Neurotoxicity Research, 2007, VOL. 12(1). pp. 1-15

F.P. Graham Publishing Co.

Comorbidity Implications in Brain Disease: Neuronal Substrates of Symptom Profiles

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(Submitted 19 January 2006; In final form 19 January 2006)

The neuronal substrates underlying aspects of comorbidity in brain disease states may be described over psychiatric and neurologic conditions that include affective disorders, cognitive disorders, schizophrenia, obsessive-compulsive disorder, substance abuse disorders as well as the neurodegenerative disorders. Regional and circuitry analyses of biogenic amine systems that are implicated in neural and behavioural pathologies are elucidated using neuroimaging, electrophysiological, neurochemical, neuropharmacological and neurobehavioural methods that present demonstrations of the neuropathological phenomena, such as behavioural sensitisation, cognitive impairments, maladaptive reactions to environmental stress and serious motor deficits. Considerations of neuronal alterations that may or may not be associated with behavioural abnormalities examine differentially the implications of discrete areas within brains that have been assigned functional significance; in the case of the frontal lobes, differential deficits of ventromedial and dorsolateral prefrontal cortex may be associated with different aspects of cognition, affect, remission or response to medication thereby imparting a varying aspect to any investigation of comorbidity.

Keywords: Neuronal systems; Regional selectivity; Cognition; Affect; Neuroimaging; Signalling; Sensitisation; Stress; Comorbidity

INTRODUCTION

Comorbidity implications within and between the neurologic and neuropsychiatric disorders remain, and seem even aggravated, by calamities of high incidence with consequential problems for both the etiology and treatment of these states (Walker and Diforio, 1997). Commonly, patients afflicted with psychiatric disorders, such as depression or schizophrenia, are at high risk for any of several substance abuse disorders, including alcohol, tobacco or unlawful substances (Colder and Chassin, 1993; Grant BF, 1995; George and Krystal, 2000; Chambers *et al.*, 2001; Dierker *et al.*, 2002; Ziedonis *et al.*, 2003), while affective and psychotic disorders may present comorbidity with disorders of cognition (Golik-Gruber *et al.*, 2003; Lewis *et al.*, 2004). In view of the occurence of particular shared genetic liabilities for comorbidity (Kendler *et al.*, 1993; Hambrecht and Hafner, 2000; Johnson JG *et al.*, 2000; Swendsen and Merikangas, 2000; Katarina *et al.*, 2004), the pres-

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ISSN 1029 8428 print/ ISSN 1476-3524 online.

ence of shared neuromorphological and anatomical features of these disorders (*e.g.*, Akbarian *et al.*, 1993; Pierri *et al.*, 1999; Drevets, 2000; Glantz and Lewis, 2000; Eastwood *et al.*, 2001). Further, the shared features of affective, psychotic and neurologic states encompass a variety of neurobiological markers (Buchanan *et al.*, 1998; Woo *et al.*, 1998; Rajkowska *et al.*, 1999; Harrison *et al.*, 2003; Coryell *et al.*, 2005), as well as the central role of neurodevelopmental prerequisites from a genetic-environmental perspective (Weinberger, 1987; Stine *et al.*, 1993; Campodonico *et al.*, 1998; Feigin *et al.*, 2001; Chambers *et al.*, 2003), all of which underline both the sufficiency and necessity of a consideration of the neuronal substrates of comorbidity.

NEUROTRANSMITTER-REGIONAL SELECTIVITY

The biogenic amines would appear to be implicated in several aspects of brain comorbid pathology with dopaminergic and serotonergic systems involved in schizophrenia, the serotonergic and noradrenergic systems in depression and anxiety disorders, dopaminergic influences in anhedonia and differential affectivity, and the maintainence of substance abuse and drug dependence (Eastwood and Harrison, 2001; Davidson *et al.*, 2002; Smelson *et al.*, 2002; Kroner *et al.*, 2005). Furthermore, the aminergic contributions have been associated with several anatomically and functionally predominant regions of the brain, including the frontal lobe, above all the prefrontal and orbitofrontal areas, hippocampus, amydala, anterior cingulate cortex, striatum, thalamus and nucleus accumbens (O'Donnell and Grace, 1995; Mayberg, 1997; Gray, 1999; Groenewegen *et al.*, 1999; LeDoux, 2000), and the prerequisite of neuronal plasticity (Spedding *et al.*, 2003; Kauer, 2004). Totterdell outlined anatomically converging dopaminergic and cortical inputs to single neurons located in the ventral striatum, as well as the convergence between different cortical inputs onto individual neurons (*cf.*, Wright and Groenewegen, 1995; Totterdell and Meredith, 1997; Rosenkranz and Grace, 2001). Thus, there is a 'gating' mechanism with excitatory inputs from the hippocampus and prefrontal cortex to the ventral element of the prefrontal-striatal-pallidal-thalamic-prefrontal loop, with major dopaminergic inputs from the ventral tegmentum and serotonergic innervation from the raphe nuclei. Against this regional-neuronal template, descriptions of the synaptic circuitry and excitatory inputs to the nucleus accumbens (Aylward and Totterdell, 1993; Ding *et al.*, 2001), its dopaminergic, serotonergic and noradrenergic innervation and the aminergic receptor distributions were provided. Afferental inputs from the hippocampus, prefrontal coretx, and amygdala (Totterdell and Smith, 1989; Callaway *et al.*, 1991; Johnson LR *et al.*, 1994; Wright *et al.*, 1996; Carr *et al.*, 1999; French and Totterdell, 2002; 2003) maintain the projections underlying the synthesis of pathways involved in drug dependence disorders, depressive disorders, and schizophrenia (*e.g.*, Totterdell and Smith, 1986; Sapolsky, 2001; Crombag *et al.*, 2005; Totterdell, 2006).

High level structural and functional resolution offered by functional magnetic resonance imaging (fMRI), markedly superior to other neuroimaging techniques, provides direct estimates of neuronal activity, thereby information on neuronal substrates, pertaining to aspects of comorbid pathology in brain disorders (*cf.*, Aber *et al.*, 2003; McClure *et al.*, 2004). For example, structural and functional imaging studies, described by Ebmeier *et al.* (2006), implicate the anterior cingulate cortex, orbitofrontal cortex, dorsolateral frontal cortex, striatum and medial temoral areas in abnormalities associated with depressive states (Ebert and Ebmeier, 1996). Thus, depressed patients presented abnormally increased activity in emotion-associated region and abnormal hypoactivity in cognition-associated regions (Drevets, 2000; Ebmeier and Kronhaus, 2002; Mayberg, 2003; Steele and Lawrie, 2004). It was found that spatial working memory performance was linked to abnormal increments in ventromedial prefrontal activity (Rose *et al.*, 2005), consistent with an 'emotional gating' model of cognitive performance in depressive states (Pochon *et al.*, 2002). It was shown too that depressed patients displayed a bias towards processing mood-congruent information, *i.e.*, an elevated respose to stimuli with negative emotional tone, whereby the responses to "sad targets" in the rostral anterior cingulate and medial prefrontal cortex were elevated (Elliott *et al.*, 2002). Other studies demonstrated that patients engaged in prolonged, elaborative

cognitive processing of emotional material (Siegle *et al.*, 2002). Taken together, a growing consensus supports the convergence of an affective-cognition component of symptom profile, not least executive functioning (Harvey *et al.*, 2004), as reflected by neuroimaging and neuropsychological studies (Shah *et al.*, 1998; Elliott *et al.*, 2000; Austin *et al.*, 2001; Fossati *et al.*, 2002; 2004; Murphy *et al.*, 2003; Porter *et al.*, 2003; Steele *et al.*, 2004).

The electrophysiological basis of potent prefrontal cortex (PFC) regulatory influences upon limbic regions, particularly the amygdala, in affective and psychotic conditions and the effects of stress were described by Grace (2006). The PFC regulation of subcortical systems involved in affective states has received much attention (Gresch *et al.*, 1994; Jedema *et al.*, 1999; Quirk *et al.*, 2000; Milad and Quirk, 2002; Correll *et al.*, 2005; Goto and Grace, 2005; 2006; Laviolette *et al.*, 2005; Valenti and Grace, 2005). Besides a functioning PFC-amygdala circuit regulation in affective states (Hariri *et al.*, 2003; Rosenkranz and Grace, 2003), hippocampus-PFC interactions within the nucleus accumbens are critical such that induction of long-term potentiation (LTP) interferes with the afferent drive to the accumbens from the other pathway (*i.e.*, PFC or hippocampus) with dopamine exerting modulatory control (Rosenkranz and Grace, 2002a,b). For example, in cocaine-sensitized animals, LTP is induced in the hippocampal-accumbens pathway with consequent disruption of the PFC-accumbens pathway control over goal-directed behaviour (*cf.*, Grace *et al.*, 1998). Genetic-environmental factors contributing to comorbidity, *e.g.*, chronic/acute stress, affect normally-functioning and dysfunctional brain at several different levels and regional sites, most particularly neuronal (Rohsenow, 1982; Abercrombie and Jacobs, 1987; Dunn, 1988; Coco *et al.*, 1992; Romelsjo and Hasin, 1992; Finlay *et al.*, 1995; 1997; Sapolsky, 1996; Mana and Grace, 1997; Caspi *et al.*, 2003; Higihara *et al.*, 2003; Gilder *et al.*, 2004). For instance, exposure to long-term stress induced a remarkable and long-lasting inhibition of LTP that could be prevented by the glucocorticoid receptor antagonist, mifepristone, thereby demonstrating the essential role of not only the hippocampus (as described by Sapolsky, 2005; but see also Sapolsky *et al.*, 1990; Nisenbaum *et al.*, 1991; Jedema *et al.*, 2001) but also the frontal cortex in the stress response cascade, as well as dopaminergic activity in the ventral tegmentum (Moore *et al.*, 2001). Additionally, both antidepressant compounds, *e.g.*, fluoxetine and tianepine, and clozapine, but not haloperidol, restored stress-disrupted LTP, suggesting that the effective compounds share the PFC as their common target by restoring the functional balance at hippocampus/PFC synapses, presumably impaired in depression and/or schizophrenia.

Szechtman and co-workers (*e.g.*, Szechtman and Woody, 2004; 2006; Taylor *et al.*, 2005; Woody and Szechtman, 2005; Woody *et al.*, 2005), taking as their point-of-departure the remarkably high prevalence of comorbidity of obsessive-compulsive disorder in patients presenting other psychiatric problems (*e.g.*, Tukel *et al.*, 2002), have developed the notion that the behavioural abnormalities expressed in the disorder (*i.e.*, obsessive-compulsiveness) stem from disturbances in the operation of a "security-motivation" system. Incorporated within the "security-motivation system", and encompassing presumably orbitofrontal-cingulate-limbic-motor elements of regional circuitry, exists a representive, biologically-primitive 'specialized' motivation, activated by potential (rather than imminent) danger signals to 'self' or 'intimate-others', that engages a set of specialized species-typical behaviours that are meant to handle the threat. To attain a "switching-off" of the security motivation system, a self-generated affective state of knowledge or particular insight must occur, a satiety signal termed "Yedasentience". The implications of affective 'constitution' appear to be of central influence for the notions that have been developed to a global view of a 'para-disordered' brain wherein the search for the neuronal substrates is under mobilization (Davidson *et al.*, 2000); implications of affect for basic aspects of personality (*e.g.*, affective, state-dependent, personality, or trait-dependent personality) must be tackled (Palomo *et al.*, 2004). Obsessive-compulsive disorder develops from failure to generate or respond to the yedasentience signal: thus, patients persist in the prolonged repetitive sequences of security-related behaviours (checking, washing, locking, unlocking, counting) reflecting the strong motivational state characteristic of the disorder. The authors have drawn attention also to the concept of "affective chronometry", that mea-

sures the temporal dynamics of emotions/affect within parameters of threshold, peak amplitude and recovery time, that may be applied to assess malfunctioning within the "security-motivation" system or "Yedasentience". From the viewpoint of notions suggesting that obsessive-compulsive disorder may preceed the diagnosis of other psychiatric disease states such as schizophrenia as well as with a predisposing incidence of Tourette's disorder, and other movement-oriented disorders, one may imply that the same gene is responsible for tics and obsessive-compulsive disorder; these various threads must reinforce implications of the relations to obsessional repetitive, or more or less stereotypic behaviours (*cf.*, Bolton *et al.*, 2000), all of which serves to impart a Braakian perspective (*cf.*, Modell *et al.*, 1989).

The comorbidity of obsessive-compulsive disorder with other psychiatry disorders is illustrated persuasively in its shared comorbidity with Trichotillomania (TTM), characterized by repetitive stereotypical hair-pulling from different sites - resulting in noticeable hair loss (Stein *et al.*, 1995; Tukel *et al.*, 2001). Both TTM and obsessive-compulsive disorder patients describe compulsive urges and ritualistic behaviours, yet marked differences exist between the disorders, *e.g.*, hair-pulling in TTM is not in response to obsessive thoughts (such as worry about harm to self or others) but rather because of an irresistible urge and the promise of gratification when pulling out hair. Furthermore, TTM maintains the hair-pulling without evolving non-self-injurious compulsive rituals, symptoms that develop chronically with regard to focus and severity, *e.g.*, from washing of hands to checking locks, stoves, appliances, etc. (Swedo and Leonard, 1992). Recently, Lochner *et al.* (2005) compared 278 male and female patients presenting obsessive-compulsive disorder with 54 patients presenting TTM over all age groups. They found that whereas obsessive-compulsive disorder patients presented significantly greater disability over lifetime, TTM patients reported a lesser response to treatment. Obsessive-compulsive disorder patients presented a higher level of comorbidity, greater harm avoidance and less novelty seeking, a higher number of maladaptive beliefs, and more sexual abuse than TTM patients. The sudy by Lochner *et al.* (2005) serves to underline problematic aspects of comorbity: TTM is classified as an impulse control disorder and may resemble conditions characterized by stereotypical self-injurious symptoms, such as skin-picking, thereby implying that important differences may exist in the underlying neuronal-regional circuitry which necessitate contrasting treatment approaches (Keuthen *et al.*, 1998; O'Sullivan *et al.*, 2000; van Minnen *et al.*, 2003).

NEUROCHEMICAL-REGIONAL SELECTIVITY IN COGNITION AND MOVEMENT

Comorbidity of functional status and regional-neuronal integrity implicates hippocampal, amygdaloid, medial septal and cortical, medial prefrontal and entorhinal involvement and participation in aversive memories through mechanisms implying glutamate receptor activation both during the consolidation phase and during the expression of memory (*e.g.*, Bianchin *et al.*, 1994). The cascade of molecular events underlying retrieval of a simple step-down conditioning task and the memory for resistence to extinction involving functional NMDA receptors in addition to activation of several signalling pathways in the hippocampus, including those mediated by PKA, ERK1/2, p38MAPK and Src provides markedly stringent analysis of neuronal molecular substates of fear and avoidance memory acquisition and extinction (Bernabeu *et al.*, 1995; Izquierdo and Medina, 1995; Maren and Quirk, 2004). Ivan Izquierdo *et al.* (2006) compared problems of memory arising from temporo-limbic and striatal malfunctioning by regarding instances of declarative or procedural memory tasks. His two majors investigative thrusts involved: (i) reversal learning in the circular water maze task whereby the declarative component is altered but the procedural one maintained (but see also reference versus working memory), and (ii) inhibitory avoidance conditioning studies suggesting the 'shift of memories' over distributed systems due to tasks initiating further learning. Collectively, these studies revealed how different brain structures and signalling pathways contributed to multiple cognitive functions (*e.g.*, Medina *et al.*, 1999). Further evidence for the neurochemical cascades underlying memories for fear conditioning is offered by a series of experiments reviewed by Cammarota *et al.* (2007), whereby

activity-dependent alterations in neuronal efficacy are considered the main events in the formations and storage of new memories (Dudai, 2002; Izquierdo and Medina, 1997; McGaugh, 2000). They demonstrated that the 'superfamily' of mitogen-activated protein kinases (MAPKs) contribute to signal transduction cascades initiated by neurotransmitters, mitogens, growth factors and various types of stress (*e.g.*, Alonso *et al.*, 2003; McGaugh and Roozendaal, 2002). It was demonstrated that modifications of the phosphorylation/activation state of different synaptic and nuclear-localized protein kinases influenced, by a variety of mechanisms, both the induction and maintainence of neuronal expressions of plasticity, as well as the cellular mechanisms underlying consolidatory processes in the acquisition of long-term memories (*cf.*, Berman DE and Dudai, 2001; Dudai, 2004). Rodriguez-Moreno *et al.* (2006) has applied electrophysiological recording techniques during acquisition and retrieval of cognitive tasks to study associative learning in mice. Activity-dependent changes occur at the hippocampal CA3-CA1 synapse in behaving mice during the acquisition and extinction of a trace conditioning paradigm. A single pulse presented at the Schaffer collateral-commisural pathway, during the CS-US interval, evoked a monosynaptic field EPSP at ipsilateral CA1 pyramidal cells, thereby altering the slope across learning. LTP evoked by train stimulation of Schaffer collaterals blocked acquisition of the associative task. Applications of NMDA antagonists were critical in preventing LTP induction, acquisition of learned eyelid responding and synaptic changes at CA3-CA1 synapses across conditioning. These experimental paradigms were tested also in transgenic (APP, PS-1) and knock-out (TrkB) mice.

Fredriksson and Archer (2006) described the influence of postnatal iron overload upon implications of the functional and interactive role of dopaminergic and noradrenergic pathways that contribute to the expressions of movement disorder. Postnatal iron overload at doses of 7.5 mg/kg (administered on Days 10-12 post partum) and above, invariably induced a behavioural syndrome consisting of an initial (1st 20-40 min of a 60-min test session) hypoactivity followed by a later (final 20 min of a 60-min test session) hyperactivity, when the mice were tested at adult ages (age 60 days or more). Following postnatal iron overload, subchronic treatment with the neuroleptic compounds, clozapine and haloperidol, dose-dependently reversed the initial hypoactivity and later hyperactivity induced by the metal. Furthermore, DA D_2 receptor supersensitivity (as assessed using the apomorphine-induced behaviour test) was directly and positively correlated with iron concentrations in the basal ganglia. The selective denervation of noradrenaline (NA) terminals using the selective NA neurotoxin, DSP4, followed by administration of the selective DA neurotoxin, MPTP, has been employed as an experimental model for 'accelerated' Parkinson's disease (PD), reflecting a striatal DA and central NA deficiency (Nishi *et al.*, 1991; Marien *et al.*, 1993; Fornai *et al.*, 1997). Brain noradrenaline (NA) denervation, using the selective NA neurotoxin, DSP4, prior to administration of the selective DA neurotoxin, MPTP, exacerbated both the functional (hypokinesia) and neurochemical (DA depletion) effects of the latter neurotoxin. Treatment with L-Dopa restored motor activity only in the animals that had not undergone NA denervation. Finally, C57/BL6 mice were administered either postnatal iron (Fe^{2+} 7.5 mg/kg, on postnatal days 10-12) or vehicle, followed by administration of either DSP4 (50 mg/kg, s.c., 30 min after injection of zimeldine, 20 mg/kg, s.c.) or vehicle (saline) at 63 days of age. Postnatal iron administration exacerbated the bradykinesia induced by MPTP and virtually abolished all spontaneous motor activity in NA-denervated mice that were MPTP-treated. Suprathreshold doses (20 mg/kg) of L-Dopa invariably restore motor activity in MPTP mice: nevertheless, postnatal iron administration reduced markedly the restoration of motor activity by suprathreshold L-Dopa (20 mg/kg) following a 60-min habituation to the test chambers. Pretreatment with DSP4 effectively eliminated the restorative effect of L-Dopa in the MPTP mice. Postnatal iron administration caused enduring higher levels of total iron content in all the groups with an increased level in mice treated with DSP4 followed by MPTP. From a perspective of Braakian notions, these divergent findings confirm the developmental and predispositional role of postnatal iron overload and prior denervation of NA upon dopaminergic functional expression and indicate a permanent vulnerability both in the noradrenergic and dopaminergic pathways following

the postnatal infliction of an iron overload.

IMMUNOLOGICAL-REGIONAL FUNCTIONING

The review by Müller and Schwarz (2006) presented a series of bridges over current notions of psychoneuroimmunological functioning and diverse findings from pharmacological, neurochemical and genetic studies implicating glutamatergic-dopaminergic substrates of comorbidity in schizophrenia (Carlsson *et al.*, 2001; Collier and Li, 2003; Kornhuber *et al.*, 2004). One aspect of dysfunctional states concerned the role of glutamatergic hypofunctioning, as mediated by NMDA-R antagonism. Other sources of etiological predisposition pertained to perinatal infection in the pathogenesis of schizophrenia (Hill, 1999; Cook and Hill, 2001; Müller, 2004) and inflammation (Leonard and Myint, 2006). The incidence of pregnancy-infections asociated with later susceptibility for has been established (Mednick *et al.*, 1988; Westergaard *et al.*, 1999; Buka *et al.*, 2001; Brown *et al.*, 2004; Koponen *et al.*, 2004). Early sensitization within the immune system may become expressed by an imbalance between Type I and Type II immune responses: the former partially inhibited and the latter over-activated (Müller *et al.*, 2000; Schwarz *et al.*, 2001). Inhibition of indoleamine dioxygenase, an enzyme located in astrocytes and microglia, is inhibited by Type II cytokines so that tryptophan is predominantly metabolised by tryptophan 2,3-dioxygenase in the astrocytes that lack the neurochemical agents for normal tryptophan metabolism. Analysis of the frontal cortex tissue of schizophrenic patients indicated an elevated expression of tryptophan 2,3-dioxygenase in comparison with indoleamine dioxygenase, which was evidenced in the astrocytes, rather than microglial cells (Miller el al., 2004), thereby implying the involvement of glial entities in the TypeI/Type 2 imbalance (Aloise *et al.*, 1997; Xiao and Link, 1999). Astrocytes, microglial cells and macrophages were implicated in the cellular localization of kynureneine metabolism (Espey *et al.*, 1997; Speciale and Schwarcz, 1993). The genetic variations and multiple functions of neuregulin-1 in a diversity of neuronal and glial tissues were implicated too in the etiology of disease process in schizophrenia (Stefansson *et al.*, 2002; 2003; Schwab *et al.*, 2003; Williams *et al.*, 2003; Numakawa *et al.*, 2004). Lack of kynurate-OHase in astrocytes allows build-up of kynurenate acid (see above, endogenous CNS NMDA-R antagonist) which is found together with an increase in tryptophan 2,3-dioxygenase activity in the CNS of schizophrenics (*cf.*, Schwarcz *et al.*, 2001). Finally, the treatment profiles of neuroleptic compounds upon cellular immune reactivity in schizophrenia was discussed (Müller *et al.*, 1991; 1997a,b; 1999; 2002). It would appear then that the immune-mediated glutamatergic-dopaminergic imbalance may be circumvented through selective intervention by anti-inflammatory cyclo-oxygenase-2 inhibitors that provide direct reduction of kynurenate acid to ameliorate the disease process.

Abnormal frontal cortical functioning (Tollefson, 1996; Gehring and Willoughby, 2002), including attention, memory and executive functioning, is observed in a wide range of neuropsychological impairments, such as set-shifting, concentration, judgement, planning and anticipation, abstract thinking, selective attention, mental sequencing and concept formation in schizophrenic individuals (Goldberg *et al.*, 1988, 1990, 1993; Gold and Harvey, 1993; Blanchard and Neale, 1994; Berman I *et al.*, 1997; Basso *et al.*, 1998; Cavedini *et al.*, 2002a). For example, the Wisconsin Card Sorting Test (Heaton, 1981; Feldstein *et al.*, 1999), a somewhat selective test of dorsolateral precortical functioning, typically has been shown to be impaired in schizophrenic patients (Berman KF *et al.*, 1986; 1992; 1995; Weinberger *et al.*, 1986; 1988; Braff *et al.*, 1991; Marenco *et al.*, 1993; Koren *et al.*, 1998; Saoud *et al.*, 1998) and in patients with frontal lobe damage (Anderson *et al.*, 1991). The Gambling Task (Bechara *et al.*, 1994), with a regional specificity for the ventromedial prefrontal cortex (Bechara *et al.*, 1998; 2000), has produced deficits in psychiatric populations (Abbruzzese *et al.*, 1995), including obsessive-compulsive patients (Cavendini *et al.*, 2002b), patients with antisocial personality disorder (Mazas *et al.*, 2000), individuals with substance abuse disorders (Bartzokis *et al.*, 2000; Grant *et al.*, 2000; Bechara *et al.*, 2001), as well as schizophrenic patients (Wilder *et al.*, 1998). Recently, in an investigation of schizophrenic patients and comparable controls, Ritter *et al.* (2004) measured regional differences in frontal

cortical, *i.e.*, ventromedial prefrontal cortex versus dorsolateral prefrontal cortex, functioning by applying the Wisconsin Card Sorting Test in comparison with the Gambling Task. They found that the schizophrenic patients (n=20) performed worse than controls (n=15) on the Gambling Task but that no differences were obtained on the Wisconsin Card Sorting Test. Once again, the central influence of decision-making in scizophrenia is to be noted (*cf.*, Carpenter *et al.*, 2000). Since the Gambling Task is considered to reflect ventromedial prefrontal cortex function it appears that in this particular instance that the patients' deficits were restticted to this region only. Nevertheless, it is possible that limitations of this study failed to replicate the volume of previous data. Whatever the case, the application of dual-performance cognitive-task criteria approaches (see also, Beninger, 2006) offers great scope for deriving etiological aspects of comorbidity, both within-task, *i.e.*, instances where two or more disorders share similar deficits, and within-disorder, *i.e.*, instances where two or more tasks that relect different functional specializations, *e.g.*, executive function versus decision-making, contribution to impairments within the same disorder/brain region. These phenomena, which may be examined at top-down levels of brain activity, constitute further neuronal substrates in comorbidity.

Cognitive impairments are certainly not limited to schizophrenia, a major instance of comorbid overlap is offered by markedly impaired cognitive abilities (Loberg and Miller, 1986; Grant I, 1987; Bolla *et al.*, 2000; Duka *et al.*, 2003), as expressed by problems in visuospatial abstracting, problem-solving, planning and organisation, learning new concepts/notions, flexibility in cognition, selective attention, abstract thinking and various specialized (more-or-less) memory skills, many of these reflecting executive functions (Ardila *et al.*, 1991; Glen *et al.*, 1988; Hambridge, 1990; Waugh *et al.*, 1989; but see also Palomo *et al.*, 2004). These deficits in cognitive functioning are associated with: limited treatment participation, elevated 'drop-out' rates, less after-care utilization and more post-treatment unemployment (Gregson and Taylor, 1977; Donovan *et al.*, 1984; Mackenzie *et al.*, 1987; Teichner *et al.*, 2002), and these individuals are less likely to obtain treatment benefits compared to unimpaired individuals, new to failure to acquire and integrate new information (Leber *et al.*, 1985; Teichner *et al.*, 2001; Aharonvich *et al.*, 2003). Application of mini-mental state examination both recruits abusers yet may be afflicted by participant exclusion due to cognitive deficits (Crum *et al.*, 1993; Cummings, 1993), thereby endorsing notions of substance abuse-dysfunctional cognition comorbidity (Miller and Saucedo, 1983; O'Farrell and Langenbucher, 1985).

In addressing incentive-learning notions, Schmidt and Beninger (2006) imply that enhanced dopaminergic transmission attributes incentive salience to contextual stimuli that reinforce behaviour, processes underlying psychostimulant-induced context-dependent sensitization contributing to addiction, dyskinseia, amphetamine-induced psychosis and psychostimulant-induced aggression. In certain respects the presentation of an unusual, perhaps counter-intuitive, demonstration of drug-induced behavioural sensitisation, namely haloperidol-induced dopamine-activity reduction leading to behavioural inhibition (not activation as in conventional sensitisation and yet fulfilling all the criterion involving classification of the sensitisation process), provided an astonishing manifestation of neuroplasticity. Remarkably, either a low dose of haloperidol or partial dopamine-depletion (50%) with 6-hydroxydopamine led to the gradual development of catalepsy with repeated testing. Further testing without drug in the case of haloperidol induced an extinction-like stepwise reduction. This highly persistent sensitisation response was shown to be susceptible only to contextual conditions; it was markedly context-dependent. These results would appear to open new horizons implicating neuroplasticity normally associated with neuropsychiatric conditions and symptomatology in neurodegenerative disorders such as Parkinson's disease. From a different, yet comorbid, perspective, the demonstration of a neostriatal habit learning system in amnesic patients and nondemented patients with Parkinson's disease implicates the role of the neostriatum (Knowlton *et al.*, 1996), and provides a parallel to the phenomena treated above. This region, the neostriatum, influences motor behaviour and motor learning, as well as acquisition of non-motor dispositions and tendencies, reliant on novel (contextual) associations, essential for incremental associative learning situations, whereby an intrinsic

neuronal substrate must consideration.

IMPLICATIONS OF COMORBIDITY

From a perspective of neurologic-psychiatric comorbidity, the Braakian notions of staging in the development of neuropathology (*cf.*, Braak *et al.*, 1994; 2000; 2003; Braak and Del Tredici, 2004), directly obvious in the neurodegenerative disorders but suitable for considerations of neuropsychiatric conditions, have contributed enormously to a necessary paradigmatic shift in the interpretation of wide-ranging observations. Suffice it to say, these standpoints, supported by multiple aspects of gene-environmental interactions, have opened a plethora of both perceivable and as yet vaguely discernible phenomena to further endow current understandings of brain disease states.

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