(6,187)}$=3.70, p <0.01; Adjusted R_2=0.078], and (c) ***Study III*** [$F_{(4,316)}$=34.09, p <0.001; Adjusted R_2=0.293], respectively, as dependent variable and Positive and Negative affect, internal and external locus of control, self-esteem, intrinsic motivation, identified regulation, external regulation and amotivation as independent variables.

(a) **Non-impulsiveness: Study I**

Predictor variable	Standardized Beta (β)
Positive affect	0.17*
Self-esteem	0.19*
Intrinsic motivation	0.20*
Identified regulation	0.20*

*p<0.05, **p<0.01. Predictor variables: Negative affect, external regulation and amotivation, internal and external locus of control were non-significant.

(b) **Non-impulsiveness: Study II**

Predictor variable	Standardized Beta (β)
Positive affect	0.20**
Amotivation	-0.15*

*p<0.05,**p<0.01. Predictor variables: Negative affect, intrinsic motivation, identified regulation and external regulation were non-significant.

(c) **Non-impulsiveness: Study III**

Predictor variable	Standardized Beta (β)
Positive affect	0.50***
Internal locus of control	0.17***

*p <0.05, **p <0.01, ***p <0.001. Predictor variables: Negative affect and external locus of control were non-significant.

control, all characteristics ensuring advantageous prognosis for successful choice behaviour and optimal decision-making.

According to Kalenscher *et al.* (2006), impulsiveness and self-control represent two antagonistic choice patterns with diametrically opposing outcomes, and yet present dispositions that govern future consequences of behaviours performed (Ainslie, 1975; Logue, 1988). As discussed above, the orbitofrontal and prefrontal regions appear intimately involved (*e.g.*, Dolan, 2007), although the notion that several other regions, such as the lateral prefrontal area and posterior parietal cortex, contributing for example to economical and rational planning, and time-reward trade-offs, offer different competing decision-making networks is also plausible (McClure *et al.*, 2004; Tanaka *et al.*, 2004; Sanfey *et al.*, 2006). The neuropharmacology of impulsiveness in decision-making implies some influence of dopaminergic neurotransmission whereby raclopride (DA D_2 antagonist) and flupenthixol and haloperidol (DA D_1/D_2 antagonists), but not SCH 23390 (DA D_1 antagonist) increased impulsive choice behaviour (Evenden, 1999; Cardinal *et al.*, 2000; Wade *et al.*, 2000). Additionally, serotonergic contributions have been well-documented in different species (Bizot *et al.*, 1999; Wolff and Leander, 2002). Winstanley *et al.* (2005) dissociated between serotonergic and dopaminergic modulation of rat medial prefrontal cortex and medial orbitofrontal cortex using microdialysis. Serotonin efflux was seen in the former not the latter, with increased 5-HT levels only under free-choice, but not under rewarded forced choice, conditions. Similarly, increased dopaminergic efflux in the medial orbitofrontal cortex was seen only after free choice conditions with increased DA efflux in the medial prefrontal cortex under both free and forced choice conditions. It was suggested that serotonin levels were associated with choice behaviour, not processing of response-outcome contingencies; on the other hand, DA levels in the medial orbitofrontal cortex were associated with choice behaviour with medial prefrontal cortex DA levels associated with response-outcome reward expectancies.

Several lines of evidence implicate serotonergic involvement in different expressions of impulsiveness: fighting and assault (Coccaro *et al.*, 1997), domestic violence (George *et al.*, 2001), suicidal behaviours (Ågren, 1980), low-lethality suicide attempts (Placidi *et al.*, 2001), patients with anger attacks (Fava *et al.*, 2000) and impulsive aggression among men (Cleare and Bond, 1997), generally relating to low serotonin function/availability (Evans *et al.*, 2000; Walderhaug *et al.*, 2002; Dolan and Anderson, 2004; Frankle *et al.*, 2005). Dolan *et al.* (2001) found low serotonin function associated with elevated impulsiveness and aggression, as well as to higher anxiety, but also to poorer executive function (Dolan *et al.*, 2002). Low serotonin functioning/efficacy, linked with low platelet monoamine oxidase (MAO) activity and the short (*S*) -allele of the serotonin transporter gene promotor region polymorphism (5-HTTLPR), has been linked to neuropathological aspects of impulsiveness (Schalling *et al.*, 1988; Hallikainen *et al.*, 1999; Gerra *et al.*, 2004; Baca-Garcia *et al.*, 2005; Clark *et al.*, 2005; Paaver *et al.*, 2006). Recently, Paaver *et al.* (2007) showed that low platelet MAO activity together with the carraige of the *S*-allele of the 5-HTTLPR were both associated with a higher error-rate and a more impulsive performance on a visual comparison task. Moreover, platelet MAO and the 5-HTTlPR *S*-allele had an interaction effects on the self-reported impulsiveness scale (BIS-11, above), *i.e.*, subjects with low platelet MAO activity carrying the *S*-allele of 5-HTTLPR showed the highest mean score for self-reported impulsiveness. Taken together, the consensus from several lines of evidence makes plausible links between serotonergic functioning and impulsiveness (Carver and Miller, 2006).

Motor and Learned Expressions: Explicit and Implicit Processes

Movement disorders and/or motor expressions of neuropsychiatric symptoms may be associated generally with neurological disease states but nevertheless the accounts rendered below serve to illustrate the utility of maintaining neurologic perspectives on psychiatry, and vice versa. DA, whether in nigrostriatal or mesolimbic pathways, contributes diversified multifunctional influences regarding motor behaviour, cognition, emotion and motivation. Gerlach *et al.* (2008) discuss the associations of the movement disorders with a broad spectrum of disorders defined

by inability to initiate movement, with hypokinetic disorders at one end of the scale, and conditions encompassing an exaggeration of motors behaviours, hyperkinetic disorders, at the other end of the scale; the former case was exemplified by Parkinson's disease and similar neurodegenerative conditions and the latter by a constellation of disorders such as Huntington's Chorea and Hemiballism but also other neuropsychiatric conditions like Tourette's syndrome, Lesch Nyhan's disease, ADHD and schizophrenia, often DA-glutamate interactions providing central features. All these disorder conditions directly or less directly reflect dysfunctional DA systems as the underlying pathophysiology in neuroanatomical, neurohumoral and neurobehavioural terms (Albin *et al.*, 1989; Mink, 2001; Biederman and Faraone, 2005; Carlsson, 2006; Björklund and Dunnett, 2007; Iversen and Iversen, 2007; Schultz, 2007; van der Kooij and Glennon, 2007). One fundamental issue highlighted in this account pertained to utility of distinctions between psychiatry and neurology but rather the further development of neurobiological approaches. It seems remarkable that several motor features associated, *e.g.*, with Tourette's syndrome, Lesch-Nyhan disease, schizophrenia and ADHD, involve multiple features of dopaminergic dysfunction (*e.g.*, Girault and Greengard, 2004; Cortese *et al.*, 2005).

Kostrzewa and co-workers (2007) maintained this broad neurobiological theme in exploring DA-receptor sensitivity in relation to stereotypic motor behaviours, in particular vacuous chewing movements (VCMs) and locomotion. They presented a series of results illustrating the influence of lesioning presynaptic terminals (*e.g.*, applying postnatal 6-hydroxydopamine) or prolonged receptor antagonist action combined with acute administrations of DA D_1 or DA D_2 agonist to elicit the behavioural responses. They suggested that DA receptor sensitivity and stereotypy may reflect receptor subsensitivity and/or modulation by receptor co-sensitization of another phenotype.

Youdim (2008) reviewed the iron-deficiency syndrome, a condition described by defective brain dopaminergic-opiate system functioning with regard to circadian behaviours, cognition and the neurohumoral alterations associated with its neuropathology (Hallgren and Sourander, 1958; Werkman *et al.*, 1964; Dallman *et al.*, 1975; Youdim and Green, 1977; Ben-Shachar *et al.*, 1986; Lozoff and Brittenham, 1986; Yehuda and Youdim, 1984; Yehuda *et al.*, 1986; Youdim *et al.*, 1986; 1989; 2000; Youdim and Yehuda, 2000). Recent studies have established that the cognitive impairments may be associated with neuroanatomical damage and zinc metabolism in the hippocampus as a result of iron-deficiency (Shoham *et al.*, 1996; Shoham and Youdim, 2000; Zecca *et al.*, 2004). In consensus, these studies and several other studies aimed at symptom definition and drug therapy, have prompted the development of the fashionably plausible contention, "dirty drugs for dirty diseases", currently an appealing concept in drug development, through descriptions of neurotoxic events, *e.g.*, oxidative stress, excitotoxicity, inflammatory processes, brain iron dysregulation, etc. in the neurodegenerative disorders and the new therapeutic strategies under development. Here, candidate drugs have been designed to act on multiple neural and biochemical targets, combining cholinesterase inhibition, monoamine oxidase inhibition, iron chelation, inhibition of glutamate release and anti-apoptotic neurorescue activity. These diverse activities were tested over a variety of animal and *in vitro* models as well as in transgenic mice. Thus, by exemplifying the iron-deficiency syndrome from functional and neurochemical perspectives the notion of multiple neurotransmitter systems underlying symptom-profiles was illustrated.

Beninger and Banasikowski (2008) reviewed DA D_3 receptor modulation of the effects of self-administered drugs on reward-rich and lean schedules, in reinstatement tests, second order schedules and acquisition and expression of conditioned place preference (CPP) and conditioned activity (Aujla and Beninger, 2004; 2005; Xi *et al.* 2006; Vazquez *et al.*, 2007). They discuss the acquisition and expression of incentive learning in relation to the role of DA (*cf.*, Beninger, 1983). Thus, a consensus of evidence highlights the position that DA acting via D_1-like and D_2 receptors is critical for acquisition. Using a conditioned activity procedure based on cocaine it was found that DA D_2 and DA D_3 receptors function differently, presenting a double dissociation with D_2 receptors necessary for *establishment*, but not *expression* (initial), of conditioned

activity; conversely, D_3 receptors were necessary for *expression* but not *establishment*. Results imply that Drd3 exert a greater influence upon the expression than in the establishment of the CPP or conditioned activity. Although the mechanism through which Drd3 modulates control of responding by conditioned incentive stimuli awaits elucidation, it has been found that the population of these receptors in the nucleus accumbens increases during conditioning.

Dopaminergic involvement is implicated in complex cognition, *e.g.*, DA D_1 and D_3 receptors are involved in working memory and other aspects of prefrontal function (Williams and Goldmam-Rakic, 1995; Glickstein *et al.*, 2002; Di Cara *et al.*, 2007). Recently, Lane *et al.* (2008) studied prefrontal executive functioning and DA D_1, D_3, 5-HT_{2A} and 5-HT_6 receptor gene variations in 216 healthy Han Chinese adults using the Wisconsin Card Sorting Test and genotyping for the four genetic variations. There was a significant difference in perseverative errors among the genotypes D_3 Ser9Gly, 5-HT_{2A} T102C and 5-HT_6 T267C but not D_1 A-48G, suggesting that these polymorphisms may contribute to prefrontal executive cognition. Symptoms derived from dysfunctioning in cognitive systems appear central to many expressions of neuropathology. The liability for cognitive deficits, including impairment of episodic memory, the explicit, conscious memory for spatial and temporal contexts of personally experienced events, associated with chronic, heavy alcohol abuse has been well documented (Horner *et al.*, 1999; Fox *et al.*, 2000; Sullivan *et al.*, 2000; Goldstein *et al.*, 2004). It has been shown too that acute alcohol consumption significantly reduces conscious recollection (Curran and Hildebrandt, 1999; Duka *et al.*, 2001). Aspects of explicit, conscious memory processes may be impaired in other respects. For example, models of working memory employ a central executive (*cf.*, Baddeley and Hitch, 1974; Baddeley, 2003), purported to own similar properties to executive functioning, *e.g.*, abstract thinking and planning, which is defective in chronic alcoholism (Ambrose *et al.*, 2001; Brokate *et al.*, 2003; Fama *et al.*, 2004; Oscar-Berman *et al.*, 2004; Zinn *et al.*, 2004). Since executive functioning appears to contribute importantly to episodic memory (Kramer *et al.*, 2005; Davidson *et al.*, 2006), defective executive functioning in chronic alcoholism ought to result in episodic memory deficits. Recently, Pitel *et al.* (2007) assessed episodic memory (tasks measuring learning, storage, encoding and retrieval, contextual memory and autonoetic consciousness components) and executive functioning (tests of organisation, inhibition, flexibility, updating and integration capability) in forty recently detoxified alcoholic inpatients and fifty-five group-matched healthy controls. They found that the alcoholic patients displayed impaired cognitive and learning abilities compared with the healthy control, including both encoding and retrieval processes, contextual memory and autonoetic consciousness, the phenomenon underlying remembering in the sense of self-recollection in the 'mental re-enactment' of previous events at which the individual was present (*cf.*, Gardiner, 2001), thereby involving episodic memory. It is distinguished from noetic consciousness, which ensures awareness of the past that is limited to feelings of familiarity of knowing, and is identified with semantic memory, involving general knowledge. One approach to episodic memory utilising 'first-person' reports of remembering thereby allowing the most elusive aspect of consciousness, its subjectivity, can be investigated scientifically. The alcoholic subjects showed deficits in each of the executive tasks applied. Pitel *et al.* (2007) concluded that these patients with chronic alcoholism presented genuine deficits of episodic memory distinct from the eventual consequences of executive dysfunctioning, implying an association with neuroimaging studies involving hippocampal atrophy in chronic alcoholism (Agartz *et al.*, 1999; Bleich *et al.*, 2003; Beresford *et al.*, 2006).

The pursuit of a symptom rationale preliminary to the neuropathology of disorder ought necessarily to be linked with analyses of biomarkers, in the present case in the particular context of cognition and the plasticity incorporated in the biochemistry of neuronal events. Sutton and co-workers (*e.g.*, Sutton *et al.*, 2004; 2006; Sutton and Schuman, 2005; 2006) have demonstrated that mode of neurotransmission may exert much influence on ongoing protein synthesis in dendrites, posing the ques-

tion: how does one maintain the stability of activation in neural circuits? Recently, it was described that local dendritic protein synthesis was implicated in many types of synaptic plasticity with regard to how neurotransmission affects ongoing protein synthesis in dendrites. Thus, the tetrodotoxin-blockade of intrinsic action potential mediated network activity in cultured hippocampal neurons inhibited the dendritic synthesis of a fluorescence translation reporter, with ongoing spontaneous neurotransmitter release bidirectionally regulating dendritic protein synthesis. Sutton *et al.* (2007) identified eukaryotic elongation factor-2 (eEF2), catalyzing ribosomal translocation during protein synthesis, a biochemical sensor in dendrites specifically and locally tuned to the quality of neurotransmission. The phosphorylation of eEF2 at Thr56 inhibits its activity thereby inhibiting protein synthesis (Redpath *et al.*, 1993). The phosphorylation of eEF2 is stimulated by strong activation of ionotropic glutamate receptors (Chotiner *et al.*, 2003), and regulated in isolated synaptic biochemical fractions (Scheetz *et al.*, 2000; Carroll *et al.*, 2004). Sutton *et al.* (2007) have shown that intrinsic action potential (AP)-mediated network activity in cultured hippocampal neurons maintains eEF2 in a relatively dephosphorylated (active) state whereas spontaneous neurotransmitter release (miniture neurotransmission) promotes markedly the phosphorylation (and inactivation) of eEF2. They indicate that eEF2 is a biochemical sensor that couples miniature synaptic events to local translational suppression in neuronal dendrites. Note that strong NMDA receptor stimulation induces several biochemical changes that promote translation initiation (Kelleher *et al.*, 2004; Gong *et al.*, 2006).

A symptom-based strategy presupposes the operational assessment of presenting symptoms along with available measures of biomakers, neuroimaging, etc., in characterizations of neuropathological states; as yet, much effort has been squandered within the constraining enclosures of diagnostic labyrinths. The present treatise attempts to explore neuropathological expressions of ongoing proximal realities of symptoms and syndromes with underlying dysfunctionality of brain regions, circuits and molecular mechanisms.

References

Agartz I, R Momenan, RR Rawlings, MJ Kerich and DW Hommer (1999) Hippocampal volume in patients with alcohol dependence. *Arch. Gen. Psychiatr.* **56**, 356-363.

Ågren (1980) Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolites in the cerebrospinal fluid: II. Suicide. *Psychiatry Res.* **3**, 225-236.

Ainslie G (1975) Specious reward: a behavioural theory of impulsiveness and impulse control. *Psychol. Bull.* **82**, 463-496.

Albin RL, AB Young and JB Penney (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci.* **12**, 366-375.

Ambrose ML, SC Bowden and G Whelan (2001) Working memory impairments in alcohol-dependent participants without clinical amnesia. *Alcohol Clin. Exp. Res.* **25**, 185-191.

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, Fourth Edition (DSM-IV). Washington, DC: APA.

Anderson SW, A Bechara, H Damasio, D Tranel and AR Damasio (1999) Impairment of social and moral behaviour related to early damage of human prefrontal cortex. *Nat. Neurosci.* **2**, 1032-1037.

Andersson G (1976) Internal-external locus of control: some methodological notes on the research and a factor analysis of a revised I-E scale. *Department of Psychology Reports, University of Göteborg* **9**, 1.

Archer T, B Adolfsson and E Karlsson (2008) Affective personality as cognitive-emotional presymptom profiles regulatory for self-reported health predispositions. *Neurotox. Res.* **14**, 21-44.

Aujla H and Beninger RJ (2004) Intra-BLA or intra-Nac infusions of the dopamine D_3 receptor partial agonist, BP 897, block intra-Nac amphetamine conditioned activity. *Behav. Neurosci.* **118**, 1324-1330.

Aujla H and RJ Beninger (2005) The dopamine D_3 receptor-preferring partial agonist BP 897 dose-dependently attenuates the expression of amphetamine-conditioned place preference in rats. *Behav. Pharmacol.* **16**, 181-186.

Baca-Garcia E, BR Salgadoa, HD Segala, CV Lorenzo, MN Acosta, MA Romeroa, MD Hernandez, JS Ruiza, JF Piqueras and J de Leone (2005) A pilot genetic study of the continuum between compulsivity and impulsivity in females: the serotonin transporter promotor polymorphism. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **29**, 713-717.

Baddeley A (2003) Working memory: looking back and looking forward. *Nat. Rev. Neurosci.* **4**, 829-839.

Baddeley A and G Hitch (1974) Working memory, In: *The Psychology of Learning and Motivation* Vol. **8** (Bower G, Ed.) (Academic Press:New York), pp 47-89.

Baker DJP, JG Eriksson, T Forsen and C Osmond (2002) Fetal origins of adult disease: strength of effects and biological basis. *Int. J. Epidemiol.* **31**, 1235-1239.

Balodis IM, TK MacDonald and MC Olmstead (2006) Instructional cues modify performance on the Iowa Gambling Task. *Brain Cogn.* **60**, 109-117.

Barratt ES, MS Stanford, TA Kent and A Felthous (1997) Neuropsychological and cognitive psychophysiological sub-

strates of impulsive aggression. *Biol. Psychiatry* **41**, 1045-1061.

Bateson P, D Barker, T Clutton-Brock, D Deb, B D'Udine, RA Foley, P Gluckman, K Godfrey, T Kirwood, MM Lahr, J McNamara, NB Metcalfe, P Monaghan, HG Spencer and SE Sultan (2004) Developmental plasticity and human health. *Nature* **430**, 419-421.

Bechara A (2005) Decision making, impulse control, and loss of willpower to resist drugs: a neurocognitive perspective. *Nat. Neurosci.* **8**, 1458-1463.

Bechara A and H Damasio (2002) Decision-making and addiction: impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* **40**, 1675-1689.

Bechara A, AR Damasio, H Damasio and SW Anderson (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**, 7-15.

Bechara A, D Tranel, H Damasio and AR Damasio (1996) Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb. Cortex* **6**, 215-225.

Bechara A, H Damasio, D Tranel and AR Damasio (1997) Deciding advantageously before knowing the advantageous strategy. *Science* **275**, 1293-1295.

Bechara A, H Damasio, AR Damasio and GP Lee (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J. Neurosci.* **19**, 5473-5481.

Bechara A, D Tranel and AR Damasio (2000) Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* **123**, 2189-2202.

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

Bechara A, H Damasio, D Tranel and AR Damasio (2005) The Iowa Gambling Task and the somatic marker hypothesis: some questions and answers. *Trends Cogn. Sci.* **9**, 159-162.

Bell DE (1982) Regret in decision-making under uncertainty. *Oper. Res.* **30**, 961-981.

Beninger RJ (1983) The role of dopamine in locomotor activity and learning. *Brain Res. Rev.* **6**, 173-196.

Beninger RJ and TJ Banasikowski (2008) Dopaminergic mechanism of reward-related incentive learning: focus on the D_3 receptor. *Neurotox. Res.* **14**, 57-70.

Ben-Shachar D, R Ashkenazi and MBH Youdim (1986) Long term consequences of early iron-deficiency on dopaminergic neurotransmission. *Int. J. Dev. Neurosci.* **4**, 81-88.

Beresford TP, DB Arciniegas, J Alfers, L Clapp, B Martin, Y Du, D Liu, D Shen and C Davatzikos (2006) Hippocampus volume loss due to chronic heavy drinking. *Alcohol Clin. Exp. Res.* **30**, 1866-1870.

Biederman J and SV Faraone (2005) Attention-deficit hyperactivity disorder. *Lancet* **366**, 237-248.

Birbaumer N, R Veit, M Lotze, C Hermann, W Grodd and H Flor (2005) Deficient fear conditioning in psychopathy. A functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* **62**, 799-805.

Bizot L, C Le Bihan, AJ Peuch, M Harnon and M Thiebot (1999) Serotonin and tolerance to delay of reward in rats. *Psychopharmacology* **146**, 400-412.

Björklund A and SB Dunnett (2007) Dopamine neuron systems in the brain: an update. *Trends Neurosci.* **30**, 194-202.

Bleich S, W Sperling, D Degner, E Graesel, K Bleich, J Wilhelm, U Havemann-Reinecke, K Javaheripour and J Kornhuber (2003) Lack of association between hippocampal volume reduction and first-onset alcohol withdrawal seizure. A volumetric MRI study. *Alcohol Alcohol.* **38**, 40-44.

Blumberg HP, HC Leung, P Skudlarski, CM Lacadie, CA Fredericks, BC Harris *et al.* (2003) A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Arch. Gen. Psychiatry* **60**, 601-609.

Bood SÅ, T Archer and T Norlander (2004) Affective personality in relation to general personality, self-reported stress, coping and optimism. *Individ. Diff. Res.* **2**, 26-37.

Bowman CH, CEY Evans and OH Turnbull (2005) Artificial time constraints on the Iowa Gambling Task: the effects on behavioural performance and subjective experience. *Brain Cogn.* **57**, 21-25.

Braff DL and MA Geyer (1990) Sensorimotor gating and schizophrenia: human and animal model studies. *Arch. Gen. Psychiatry* **47**, 181-188.

Braff DL, MA Geyer and NR Swerdlow (2001) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* **156**, 234-258.

Breslin FC, MB Sobell, H Cappell, S Vakili and CX Poulos (1999) The effects of alcohol, gender and sensation-seeking on the gambling choices of social drinkers. *Psychol. Addict. Behav.* **13**, 243-252.

Brokate B, H Hildebrandt, P Eling, H Fichtner, K Runge and C Timm (2003) Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: continuity or discontinuity? *Neuropsychology* **17**, 420-428.

Bulik CM, PF Sullivan, FA Carter and PR Joyce (1997) Lifetime comorbidity of alcohol dependence in women with bulimia nervosa. *Addict. Behav.* **22**, 437-446.

Byrne RM (2002) Mental models and counterfactual thoughts about what might have been. *Trends Cogn. Sci.* **6**, 426-431.

Cardinal RN, TW Robbins and BJ Everitt (2000) The effects of d-amphetamine, chlordiazepoxide, α-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delated reinforcement in rats. *Psychopharmacol*ogy **152**, 362-375.

Carlsson A (2006) The neurochemical circuitry in schizophrenia. *Pharmacopsychiatry* **39** [Suppl. 1], S10-S14.

Carroll M, O Warren, X Fan and WS Sossin (2004) 5-HT stimulates eEF2 dephosphorylation in a rapamycin-sensitive manner in Aplysia neurites. *J. Neurochem.* **90**, 1464-1476.

Carver CS (2005) Impulse and constraint: perspectives from personality psychology, convergence with theory in other areas, and potential for integration. *Pers. Soc. Psychol. Rev.* **9**, 312-333.

Carver CS and CJ Miller (2006) Relations of serotonin function to personality: current views and a key methodological issue. *Psychiatr. Res.* **144**, 1-15.

Chotiner JK, H Khorasani, AC Nairn, TJ O'Dell and JB Watson

(2003) Adenylyl cyclase-dependent form of chemical long-term potentiation triggers translational regulation at the elongation step. *Neuroscience* **116**, 743-752.

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

Chun MM (2005) Drug-induced amnesia impairs implicit relational memory. *Trends Cogn. Sci.* **9**, 355-357.

Chun MM and Y Jiang (2003) Implicit, long-term spatial contextual memory. *J. Exp. Psychol. Learn. Mem. Cogn.* **29**, 224-234.

Chun MM and EA Phelps (1999) Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. *Nat. Neurosci.* **2**, 844-847.

Cilia J, PD Hatcher, C Reavill and DNC Jones (2005) Long-term evaluation of isolation-rearing induced prepulse inhibition deficits in rats: an update. *Psychopharmacology* **180**, 57-62.

Clark L, R Cools and TW Robbins (2004) The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. *Brain Cogn.* **55**, 41-53.

Clark L, JP Roiser, R Cools, DC Rubinsztein, BJ Sahakian and TW Robbins (2005) Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. *Psychopharmacology* **182**, 570-578.

Cleare AJ and AJ Bond (1997) Does serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. *Psychiatr. Res.* **69**, 89-95.

Coccara EF, RJ Kavoussi, TB Cooper and RL Hauger (1997) Central serotonin activity and aggression: inverse relationship to prolactin response to D-fenfluramine, but not CSF 5-HIAA concentration. *Am. J. Psychiatry* **154**, 1430-1435.

Coricelli G, HD Critchley, M Joffily, JP O'Doherty, A Sirigu and RJ Dolan (2005) Regret and its avoidance: a neuroimaging study of choice behaviour. *Nat. Neurosci.* **8**, 1255-1262.

Coricelli G, RJ Dolan and A Sirigu (2007) Brain, emotion and decision making: the paradigmatic example of regret. *Trends Cogn. Sci.* **11**, 258-265.

Cortese L, MP Caligiuri, AK Malla, R Manchanda, J Takhar and R Haricharan (2005) Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr. Res.* **75**, 65-75.

Csomor PA, RR Stadler, J Feldon, BK Yee, MA Geyer and FX Vollenweider (2008) Haloperidol differentially modulates prepulse inhibition and P50 suppression in healthy humans stratified for low and high gating levels. *Neuropsychopharmacol*. **33**(3), 497-512. Epub 2007 Apr 25.

Cuesta MJ, MD Ugarte, T Goicoa, T Goicoa, S Eraso and V Peralta (2007) A taxometric analysis of schizophrenia symptoms. *Psychiatr. Res.* **150**, 245-253.

Curran HV and M Hildebrant (1999) Dissociative effects of alcohol on recollective experience. *Conscious Cogn.* **8**, 497-509.

Dallman PR, MA Siimes and EC Manies (1975) Brain iron: persistent deficiency following short-term iron deprivation in the young rat. *Br. J. Haematol.* **31**, 209-215.

Damasio AR (1998) The somatic marker hypothesis and the possible functions of the prefrontal cortex, In: *The Prefrontal Cortex. Executive and Cognitive Functions* (Roberts AC, TW Robbins and L Weiskrantz, Eds.) (Oxford University Press:Oxford), pp 36-50.

Damasio AR (2000) A neural basis for sociopathy. *Arch. Gen. Psychiatry* **57**, 128-129.

Davidson PS, AK Troyer and M Moscovitch (2006) Frontal lobe contributions to recognition and recall: linking basic research with clinical evaluation remediation. *J. Int. Neuropsychol. Soc.* **12**, 210-223.

Deci EL and RM Ryan (1985) *Intrinsic Motivation and Self-Determination in Human Behaviour* (Plenum:New York).

Deci EL and RM Ryan (1991) A motivational approach to self: integration in personality, In: *Nebraska Symposium on Motivation*, vol. **38**. *Perspectives on Motivation* (Dienstbier R, Ed.) (University of Nebraska Press:Lincoln, NE), pp 237-288.

DeMartino B, D Kumaran, B Seymour and RJ Dolan (2006) Frames, biases, and rational decision-making in the human brain. *Science* **313**, 684-687.

Denburg NL, D Tranel and A Bechara (2005) The ability to decide advantageously declines prematurely in some normal older adults. *Neuropsychologia* **43**, 1099-1106.

Di Cara B, F Panayi, A Gobert, a Dekeyne, D Sicard, L De Groote and MJ Millan (2007) Activation of D_1 receptors enhances cholinergic transmission and social cognition: a parallel dialysis and behavioural study in rats. *Int. J. Neuropsychopharmacol.* **10**, 383-399.

Dolan MC and IM Anderson (2004) The relationship between serotonergic function and the Psychopathy Checklist: screening version. *J. Psychopharmacol.* **17**, 216-222. Dolan MC and I Park (2002) The neuropsychology of antisocial personality disorder. *Psychol. Med.* **32**, 417-427.

Dolan MC, IM Anderson and JFW Deakin (2001) Relationship between 5-HT function and impulsivity and aggression in male offenders with personality disorder. *Br. J. Psychiatry* **178**, 352-359.

Dolan MC, JFW Deakin, N Roberts and IM Anderson (2002) Serotonergic and cognitive impairment in impulsive aggressive personality disordered offenders: are there implications for treatment? *Psychol. Med.* **32**, 105-117.

Dolan RJ (2007) Keynote address: revaluing the orbital prefrontal cortex. *Ann. NY Acad. Sci.* **1121**, 1-9.

Duka T, R Weissenborn and Z Dienes (2001) State-dependent effects of alcohol on recollective experience, familiarity and awareness of memories. *Psychopharmacol*. **153**, 295-306.

Ekelund J, I Hovatta, A Parker, T Paunio, T Varilo, R Martin, J Suhonen, P Ellonen, G Chan, JS Sinsheimer, E Sobel, H Juvonen, R Arajärvi, T Partonen, J Suvisisaari, J Lönnqvist, J Meyer and L Peitonen (2001) Chromosome 1 loci in Finnish schizophrenia families. *Hum. Mol. Genet.* **10**, 1611-1617.

Epstein S (1994) Integration of the cognitive and the psychodynamic unconscious. *Am. Psychol.* **49**, 709-724.

Erbin-Roesemann MA and L Simms (1997) Work locus of control: the intrinsic factor behind empowerment and work excitement. *Nursing Econom.* **15**, 183-190.

Evans J, H Platts, S Lightman and D Nutt (2000) Impulsive-ness and the prolactin response to d-fenfluramine. *Psychopharmacology* **149**, 147-152.

Evenden JL (1999) Varieties of impulsivity. *Psychopharmacology* **146**, 348-361.

Fama R, A Pfefferbaum and EV Sullivan (2004) Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function and age. *Alcohol Clin. Exp. Res.* **28**, 1657-1665.

Fava M, RD Vuolo, EC Wright, AA Nierenberg, JE Alpert and JF Rosenbaum (2000) Fenfluramine challenge in unipolar depression with and without anger attacks. *Psychiatr. Res.* **94**, 9-18.

Fellows LK and MJ Farah (2005) Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cereb. Cortex* **15**, 58-63.

Fossati A, A Di Ceglia, E Acquarini and ES Barratt (2001) Psychometric properties of an Italian version of the Barratt Impulsiveness Scale-11 (BIS-11) in nonclinical subjects. *J. Clin. Psychol.* **57**, 815-828.

Fox AM, M Coltheart, N Solowij, PT Michie and GA Fox (2000) Dissociable cognitive impairments in problem drinkers. *Alcohol Alcohol.* **35**, 52-54.

Frangou S, V Raymont, J Kingston and SS Shergill (2003) Investigating the functional interface between dorsal and ventral prefrontal circuitry in bipolar disorder. *Bipolar Disord.* **5**, 47-48.

Frank MJ and ED Claus (2006) Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making and reward. *Psychol. Rev.* **113**, 300-326.

Frankle WG, I Lombrdo, AS New, M Goodman, PS Talbot, Y Huang, D Hwang, M Slifstein, S Curry, A Abi-Dargham, M Laurelle and LJ Siever (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [^{11}C]McN 5652. *Am. J. Psychiatry* **162**, 915-923.

Gardiner HG (1971) Utilization of corpsmen in the occupational health setting. *Occup. Health Nurs.* **19**, 23-25

Gennaro RJ, DJ Herrmann and M Sarapata (2006) Aspects of the unity of consciousness and everyday memory failures. *Consciousness Cogn.* **15**, 372-385.

George DT, JC Umhau, MJ Phillips, D Emmela, PW Ragan, SE Shoaf and RR Rawlings (2001) Serotonin, testosterone, and alcohol in the etiology of domestic violence. *Psychiatr. Res*. **104**, 27-37.

Gerlach M, P Riederer, C Mehler-Wex and A Warnke (2008) Dopamine dysfunctions in motor abnormalities linked to neurological diseases and psychiatric disorders, In: *Beyond Neuropsychiatric Diagnostics: Symptoms Not Disorders* (Palomo T, RJ Beninger, RM Kostrzewa and T Archer, Eds.) (Fundación Cerebro y Mente:Madrid, Spain) (in press).

Gerra G, L Garofano, G Santoro, S Bosari, C Pellegrini, A Ziamovic, G Moi, M Bussandri, A Moi, F Brambilla and C Donnini (2004) Association between low activity serotonin transporter promotor genotype and heroin dependence: behavioural and personality correlates. *Am. J. Med. Genet.* **126**, 37-42.

Geyer MA (2006) Are cross-species measures of sensorimotor gating useful for the discovery of precognitive cotreatments for schizophrenia? *Dialog Clin. Neurosci.* **8**, 9-16.

Geyer MA (2008) Geyer MA (2008) Developing translational animal models for symptoms of schizophrenia or bipolar mania. *Neurotox. Res.* **14**, 71-78.

Geyer MA, KL McIlwain and R Paylor (2002) Mouse genetic models for prepulse inhibition: an early review. *Mol. Psychiatry* **7**, 1039-1053.

Gilovich T and VH Melvec (1994) The temporal pattern to the experience of regret. *J. Pers. Soc. Psychol.* **67**, 357-365.

Girault J-A and P Greengard (2004) The neurobiology of dopamine signalling. *Arch. Neurol.* **61**, 641-644.

Glickstein SB, PR Hof and C Schmauss (2002) Mice lacking dopamine D_2 and D_3 receptors have spatial working memory deficits. *J. Neurosci.* **22**, 5619-5629.

Goldstein RZ, AC Leskovjan, AL Hoff, R Hitzemann, F Bashan, SS Khalsa, GJ Wang, JS Fowler and ND Volkow (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia* **42**, 1447-1458.

Gong R, CS Park, NR Abbassi and SJ Tang (2006) Roles of glutamate receptors and the mammalian target of rapamycin (mTOR) signaling pathway in activity-dependent dendritic protein synthesis in hippocampal neurons. *J. Biol. Chem.* **281**, 18802-18815.

Grant S, C Contoreggi and ED London (2000) Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* **38**, 1180-1187.

Guay F, RJ Vallerand and C Blanchard (2000) On the assessment of Situational Intrinsic and Extrinsic Motivation: the Situational Motivation Scale (SIMS). *Motiv. Emot.* **24**, 175-213.

Gutbrod K, C Krouzel, H Hofer, R Muri, W Perrig and R Ptak (2006) Decision-making in amnesia: Do advantageous decisions require conscious knowledge of previous behavioural choices? *Neuropsychologia* **44**, 1315-1324.

Hallgren B and P Sourander (1958) The effect of age on the non-haem iron in the human brain. *J. Neurochem.* **3**, 41-51.

Hallikainen T, T Saito, HM Lachman, J Volavka, T Pojhanen, J Kauhanen, E Syvälahti, J Hietala and J Tihonen (1999) Association between low activity serotonin transporter promotor genotype and early onset akcoholism with habitual impulsive violent behaviour. *Mol. Psychiatry* **4**, 385-388.

Hare RD and MJ Quinn (1971) Psychopathy and autonomic conditioning. *J. Abnormal Psychol.* **77**, 223-235.

Hare RD, J Frazelie and DN Cox (1978) Psychopathy and physiological responses to threat of an aversive stimulus. *Psychophysiol*ogy **15**, 165-172.

Henry JC, T van Amelsvoort, RG Morris, MJ Owen, DGM Murphy and KC Murphy (2002) An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). *Neuropsychologia* **40**, 471-478.

Hinson JM, TL Jameson and P Whitney (2002) Somatic markers, working memory, and decision-making. *Cogn Affect Behav. Neurosci.* **2**, 341-353.

Hirshman E, A Passannante and A Henzler (1999) The effect of midazolam on implicit memory tests. *Brain Cogn.* **41**, 351-364.

Horner MD, LR Waid, DE Johnson, PK Latham and RF Anton (1999) The relationship of cognitive functioning to amount of recent and lifetime alcohol consumption in outpatient alcoholics. *Addict. Behav.* **24**, 449-453.

Hsu M, M Bhatt, R Adolphs, D Tranel and CF Camerer (2005) Neural systems responding to degrees of uncertainty in human decision-making. *Science* **310**, 1680-1683.

Huebner ES and T Dew (1995) Preliminary validation of the positive and negative affect schedule with adolescents. *J. Psycho.-Educ. Assess.* **13**, 286-293.

Huettel SA, CJ Stowe, EM Gordon, BT Warner and ML Platt (2006) Neural signatures of economic preferences for risk and ambiguity. *Neuron* **49**, 765-775.

Hwu HG, CM Liu, CSJ Fann, WC Ou-Yang and SFC Lee (2003) Linkage of schizophrenia with chromosome 1q loci in Taiwanese families. *Mol. Psychiatry* **8**, 445-452.

Iversen SD and LL Iversen (2007) Dopamine: 50 years in perspective. *Trends Neurosci.* **30**, 188-193.

Kalenscher T, T Ohmann and O Gunturkun (2006) The neuroscience of impulsive and self-controlled decisions. *Int. J. Psychophysiol.* **62**, 203-211.

Keilp JG, HA Sackeim and JJ Mann (2005) Correlates of trait impulsiveness in performance measures and neuropsychological tests. *Psychiatr. Res.* **135**, 191-201.

Kelleher RJ, A Govindarajan, HY Jung, H Kang and S Tonegawa (2004) Translational control by MAPK signalling in long-term synaptic plasticity and memory. *Cell* **116**, 467-479.

Koenigs M and D Tranel (2007) Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimate Game. *J. Neurosci.* **27**, 951-956.

Kostrzewa RM, N-Y Huang, JP Kostrzewa, P Nowak and R Brus (2007) Modeling tardive dyskinesia: predictive 5-HT_{2C} receptor antagonist treatment. *Neurotox. Res*. **11**, 41-50.

Kramer JH, HJ Rosen, AT Du, N Schuff, C Hollnagel, MW Weiner, BL Miller and DC Delis (2005) Dissociations in hippocampal and frontal contributions to episodic memory performance. *Neuropsychol*. **19**, 799-805.

Kyngdon A and M Dickerson (1999) An experimental study of the effect of prior alcohol comsumption on a simulated gambling activity. *Addict*. **94**, 697-707.

LaBar KS and r Cabeza (2006) Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* **7**, 54-64.

Lajiness-O'Neill R, I Beaulieu, A Asamoah, JB Titus, E Bawle, S Ahmad, JW Kirk and R Pollack (2006) The neurospychological phenotype of velocardiofacial syndrome (VCFS): relationship to psychopathology. *Arch. Clin. Neuropsychol.* **21**, 175-184.

Lane H-Y, Y-C Liu, C-L Huang, C-L Hsieh, Y-L Chang, L Chang, Y-C Chang and W-H Chang (2008) Prefrontal executive function and D_1, D_3, 5-HT_{2A} and 5-HT_6 receptor gene variations in healthy adults. *J. Psychiatr. Neurosci.* **33**, 47-53.

Lefcourt HM (1991) Locus of control, In: *Measures of Personality and Social Psychology*, Vol. **1** (Robinson C, P Shaver & L Wrightman, Eds.) (Academic Press: San Diego, CA), pp 552-569.

Lemaire V, M Koehl, M Le Moal and DN Abrous (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc. Natl. Acad. Sci. USA* **97**, 11032-11037.

Le Moal M, M Koehl, M Vallée, V Lemaire, S Maccari and N Abrous (2008) From integrative and behavioural neurosciences to experimental psychopathology. Theoretical considerations, In: *Beyond Neuropsychiatric Diagnostics: Symptoms Not Disorders* (Palomo T, RJ Beninger, RM Kostrzewa and T Archer, Eds.) (Fundación Cerebro y Mente:Madrid, Spain) (in press).

Levenson H (1974) Activism and powerful others: distinctions within the concept of internal-external locus of control. *J. Person. Assess.* **38**, 377-383.

Li CR and S-H Chen (2007) Obsessive-compulsiveness and impulsivity in a non-clinical population of adolescent males and females. *Psychiatr. Res.* **149**, 129-138.

Lilienfeld SO and BP Andrews (1996) Development and preliminary validation of of a self-report measure of psychopathic personality traits in noncriminal populations. *J. Pers. Assess.* **66**, 488-524.

Logue AW (1988) Research on self-control: an integrating framework. *Behav. Brain Sci.* **11**, 665-709.

Lozoff B and GM Brittenham (1986) Behavioural aspects of iron deficiency. *Prog. Hematol.* **14**, 23-53.

Lykken DT (1957) A study of anxiety in the sociopathic personality. *J. Abnorm. Soc. Psychol.* **55**, 6-10.

Lynskey MT and W Hall (2001) Attention deficit hyperactive disorder and substance use disorders: is there a causal link? *Addict*. **96**, 815-822.

Majerus S, M Van der Linden, V Braissand and S Eliez (2007) Verbal short-term memory in individuals with chromosome 22q11.2 deletion: specific deficit in serial order retention capacities. *Am. J. Ment. Retard.* **112**, 79-93.

Manes F, B Sahakian, L Clark, R Rogers, N Antoun, M Aitken and TW Robbins (2002) Decision-making processes following damage to the prefrontal cortex. *Brain* **125**, 624-639.

Manns JR and LR Squire (2001) Perceptual learning, awareness, and the hippocampus. *Hippocampus* **11**, 776-782.

Matsuura M, N Adachi, Y Oana, Y Okubo, M Kato, T Nakano and N Takei (2004) A polydiagnostic and dimensional comparison of epileptic psychoses and schizophrenia spectrum disorders. *Schizophr. Res.* **69**, 189-201.

McClure SM, DI Laibson, G Loewenstein and JD Cohen (2004) Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503-507.

Metcalfe J and W Mischel (1999) A hot/cool-systems analysis of delay of gratification: dynamics of willpower. *Psychol. Rev.* **106**, 3-19.

Millet P (2005) Locus of control and its relation to working life: studies from the fields of vocational rehabilitation and small firms in Sweden. Doctoral Dissertation, Arbetslivsinstitutet [Work life Institute], Luleå Technical University, Luleå, Sweden.

Millet P and K Sandberg (2003) Locus of control and its relationship with rehabilitation outcomes of unemployed sick leavers in Sweden. *J. Vocation. Rehab.* **19**, 59-66.

Mink JW (2001) Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatr. Neurol.* **25**, 190-198.

Mitchell DGV, E Colledge, A Leonard and RJR Blair (2002) Risky decisions and response reversal: is there evidence of orbitofrontal dysfunction in psychopathic individuals? *Neuropsychologia* **40**, 2013-2022.

Mungas D (1988) Psychometric correlates of episodic violent behaviour: a multidimensional neuropstchological approach. *Brit. J. Psychiatry* **152**, 180-187.

Murphy FC, JS Rubinsztein, A Michael, RD Rogers, TW Robbins, ES Paykel and BJ Sahakian (2001) Decision-making cognition in mania and depression. *Psychol. Med.* **31**, 679-693.

Norlander T, SA Bood and T Archer (2002) Performance during stress: affective personality, age and regularity of physical exercise. *Soc. Behav. Person.* **30**, 495-508.

Olivier B, C Leahy, T Mullen, R Paylor, FE Groppi, Z Sarnyai and D Brunner (2001) The DBA/2J strain and prepulse inhibition of startle: a model system to test antipsychotics? *Psychopharmacology* **156**, 273-283.

Ortner CNM, TK MacDonald and MC Olmstead (2003) Alcohol intoxication reduces impulsivity in the delay-discounting paradigm. *Alcohol Alcohol.* **38**, 151-156.

Oscar-Berman M, SM Kirkley, DA Gansler and A Couture (2004) Comparison of Korsakoff and non-Korsakoff alcoholics on neuropsychological tests of prefrontal brain functioning. *Alcohol Clin. Exp. Res.* **28**, 667-675.

Paaver M, D Eensoo, A Pulver and J Harro (2006) Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers. *Psychopharmacology* **186**, 32-40.

Paaver M, N Bordquist, J Parik, M Harro, L Oreland and J Harro (2007) Platelet MAO activity and the 5-HTT gene promotor polymorphism are associated with impulsivity and cognitive style in visual information processing. *Psychopharmacology* **194**, 545-554.

Palmer AA, SC Dulawa, AA Mottiwala, LH Conti, MA Geyer and MP Printz (2000) Prepulse startle deficit in Brown-Norway rat. A potential genetic model. *Behav. Neurosci.* **114**, 374-388.

Palomo T, RJ Beninger, RM Kostrzewa and T Archer (2004) Gene-environment interplay in affect and dementia: emotional modulation of cognitive expression in personal outcome. *Neurotox. Res.* **6**, 159-173.

Palomo T, RJ Beninger, RM Kostrzewa and T Archer (2007) Treatment consideration and manifest complexity in comorbid neuropsychiatric disorders. *Neurotox. Res.* **12**, 43-60.

Partridge C and M Johnston (1989) Perceived control of recovery from physical disability: measurements and prediction. *Br. J. Clin. Psychol.* **28**, 53-60.

Patton JH, MS Stanford and ES Barratt (1995) Factor structure of the Barratt Impulsiveness Scale. *J. Clin. Psychol.* **51**, 768-774.

Perry W, A Minassian, D Feifel and DL Braff (2001) Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biol. Psychiatry* **50**, 418-424.

Peters E and P Slovic (2000) The springs of action: affective and analytical information processing in choice. *Pers. Soc. Psychol. Bull.* **26**, 1465-1475.

Petronis A (2004) The origin of schizophrenia: genetic thesis epigenetic antithesis and resolving synthesis. *Biol. Psychiatry* **55**, 965-970.

Petry NM, WK Bickel and M Arnett (1998) Shortened time horizons and insensitivity to future consequences in heroin addicts. *Addict*. **93**, 729-738.

Piazza PV and M Le Moal (1996) Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons." *Ann. Rev. Pharmacol. Toxicol.* **36**, 359-378.

Pihl RO, SS Paylan, A Gentes-Hawn and PNS Hoaken (2003) Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcohol Clin. Exp. Res.* **27**, 773-779.

Pitel AL, H Beaunieux, T Witkowski, F Vabret, B Guillery-Girard, P Quinette, B Desgranges and F Eustache (2007) Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcohol Clin. Exp. Res.* **31**, 1169-1178.

Placidi GPA, MA Oquendo, FSM Malone, YD Hassig, SP Ellis and JJ Mann (2001) Aggressivity, suicide attempts and depression relationship to cerebrospinal fluid and monoamine metabolite levels. *Biol. Psychiatry* **50**, 783-791.

Polster MR, RA McCarthy, G O'Sullivan, PA Gray and GR Park (1993) Midazolam-induced amnesia: implications for the implicit/explicit memory distinction. *Brain Cogn.* **22**, 244-265.

Potter AS and PA Newhouse (2004) Effects of acute nicotine administration on behavioural inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology* **176**, 182-194.

Powell SB and MA Geyer (2002) Developmental markers of psychiatric disorders as identified by sensorimotor gating. *Neurotox. Res.* **4**, 489-502.

Ptak R, K Gutbrod, W Perrig and A Schnider (2001) Probabilistic learning with limbic or prefrontal damage. *Behav. Neurosci.* **115**, 993-1001.

Rapp PR and DG Amaral (1992) Individual differences in the cognitive and neurobiological consequences of normal aging. *Trends Neurosci.* **15**, 340-345.

Reason JT (1979) Actions not as planned: the price of automatization, In: *Aspects of Consciousness* (Underwood G and R Stevens, Eds.) (Academic Press:London), pp 67-89.

Reason JT (1984) Absent-mindedness and cognitive control, In: *Everyday Memory, Actions and Absent Mindedness* (Harris J and P Morris, Eds.) (Academic Press:London), pp 53-70.

Redpath NT, NT Price, KV Severinov and CG Proud (1993) Regulation of elongation factor-2 by multisite phosphorylation. *Eur. J. Pharmacol.* **213**, 689-699.

Rogers RD (2003) Neuropsychological investigations of the impulsive personality disorders. *Psychol. Med.* **33**, 1335-1340.

Rosenbaum RS, DT Stuss, B Levine and E Tulving (2007) Theory of mind is independent of episodic memory. *Science* **318**, 1257.

Rosenberg M (1965) *Society and the Adolescent Self-Image* (Princeton University Press:Princeton, NJ).

Rosenman S, A Korten, J Medway and M Evans (2003) Dimensional vs. categorical diagnosis in psychosis. *Acta Psychiatr. Scand.* **107**, 378-384.

Rotter JB (1966) Generalized expectancies for internal versus external control of locus of reinforcement. *Psychol. Monogr.* **80** (Whole no. 609).

Rubinsztein JS, A Michael, ES Paykel and BJ Sahakian (2000) Cognitive impairment in remission in bipolar affective disorder. *Psychol. Med.* **30**, 1015-1036.

Rustichini A (2005) Neuroscience. Emotion and reasoning in making decisions. *Science* **310**, 1624-1625.

Rutter M, A Pickles, R Murray and L Eaves (2001) Testing hypotheses on specific environmental causal effects on behaviour. *Psychol. Bull.* **127**, 291-324.

Rutter M, TE Moffit and A Caspi (2006) Gene-environment interplay and psychopathy: multiple varieties but real effects. *J. Child Psychol. Psychiatry* **47**, 226-261.

Sachs NA, A Sawa, SE Holmes, LE Delisi and RL Margolis (2005) A frameshift mutation in disrupted in schizophrenia 1 in an American family with schizophrenia and schizoaffective disorder. *Mol. Psychiatry* **10**, 758-764.

Sanfey AG, JK Rilling, JA Aronsson, LE Nyström and JD Cohen (2003) The neural basis of economic decision-making in the Ultimate Game. *Science* **300**, 1755-1758.

Sanfey AG, G Loewenstein, SM McClure and JD Cohen (2006) Neuroeconomics: cross-currents in research on decision-making. *Trends Cogn. Sci.* **10**, 108-116.

Schaer M, JE Schmitt, B Glaser, F Lazeryras, J Delavelle and S Eliez (2006) Abnormal patterns of cortical gyrification in velo-cardio-facial syndrome (deletion 22q11.2): an MRI study. *Psychiatr. Res.* **146**, 1-11.

Schalling D, G Edman, M Åsberg and L Oreland (1988) Platelet MAO activity associated with impulsivity and aggressivity. *Pers. Indiv. Diff.* **9**, 597-605.

Scheetz AJ, AC Nairn and M Constantine-Paton (2000) NMDA receptor-mediated control of protein synthesis at developing synapses. *Nat. Neurosci.* **3**, 211-216.

Schultz W (2007) Multiple dopamine functions at different time courses. *Ann. Rev. Neurosci.* **30**, 259-288.

Serretti A and P Olgiati (2004) Dimensions of major psychoses: a confirmatory factor analysis of six competing models. *Psychiatr. Res.* **127**, 101-109.

Shoham S and MBH Youdim (2000) Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases. *Cell. Mol. Biol.* **46**, 743-760.

Shoham S, Y Glinka, Z Tanne and MBH Youdim (1996) Brain iron: function and dysfunction in relation to cognitive processes, In: *Iron Nutrition in Health and Disease* (Hallberg L and NG Asp, Eds.) (John Libbey & Co.:London), pp 205-218.

Shprintzen RJ (2000) Velo-cardio-facal syndrome: a distinctive behavioral phenotype. *Ment. Retard. Dev. Disabil. Res. Rev.* **6**, 142-147.

Shprintzen RJ, RB Goldberg, ML Lewin, EJ Sidoti, MD Bekman, RV Argamaso and D Young (1978) A new syndrome involving cleft palate, cardiac anomalies, typical facies and learning disabilities: velo-cardio-facial syndrome. *Cleft Palate J.* **15**, 556-562.

Sloman SA (1996) The empirical case for two forms of reasoning. *Psychol. Bull.* **119**, 3-22.

Someya T, K Sakado, T Seki, M Kojima, C Reist, SW Tang and S Takahashi (2001) The Japanese version of the Barratt Impulsiveness Scale, 11th version, (BIS-11): its reliability and validity. *Psychiatr. Clin. Neurosci.* **55**, 111-114.

Steidl S, S Mohi-uddin and AK Anderson (2006) Effects of emotional arousal on multiple memory systems: evidence from declarative and procedural learning. *Learn. Mem.* **13**, 650-658.

Sullivan EV, MJ Rosenbloom and A Pfefferbaum (2000) Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin. Exp. Res.* **24**, 611-621.

Sutton MA and EM Schuman (2005) Local translational control in dendrites and its role in long-term synaptic plasticity. *J. Neurobiol.* **64**, 116-131.

Sutton MA and EM Schuman (2006) Dendritic protein synthesis, synaptic plasticity, and memory. *Cell* **127**, 49-58.

Sutton MA, NR Wall, GN Aakalu and EM Schuman (2004) Regulation of dendritic protein synthesis by miniature synaptic events. *Science* **304**, 1979-1983.

Sutton MA, HT Ito, P Cressy, C Kempf, JC Woo and EM Schuman (2006) Miniture neurotransmission stabilizes synaptic function via tonic suppression of local dendritic protein synthesis. *Cell* **125**, 785-799.

Sutton MA, AM Taylor, HT Ito, A Pham and EM Schuman (2007) Postsynaptic decoding of neural activity: eEF2 as a biochemical sensor coupling miniature synaptic transmission to local protein synthesis. *Neuron* **55**, 648-661.

Swann AC, P Pazzaglia, A Nicholls, DM Dougherty and FG Moeller (2003) Impulsivity and phase of illness in bipolar disorder. *J. Affect. Disord.* **73**, 105-111.

Swann AC, DM Dougherty, PJ Pazzaglia, M Pham and FG Moeller (2004) Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disord.* **6**, 204-212.

Swann AC, D Birnbaum, AA Jagar, DM Dougherty and FG Moeller (2005) Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biol. Psychiatry* **57**, 1209-1211.

Swerdlow NR, J Talledo, AN Sutherland, D Nagy and JM Shoemaker (2006) Antipsychotic effects on prepulse inhibition in normal 'low gating' humans and rats. *Neuropsychopharmacol*. **31**, 2011-1021. Epub 2006 Feb 8.

Swillen A, L Vandeputte, J Cracco, B Maers, P Ghesquière, K DeVriendt and JP Fryns (1999) Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability. *Child. Neuropsychol.* **5**, 230-241.

Tanaka SC, K Doya, G Okada, K Ueda, Y Okamoto and S Yamawaki (2004) Prediction of immediate and future rewards differentially recruits corticobasal ganglial loops. *Nat. Neurosci.* **7**, 887-893.

Tomb I, M Hauser, P Deldin and A Caramazza (2002) Do somatic markers mediate decisions on the gambling task? *Nat. Neurosci.* **5**, 1103-1104.

Tseng MS (1970) Locus of control as a determinant of job proficiency, employability, and training satisfaction of vocational rehabilitation clients. *J. Counsell. Psychol.* **17**, 487-491.

Vallee M, W Mayo, F Dellu, M Le Moal, H Simon and S Maccari (1997) Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. *J. Neurosci.* **17**, 2626-2636.

Vallee M, S Maccari, F Dellu, M Le Moal, H Simon and W Mayo (1999) Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. *Eur. J. Neurosci.* **11**, 2906-2918.

Vallerand RJ, MR Blais, NM Brière and LG Pelletier (1989) Construction and validation of the Academic Motivation

Scale. *Can. J. Behav. Sci.* **21**, 323-349.

Van der Kooij MA and JC Glennon (2007) Animal models concerning the role of dopamine in attention-deficit hyperactivity disorder. *Neurosci. Biobehav. Rev.* **31**, 597-618.

Vazquez V, S Weiss, B Giros, MP Martres and V Dauge (2007) Maternal deprivation and handling modify the effect of the dopamine D_3 receptor agonist, BP 897, on morphine-conditioned place preference in rats. *Psychopharmacology* **193**, 475-486.

Vazza G, C Bertolin, E Scudellaro, A Vettori, F Boaretto, S Rampinelli, G De Sanctis, G Perini, P Peruzzi and ML Mostacciuolo (2007) Genome-wide scan supports the existence of a susceptibility locus for schizophrenia and bipolar disorder on chromosome 15q26. *Mol. Psychiatry* **12**, 87-93.

Veit R, H Flor, M Erb, C Hermann, M Lotze, W Grodd and N Birnbaumer (2002) Brain circuits involved in emotional learning in antisocial behaviour and social phobia in humans. *Neurosci. Lett.* **328**, 233-236.

Verfaellie M, E Martin, K Page, E Parks and MM Keane (2006) Implicit memory for novel conceptual associations in amnesia. *Cogn. Affect. Behav. Neurosci.* **6**, 91-101.

Verhoeven WMA and S Tuinier (2001) Two steps forward, one step back: paradigmatic changes in psychiatry. *J. Neural Transm.* **108**, 617-627.

Verhoeven WMA and S Tuinier (2006) Prader-Willi syndrome: atypical psychoses and motor dysfunctions. *Int. Rev. Neurobiol.* **72**, 119-130.

Verhoeven WMA and S Tuinier (2008) Clinical perspectives on the genetics of schizophrenia: a bottom-up orientation. *Neurotox. Res.* **14**, (in press).

Verhoeven WMA, JIM Egger and S Tuinier (2007) Thoughts on the behavioural phenotypes in Prader-Willi syndrome and velo-cardio-facial syndrome: a novel approach. *Acta Neuropsychiatry* **19**, 1-7.

Wade TR, H de Wit and JB Richards (2000) Effects of dopaminergic drugs on delayed reward as a measure of impulsive behaviour in rats. *Psychopharmacology* **150**, 90-101.

Walderhaug E, H Lunde, JE Nordvik, NI Landro, H Refsum and A Magnusson (2002) Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. *Psychopharmacology* **164**, 385-391.

Watson D and L Clark (1984) Negative affectivity: the disposition to experience aversive negative states. *Psychol. Bull.* **96**, 465-490.

Watson D, LA Clark and A Tellegen (1988a) Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Person. Soc. Psychol.* **54**, 1063-1070.

Watson D, LA Carey and G Carey (1988b) Positive and negative affectivity and their relation to anxiety and depressive disorders. *J. Abnorm. Psychol.* **97**, 346-353.

Weller JA, IP Levin, B Shiv and A Bechara (2007) Neural correlates of adaptive decision making for risky gains and losses. *Psychol. Sci.* **18**, 958-964.

Werkman S, L Shifman and T Shelly (1964) Psychosocial correlates of iron deficiency in early childhood. *Psychosom. Med.* **26**, 125-134.

Wijers FWHM, WMA Verhoeven and S Tuiner (2005) The enigmatic phenotype: relevant signs and symptoms in schizophrenia. *Eur. J. Psychiatry* **19**, 215-230.

Williams GV and PS Goldman-Rakic (1995) Modulation of memory fields by dopamine D_1 receptors in prefrontal cortex. *Nature* **376**, 572-575.

Williams HJ, MJ Owen and MC O'Donovan (2007) Is COMT a susceptibility gene for schizophrenia? *Schizophr. Bull.* **33**, 635-641.

Winstanley CA, DE Theobald, J Dalley, RN Cardinal and TW Robbins (2005) Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb. Cortex* **16**, 106-114.

Wolff MC and JD Leander (2002) Selective serotonin reuptake inhibitors decrease impulsive behaviours as measured by an adjusting delay procedure in the pigeon. *Neuropsychopharmacol*. **27**, 421-429.

Xi Z-X, AH Newman, JG Gilbert, AC Pak, X-Q Peng, CR Ashby, L Gitajn and EL Gardner (2006) The novel dopamine D_3 receptor antagonist NGB 2904 inhibits cocaine's rewarding effects and cocaine-induced reinstatement of drug-seeking behaviour in rats. *Neuropsychopharmacol*. **31**, 1393-1405.

Yehuda S and MBH Youdim (1984) The increased opiate action of β-endorphin in iron-deficient rats: the possible involvement of dopamine. *Eur. J. Pharmacol.* **105**, 245-251.

Yehuda S, MBH Youdim and M Mostofsky (1986) Brain iron deficiency causes reduced learning capacity in rats. *Pharmacol. Biochem. Behav.* **25**, 141-145.

Youdim MBH (2008) Brain iron deficiency and excess: cognitive impairment and neurodegeneration with involvement of striatum and hippocampus. *Neurotox. Res.* **14**, 45-56.

Youdim MBH and AR Green (1977) Biogenic amine metabolism and functional activity in iron-deficient rats: behavioural correlates. *Ciba Found. Symp.* **51**, 201-223.

Youdim MBH and S Yehuda (2000) The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. *Cell. Mol. Biol.* **46**, 491-500.

Youdim MBH, MA Sills, WE Heydron, GJ Creed and DM Jacobowitz (1986) Iron deficiency alters discrete proteins in rat caudate nucleus and nucleus accumbens. *J. Neurochem.* **47**, 794799.

Youdim MBH, D Ben-Shachar and S Yehuda (1989) Putative biological mechanisms of the effect iron-deficiency on brain biochemistry and behaviour. *Am. J. Clin. Nutr.* **50**, 607-617.

Youdim MBH, N Zamir and S Yehuda (2000) Antinociception in iron-deficient rats related to subsensitivity of dopamine D_2 receptor induced increase of opiate peptides. *Nutr. Neurosci.* **3**, 357-365.

Young JW, AKL Goey, VL Masten, R Sharp, MP Paulus, W Perry and MA Geyer (2007) Genetic and acute pharmacological animal models of bipolar disorder mania: mimicking recent insights of disordered movement and exploration. *Biol. Psychiatry* **61**, 38S.

Zecca L, MBH Youdim, P Riederer, JR Connor and RR Crichton (2004) Iron, brain aging and neurodegenerative disorders. *Nat. Rev. Neurosci.* **5**, 863-873.

Zinn S, R Stein and HS Swartzwelder (2004) Executive functioning early in abstinence from alcohol. *Alcohol Clin. Exp. Res.* **28**, 1338-1346.