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The Vulnerability to Alcohol and Substance Abuse in Individuals Diagnosed with Schizophrenia

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Individuals with schizophrenia are at increased risk for developing substance abuse disorders. Here, we consider factors that might elevate their risk for substance abuse. The tendency among schizophrenic individuals to overvalue drug-like rewards and to devalue the potential negative consequences of substance abuse may be a contributing factor to their substance abuse risk. This bias, which may partly reflect the convergence of glutamatergic and dopaminergic input to the limbic striatum, also may contribute to disadvantageous decision-making and other impulsive behavior. This propensity to seek drug-like rewards is augmented by alterations in nicotinic cholinergic, GABAergic, glutamatergic, and cannabinnoid receptor function associated with schizophrenia that increase the abuse liability of low doses of nicotine, ethanol, and perhaps cannabis, and augment the dysphoric effects of higher doses of ethanol and cannabis. The distortions in reward processing and altered response to substances of abuse also increase the likelihood that individuals with schizophrenia will self-medicate their subjective distress with abused substances. The focus on distinctions between motivation and reward with respect to substance abuse risk by schizophrenic patients suggests a need for a reconsideration of the construct of "negative symptoms" for this dually-diagnosed patient group.

Keywords: Schizophrenia; Alcoholism; Substance abuse; Frontal cortex; Hippocampus; Striatum; Glutamate; Dopamine; GABA; Vulnerability; Dual-diagnosis

INTRODUCTION: INCREASED SUBSTANCE ABUSE RISK AMONG SCHIZOHPRENIC PATIENTS AND ITS NEGATIVE IMPACT

Alcohol and substance abuse by schizophrenic patients is an important public health concern (Bartels *et al.*, 1993; Blanchard *et al.*, 2000; Dixon 1999; O'Brien *et al.*, 2004; Xie *et al.*, 2005). These reviews indicate that patients who abuse drugs other than nicotine have poorer adherence to treatment, worse clinical outcomes, increased suicide risk, poorer vocational function and greater involvement in crime.

Schizophrenic patients are at greater risk for

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developing alcohol and substance abuse disorders than the general population. The Epidemiologic Catchment Area Study reported a 4.6-fold increase in the prevalence of any substance abuse and a 3.3-fold increase in the prevalence of alcohol abuse or dependence in schizophrenic individuals compared to the general population (Regier *et al.*, 1990). Schizophrenic individuals most commonly abuse the same substances as the general population, nicotine, alcohol, and cannabis (Anthony *et al.*, 1994; Seibyl *et al.*, 1993).

This discussion builds on prior reviews (Chambers *et al.*, 2001; Krystal *et al.*, 1999) in suggesting that the pathophysiology and pharmacotherapy of schizophrenia contributes to the excess vulnerability to alcoholism and substance abuse relative to the general population. It also highlights neuroimaging and psychopharmacology data that provide new insights into the increased risk for substance abuse associated with schizophrenia.

HERITABLE AND ENVIRONMENTAL RISK FACTORS FOR ALCOHOL AND SUBSTANCE ABUSE AND DEPENDENCE BY INDIVIDUALS DIAGNOSED WITH SCHIZOPHRENIA

Heritability of Substance Abuse in Schizophrenic Patients

Family and twin studies indicate that the heritable risk for schizophrenia is distinct from the heritable risk for alcohol and substance abuse,and suggests that dually-diagnosed individuals have heritable vulnerabilities to both disorders. Schizophrenic individuals with first degree relatives who meet diagnostic criteria for alcohol and substance abuse disorders show greater risk for substance abuse than other schizophrenic patients (Gershon *et al.*, 1988; Noordsy *et al.*, 1994; Cantor-Graae *et al.*, 2001). Similarly, a twin study found that monozygotic twins of individuals with schizophrenia and alcoholism showed increased rates of both disorders compared to dizygotic twins (Kendler, 1985). However, the presence of a substance abuse disorder does not increase the likelihood of having a family history of schizophrenia in schizophrenic patients (DeQuardo *et al.*, 1994). The incidence of schizophrenia is not increased in the children of alcohol dependent parents (Bidaut-Russell *et al.*, 1994; Kendler *et al.*, 1996), and the incidence of alcohol dependence, substance abuse or antisocial personality disorder in family members is not increased in schizophrenic individuals who do not have a comorbid substance abuse disorder (Fowler *et al.*, 1975; Baron *et al.*, 1985; Kendler *et al.*, 1985a,b; 1993; Gershon *et al.*, 1988; Erlenmeyer-Kimling *et al.*, 1997; Kendler and Gardner, 1997). In contrast, the unaffected co-twins of schizophrenic individuals show increased rates of smoking and have more unsuccessful attempts to quit smoking than a non-schizophrenic comparison group (Lyons *et al.*, 2002). Thus, there may be overlap in the heritability of smoking and schizophrenia.

The heritable risk for alcohol and substance abuse expressed by schizophrenic patients may be reflected in clinical traits including sociopathy, mood and anxiety disorders, and attention deficit hyperactivity disorder (Merikangas and Avenevoli, 2000; Clark *et al.*, 2004; Nurnberger *et al.*, 2004). When comorbid with schizophrenia, sociopathy increases the prevalence and severity of substance abuse problems, as much as ten-fold (Mueser *et al.*, 1997; Mueser *et al.*, 1999; Galen *et al.*, 2000). Mood disorders increase the risk for substance abuse in the general population (Frye *et al.*, 2003), and mood and anxiety symptoms are among the most common targets for self-medication with abused substances among individuals with schizophrenia (Brunette *et al.*, 1997; Mueser *et al.*, 1995; Goswami *et al.*, 2004). Mood and anxiety symptoms are extremely common symptoms in schizophrenic patients (Hafner *et al.*, 2005). However, mood and anxiety disorders appear to be inherited via risk mechanisms distinct from schizophrenia (Kendler *et al.*, 1981; 1982; 1994). There are increased rates of mood disturbance in the families of schizophrenic patients with intermittent episodes of mood disturbance (Kendler and Hays, 1983) and in the families of schizoaffective disorder patients (Kendler *et al.*, 1995).

Environmental Risk Factors for Substance Abuse by Schizophrenic Individuals

Social factors may contribute to the risk for substance abuse (Drake *et al.*, 2002). Substance-abusing schizophrenic patients are more likely to show characteristics that increase their exposure to illicit substances, such as lower educational attainment, homelessness, and childhood conduct problems (Swartz *et al.*, 2006). The unemployment and social isolation associated with schizophrenia may increase the value of acceptance by substance-abus-

ing groups. Also, the relatively low performance demands associated with substance abuse may suit vocationally disabled individuals.

Environmental factors also may shape the pattern of abused substances among schizophrenic individuals. For example, the rates of each type of substance abuse and the relative prevalence among the abused substances varies substantially in studies conducted in urban and rural settings, in different regions of a given country, and across countries (Schneier and Siris, 1987; Dixon, 1999; Duke *et al.*, 2001; Kavanagh *et al.*, 2002; McReadie and Group, 2002). This variable pattern reflects local availabilities of abused substances and regional patterns of substance use (Mueser *et al.*, 1990; Verdoux *et al.*, 1996; Lambert *et al.*, 1997).

Local environments also moderate the risk for substance abuse by influencing the likelihood that schizophrenic individuals would be exposed to traumatizing events that aggravate the propensity for substance abuse (Gearon *et al.*, 2001; 2003; Mueser *et al.*, 2002; Resnick *et al.*, 2003; Scheller-Gilkey *et al.*, 2004). Substance abusing-schizophrenic patients are exposed to potentially traumatic life events at a higher rate than other schizophrenic patients or the general population. For example, a recent study found an average of 8 potentially traumatic life events in a sample of schizophrenic women with substance abuse disorders (Gearon *et al.*, 2003). Local environments also may attenuate substance abuse risk by providing social supports (Mueser *et al.*, 1990).

REWARD- AND PUNISHMENT-RELATED MOTIVATIONAL DISTURBANCES MAY CONTRIBUTE TO SUBSTANCE ABUSE RISK IN INDIVIDUALS WITH SCHIZOPHRENIA.

Clinical Evidence of Reward- and Punishment-Related Motivation Dysfunction as a Risk Factor for Substance Abuse

Deficits in the motivational impact of natural rewards may predispose individuals to seek out relatively more intense and immediate rewards, as are associated with exposure to abused substances. Thus, individuals prone to addiction have been described as "under-stimulated" or "sensation-seeking" (Zuckerman 1979; Hesselbrock and Hesselbrock 1992; Epstein *et al.*, 1994). The relative overvaluation of immediate punishments, such as abstinence syndromes and conditioned drug withdrawal states (Heinz *et al.*, 2003), also may contribute to negative reinforcement of drug use. They also show exaggerated devaluation of delayed rewards, "delay discounting" (Hesselbrock and Hesselbrock, 1992; Petry, 2002; Petry *et al.*, 2002). Further, the devaluation of delayed punishments (Bechara *et al.*, 2002) reduces the impact of legal and medical risks that often discourage substance use.

These motivation disturbances may emerge from dysfunction within a distributed circuit (FIG. 1) involving the cortical (ventro-medial frontal cortex), limbic (amygdala, hippocampus), and dopaminergic (ventral tegmental area) inputs into the nucleus accumbens (ventral striatum in humans) (Robbins and Everitt, 1996; Everitt *et al.*, 1999; Cardinal *et al.*, 2002). The components of this circuitry are differentially associated with stages of reward processing. The amygdala signals rewards and punishments, the ventral striatum is engaged in predicting subsequent rewards and punishments, and the ventral prefrontal cortex (orbital, insula) assigns affective valence and value to stimuli. Outputs of this system include the dorsolateral prefrontal cortex, involved in selecting responses, central nucleus of the amygdala and hypothalamus to orchestrate the peripheral physiologic response, and brainstem monoamine nuclei that, in turn, enhance the cortico-limbic processing of environmental stimuli.

The orbital or ventromedial prefrontal cortex (VMPFC) is involved in balancing the impact of potential risks and rewards upon behavior (Bussey *et al.*, 1997; Rolls, 1999). Humans with damage to the VMPFC show a pattern of "myopic" decision making in that they choose larger immediate rewards associated with more substantial long-term penalties instead of options that are more favorable overall, but offer smaller immediate rewards (Bechara *et al.*, 2000b). The VMPFC lesion patients also show deficient physiologic arousal in anticipation of reward, suggesting that their high-risk decision making was not informed by emotional signals of alarm (Bechara *et al.*, 2000a).

Individuals with primary substance abuse and dependence disorders exhibit maladaptive patterns of risky decision-making (Rogers *et al.*, 1999). One subgroup showed a pattern of "myopia for the future" similar to the VMPFC-damaged patients

(Bechara *et al.*, 2001; 2002). A larger group of substance abusers showed exaggerated reward bias. They had increased physiologic reactivity to the anticipation of reward, but not neutral or punishment conditions. While they incorrectly chose larger immediate rewards despite greater future losses, this group of substance abusers correctly chose bigger immediate punishments that were associated with larger delayed rewards. A third group of patients performed normally on this task perhaps indicative of a group that abused substances for reasons other than poor impulse control.

Also, resting deficits in orbital frontal cortex (OFC) metabolism are associated with substance dependence and cognitive disinhibition (Goldstein *et al.*, 2001). However, reductions in basal ganglia metabolism, rather than OFC metabolism, were associated with a family history of alcohol dependence in healthy individuals(Volkow *et al.*, 1995). As will be discussed later, reduced ventral striatal activity may contribute to motivation deficits that promote addiction.

Alcohol dependence and alcoholism risk are associated with central striatal activation deficits during the anticipation of reward even though the cortical activation patterns associated with reward signals are intact. These processes have been probed using the "Monetary Incentive Delayed Response Task" (MIDT) (Knutson *et al.*, 2001a,b; 2003; Hommer *et al.*, 2003; Bjork *et al.*, 2004). The standard version of this task involves the presentation of a cue that predicts potential rewards and punishments of varying magnitudes. This cue is followed by a delay period, during which, imaging studies evaluate cortical activation patterns associated with the changes in motivational state related to the anticipation of reward or punishment. After this delay, a cue is presented and subjects are required to push a button as rapidly as possible. Following this action, another cue is presented that signals the delivery of reward or punishment.

When healthy subjects perform the MIDT during fMRI, several brain regions are activated, including the amygdala and ventral striatum. The magnitude of anticipated rewards and the associated positive emotional reaction to anticipated reward, is preferentially correlated with activation of the ventral striatum. A growing literature suggests that recovering alcohol dependent patients show deficits in their ventral striatal activation during the anticipation of reward (D. Hommer, presented to ICANA and reported in Vastag, 2004). As presented in figure 2, preliminary data also suggest that individuals with a family history of alcohol dependence show deficits in ventral striatal activation during the anticipation of rewards and punishments (G. Pearlson, personal communication). In contrast, the presentation of the reward signal activates the medial prefrontal cortex and posterior cingulate gyrus. Alcohol dependent patients are not distinguished from healthy subjects by their cerebral response to the reward signal. Similar activation deficits have emerged using similar reward processing paradigms in smokers (Martin-Solch *et al.*, 2001).

Evidence of Reward- and Punishment-Related Motivational Dysfunction Associated with Schizophrenia

Schizophrenic patients exhibit disturbances in the processing of rewards and punishments. Adolescent individuals with schizophrenia show reduced preference for social rewards compared to healthy adolescents (Layne and Wallace, 1982), and reduced levels of reward dependence as a personality trait compared to their healthy siblings and healthy comparison subjects (Kurs *et al.*, 2005).

There is evidence that patients with schizophrenia show deficits in both the motivational and consummatory aspects of reward and punishment. Studies of the effects of reward and punishment upon learning by schizophrenic patients became a major research focus as investigators in the 1950s began to explore the potential role for manipulating rewards and punishments in the psychosocial treatment of schizophrenia. These studies suggested that schizophrenic patients may have deficits in sustaining reward-related motivational states (Garmezy, 1952). These deficits may contribute to the finding that individuals with schizophrenia tend to learn more rapidly under conditions of punishment than reward whereas healthy individuals tend to learn more rapidly under conditions of reward (Cohen, 1956; Ullman and Forsythe, 1959).

One would predict similar relationships between motivation disturbances and substance abuse in schizophrenic patients as were observed in non-schizophrenic substance abusers. This view is consistent with studies indicating that substance-abusing schizophrenic patients show elevated levels of sensation-seeking (Dervaux *et al.*, 2001; 2004).

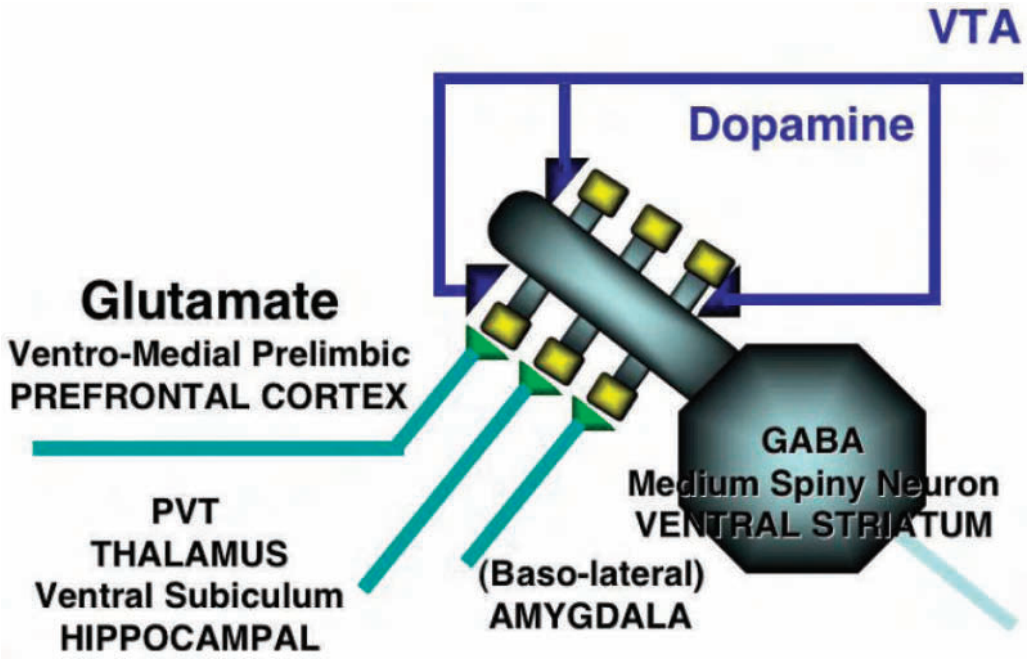

FIGURE 1 This paper presents the convergence of glutamatergic input from cortical and limbic structures and dopaminergic input from the ventral tegmental area (VTA) upon the dendritic spines of medium spiny neurons located in the ventral striatum. PVT: paraventricular nucleus of the thalamus.

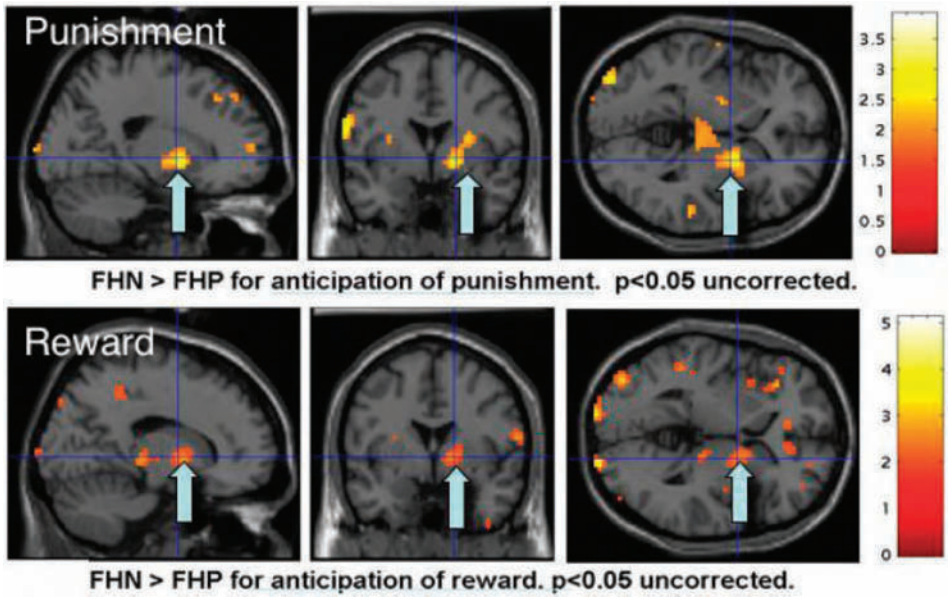

FIGURE 2 This figure depicts the differential activation of cortical and limbic circuitry in healthy individuals with a family history of alcohol dependence (FHP) and without a family history of alcohol dependence (FHN). Subjects performed a modified version of the Monetary Incentive Delay Task during event-related functional magnetic resonance imaging. In this task, subjects are presented with cues that predict the magnitude of subsequent rewards and punishments (Knutson *et al.*, 2001c). Data from 6 pairs of subjects were analyzed using a voxel-based approach (SPM2) and the results are presented. The top figure presents regions that show greater activation in FHN subjects than FHP subjects in anticipation of reward, while the bottom figure displays regions where FHN show greater activation than FHP in anticipation of punishment. The arrows point to a striatal subregion where FHN healthy subjects show significantly greater activation than FHP healthy subjects during the anticipation of reward and punishment (G. Pearlson, unpublished data).

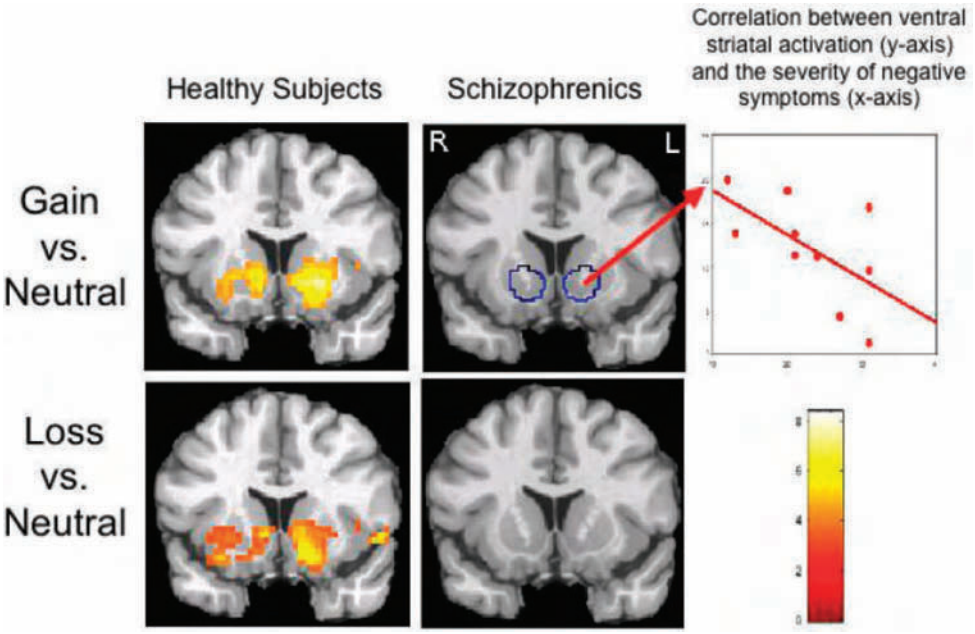

FIGURE 3 Top: This figure presents fMRI evidence of ventral striatal activation associated with anticipation of reward in healthy subjects (top left) and the absence of significant activation of this region during the anticipation of reward in schizophrenic individuals (top middle). In schizophrenics, low activation of the left ventral striatum by reward cues was correlated with increased severity of negative symptoms (Spearman's R=-0.66, P=0.038; top-right). Bottom: Healthy subjects showed activation of the ventral striatum bilaterally during the presentation of loss versus neutral cues (bottom-left); that was not observed in unmedicated schizophrenic individuals (bottom-center). [All slices are shown at MNI y-coordinate 9, for illustrative purpose P <0.005 uncorrected, cluster level 20]. This figure is slightly modified from (Juckel *et al.*, 2005).

Also, schizophrenic patients over-value the benefits of smoking relative to other rewards that they experience (Spring *et al.*, 2003). As summarized in table II, studies tend to support the hypothesis that schizophrenic patients exhibit a bias in their responding to reward that resembles individuals with primary substance abuse disorders and patients with damage to the ventromedial prefrontal cortex (Wilder *et al.*, 1998; Beninger *et al.*, 2003; Ritter *et al.*, 2004; Shurman *et al.*, 2005). While there are inconsistencies across studies, schizophrenic patients show evidence of overvaluing immediate rewards and devaluing delayed punishments relative to healthy comparison groups. These deficits appear to be differentially modulated by clozapine and typical neuroleptic pharmacotherapy (Beninger *et al.*, 2003). The impairments in decision making show modest correlations with the level of negative symptoms in some studies (Shurman *et al.*, 2005), but are relatively independent of magnitude of deficits in executive cognitive functions associated with dorsolateral prefrontal cortex networks (Ritter *et al.*, 2004). Also, these findings may be consistent with other deficits exhibited by schizophrenic individuals in functions associated with the OFC, including olfactory identification (Hurwitz *et al.*, 1988; Seidman *et al.*, 1991).

The deficits in the circuitry underlying the anticipation of rewards and punishments appear to be similar in schizophrenic patients and non-schizophrenic individuals with substance abuse disorders. As presented in figure 3, schizophrenic individuals showed ventral striatal activation deficits on the Monetary Incentive Delay Task during a period when they anticipated working for reward and when they anticipated working to avoiding punishment (Juckel *et al.*, 2005). This study also found that the deficit in striatal activation in anticipation of reward was correlated with the severity of negative symptoms, perhaps indicative of a link between motivational deficits in patients and impaired ventral striatal function.

Do Deficits in Ventral Striatal Activation in Schizophrenia and in Substance Abuse Disorders Suggest a Common Dopaminergic Dysfunction Associated with Both Conditions? Considering the answer to this question requires a speculative foray into neurobiology theory. The ventral striatal activation associated with the anticipated reward magnitude in the MIDT is predicted to be associated with activation of dopaminergic ventral tegmental area input into the ventral striatum. Dopaminergic projections to the ventral striatum are activated by uncertainty, unexpected rewards or punishments, and by cues that predict expected rewards (Schultz, 1998; Fiorillo *et al.*, 2003). The extent of dopamine neuronal activation exhibited in anticipation of reward is proportionate to the magnitude of the expected reward (Cromwell and Schultz,

Table I Intensity of smoking by matched schizophrenic patients and non-schizophrenic comparison subjects (modified from McReadie and Group, 2002).

Number of cigarettes	Schizophrenic Subjects (n=125) N (%)	Non-Schizophrenic Subjects (n=82) N (%)
<10	9 (7%)	19 (24%)
10-29	66 (53%)	55 (66%)
≥30	50 (40%)	8 (10%)

Association of schizophrenia and heavy smoking: χ^2=27.23, p <0.0001

Table II Abnormal performance of schizophrenic patients on the Iowa Gambling Task.[d]

	N (SZ/HS)	Earnings	Disadvantageous Decision Pattern[a]
Wilder *et al.*	12/30	No group difference	No group difference
Beninger *et al.*	36/18	Reduced[b]	Disadvantageous[b]
Ritter *et al.*	20/15	Reduced	Disadvantageous
Shurman *et al.*	39/10	Reduced	Disadvantageous[c]

a. The Iowa Gambling Task presents subjects with two disadvantageous decks that are associated with higher immediate gains but overall greater penalties and two "good" decks that produce lower initial gains but overall reduced penalties. The disadvantageous decision pattern has been called "reward myopia" because of its relative bias to immediate rewards at the expense of reduced earnings.

b. A disadvantageous decision making pattern was observed in a subgroup of patients treated with atypical neuroleptics (n=18), but not in a subgroup treated with typical neuroleptics (n=18).

c. Schizophrenic patients in this study showed a distinctive pattern of decision making. They exhibited a disadvantageous pattern of decision making by chosing the two disadvantageous decks at increased levels compared to healthy subjects. However, they chose one of the two advantageous decks at a level that was not statistically reduced compared to healthy subjects.

d. Literature cited: (Beninger *et al.*, 2003; Ritter *et al.*, 2004; Shurman *et al.*, 2005; Wilder *et al.*, 1998)

2003; Tobler *et al.*, 2005). Consistent with this view, dopamine levels rise in the rodent nucleus accumbens both in anticipation and during alcohol self-administration (Melendez *et al.*, 2002).

Primary substance abuse disorders are associated with deficits in dopamine release within the ventral striatum. These deficits are presumed to contribute to functional impairments of the ventral striatum. Several studies indicate that alcohol and drug dependent individuals show reductions in ligand binding to dopamine D_2 receptors throughout the striatum (Martinez *et al.*, 2005; Volkow *et al.*, 1996). Dopamine D_2 receptor deficits in the ventral striatum in alcohol dependent patients are correlated with the extent of craving produced by exposure to alcohol cues (Heinz *et al.*, 2004). The reduction in striatal D_2 receptor density in methamphetamine users also correlated with reductions in OFC metabolic rate, suggesting an association with impulsivity (Volkow *et al.*, 2001). In addition, cocaine dependent individuals show reductions in amphetamine stimulated dopamine release in all striatal subregions (Martinez *et al.*, 2004). In contrast, recovering alcohol dependent patients show reductions in amphetamine-stimulated dopamine that are restricted to the ventral striatum (Martinez *et al.*, 2005). The findings of reduced amphetamine-stimulated dopamine release are consistent with evidence of reduced basal striatal dopaminergic activation as reflected by [^{18}F]DOPA uptake (Heinz *et al.*, 2005). These findings suggest that reductions in dopamine release and perhaps the postsynaptic response to dopamine contribute to the deficits in ventral striatal activation during the anticipation of reward and punishment in substance abusing patients.

Schizophrenia, however, is associated with striatal dopaminergic hyperactivity. There is evidence of increased level of basal dopaminergic activity as suggested by the level of [^{18}F]DOPA uptake (Reith *et al.*, 1994) and the increase in D_2 receptor availability to [^{11}C]raclopride following catecholaminergic depletion (Abi-Dargham *et al.*, 2000). Patients also exhibit increased dopamine release following amphetamine administration, and the extent of amphetamine-stimulated dopamine release is highly correlated with the worsening of psychosis (Laruelle *et al.*, 1996; Breier *et al.*, 1997; Abi-Dargham *et al.*, 1998).

Is the dopaminergic hyperactivity associated with schizophrenia inconsistent with the substance abuse-related dopaminergic deficit in ventral striatum? There is some evidence that might be consistent with the possibility that a ventral striatal dopamine deficit occurs in a subgroup of patients diagnosed with schizophrenia that may resemble the reduction in dopamine release seen in primary substance abusers. First, the dopaminergic hyperactivity associated with schizophrenia is only found in that subgroup of patients who show psychotic worsening following amphetamine and who have had a recent hospitalization (Laruelle *et al.*, 1996; 1999). It is not yet clear whether the subgroup of patients with striatal dopaminergic hyperactivity are at greater or less risk for substance abuse than other patients. Second, the schizophrenia-related increases in resting striatal [^{18}F]DOPA uptake (Dao-Castellana *et al.*, 1997) and amphetamine-stimulated dopamine release (M. Laruelle, personal communication) are primarily localized to the caudate or "cognitive striatum" rather than the ventral striatum. This observation may be consistent with other data suggesting that a subgroup of patients with schizophrenia may exhibit resting deficits in [^{18}F]DOPA uptake in the ventral striatum (Elkashef *et al.*, 2000). Further, since optimal treatment with many antipsychotic medications blocks 60-80% of the D_2 receptors in the striatum (Kapur *et al.*, 1999), it is possible that pharmacotherapy may create a deficit in ventral striatal dopaminergic function that contributes to addiction risk. If so, then the apparent differential effects of clozapine compared to other antipsychotics upon risky decision making (Beninger *et al.*, 2003) and substance abuse (Noordsy and Green, 2003) could reflect the reduced dopamine deficit produced by clozapine compared to other medications (Kapur *et al.*, 1999).

Alternatively, the ventral striatal dysfunction among schizophrenic patients could be associated with increased ventral striatal dopaminergic activity. First, as reviewed earlier, substance abuse risk among schizophrenic patients is associated with stress and clinical instability, factors that were associated with increased striatal dopamine release in schizophrenic patients (Laruelle *et al.*, 1999). Second, the rewarding effects of amphetamine are associated with increased striatal dopamine release in humans, and greater dopaminergic response might then be predicted to increase the abuse liability of psychostimulants (Abi-Dargham *et al.*, 2003).

Third, there appears to be a non-linear ("inverted-U") relationship between the extent of dopaminergic activation and ventral striatal activation in the delayed response task. Amphetamine administration attenuates, rather than augments, ventral striatal activation during the anticipatory phase of the MIDT (Knutson *et al.*, 2004). Thus, in schizophrenic patients it is possible that disturbances in processing the motivational properties of rewards and punishments associated with ventral striatal dysfunction may be associated with dopaminergic hyperactivity, while in primary substance abusers it may be associated with deficient dopaminergic activation.

Abnormalities in VMPFC and hippocampus associated with schizophrenia may contribute to ventral striatal dysfunction associated with schizophrenia. The OFC has an extensive projection to the ventral striatum. OFC deficits in schizophrenic patients suggested by abnormal performance of the Iowa Gambling Task, reviewed earlier, are paralleled by neuronal abnormalities in this region in post-mortem studies (Deakin and Simpson, 1997b). Similarly, post-mortem, structural neuroimaging, and functional neuroimaging studies describe a range of deficits associated with schizophrenia (Bilder *et al.*, 1995; Deakin and Simpson, 1997a; Kegeles *et al.*, 2000). The hippocampus plays a critical role in gating nucleus accumbens activity (O'Donnell and Grace, 1995). Ventral hippocampal lesions in animals disrupt the gating of ventral striatal activity by the hippocampus and contribute to limbic dopaminergic hyperactivity (Goto and O'Donnell, 2002). The effect of neonatal hippocampal lesion upon the gating of ventral striatal activity can be mimicked by systemic administration of the NMDA glutamate receptor antagonist, phencyclidine (O'Donnell and Grace, 1998). Hippocampal deficits associated with schizophrenia contribute to striatal dopaminergic hyperactivity in patients with schizophrenia. Based on the preclinical studies, it is possible that hippocampal deficits in NMDA receptor subunit gene expression and ligand binding to NMDA receptors in both post-mortem and SPECT neuroimaging studies contribute to the deficits in NMDA receptor function associated with schizophrenia (Gao *et al.*, 2000; Meador-Woodruff and Healy, 2000; Pilowsky *et al.*, 2006). This evidence of decreased hippocampal NMDA receptor function associated with schizophrenia may conflict with evidence of increased NMDA receptor function associated with alcohol dependence (Krystal *et al.*, 2003b; Petrakis *et al.*, 2004a). Perhaps these differences in NMDA receptor function between alcoholism and schizophrenia contribute to possible differences in dopaminergic regulation in these two disorders.

Thus, there appears to be convergence between disturbances in the function of motivation circuitry in schizophrenia and primary substance abuse disorders, but potentially important differences in the underlying neurobiology. These differences raise the possibility that the risk factors for substance abuse among schizophrenic patients may be somewhat unique to this diagnostic context. This distinction between network dysfunction and underlying neurobiology may contribute to the separate heritabilities of schizophrenia and substance abuse disorders, *i.e.*, the increased risk for substance abuse among relatives of schizophrenic patients may only occur in the context of development of the diagnosis of both substance abuse and schizophrenia. It may not be present in family members of individuals with schizophrenia who do not possess the necessary network dysfunction to produce the risk for substance abuse in the proband. To the extent that family members manifest reduced levels or only a component of the network dysfunction associated with schizophrenia, these individuals also may not manifest the full substance risk associated with their relatives diagnosed with schizophrenia.

Substance Abuse Risk and the Deconstruction of Negative Symptoms: Potential Distinctions Between Amotivation and Anhedonia

The schizophrenia research literature describing the relationship between negative symptoms and substance abuse risk contains an apparent contradiction. Negative symptoms are identified by individuals with schizophrenia as targets of substance abuse. They report stimulation- and pleasure-seeking as being among the most common objectives of substance abuse (Dixon *et al.*, 1990; Fenton *et al.*, 1997; Goswami *et al.*, 2004). However, the published literature suggests that the level of negative symptoms is only weakly linked to the level of comorbidity with substance abuse among schizophrenic patients (Brunette *et al.*, 1997). This weak correlation may not be surprising since negative symptoms may be primary to the illness or

secondary to substance abuse, antipsychotic medications, or perhaps a consequence of withdrawal from abused substances. Also, when not using substances, schizophrenic patients with a history of substance abuse have lower levels of negative symptoms than other schizophrenic patients (Dixon *et al.*, 1991; Lysaker *et al.*, 1994). Similarly, deficits in GABA neuronal integrity in the prefrontal cortex, associated with schizophrenia, are reduced in the subgroup of patients with histories of substance abuse (Pierri *et al.*, 1999). These GABA deficits may contribute to negative symptoms and cognitive dysfunction in schizophrenic patients (Krystal *et al.*, 2003a).

One possible reason for this apparent conflict is that deficits associated with the anticipation or motivational impact of rewards and punishments (amotivation) may be positively associated with addiction risk, while primary reward deficits (anhedonia or perhaps blunted affect) may be protective against substance abuse. Primary substance abusers show the motivational dysfunction in common with schizophrenic patients, but not the primary anhedonia (Heinz, 1999; Bechara *et al.*, 2002).

Anhedonia is a cardinal negative symptom of schizophrenia (Green *et al.*, 1999; Juckel *et al.*, 2003), particularly the deficit syndrome (Carpenter *et al.*, 1988). Schizophrenic patients with the deficit syndrome are relatively impaired in their ability to recognize affect (Bryson *et al.*, 1998). The insensitivity to reward and punishment appears to contribute to poor social and vocational outcomes, but they appear to paradoxically protect schizophrenic patients from attempting suicide or engaging in substance abuse (Fenton and McGlashan, 1994; Kirkpatrick *et al.*, 1996). Recent studies provide physiological evidence supporting the earlier clinical observations. Studies now report both electrophysiologic and cerebral metabolic evidence of reduced response to rewarding stimuli (Brecher and Begleiter, 1983; Crespo-Facorro *et al.*, 2001).

ALTERED RESPONSES TO SUBSTANCES OF ABUSE MAY INFLUENCE THE PREVALENCE AND PATTERN OF SUBSTANCE ABUSE RISK AMONG PATIENTS WITH SCHIZOPHRENIA

Alterations in the response to particular drugs may affect the prevalence and pattern of substance abuse by schizophrenic patients. In particular, the expression of the pathophysiology of schizophrenia may change the nature of the effects of abused substances in a manner that increases their abuse liability. This hypothesis builds on a large literature, primarily within the alcoholism field, that populations at risk for abusing a particular substance exhibit reduced dysophric effects or increased euphoric effects in response to that particular abused substance (Pollock, 1992; Schuckit and Smith, 1996; Heath *et al.*, 1999).

Schizophrenic individuals abuse substances in ways that distinguish them from the general population (Schneier and Siris, 1987). As noted in table I, when abusing nicotine, schizophrenic patients tend to smoke more heavily than non-schizophrenic smokers (McReadie and Group, 2002). Other data suggest that when matched to healthy subjects on the number of smoked cigarettes, schizophrenic patients extract more nicotine than healthy individuals (Jacobsen *et al.*, 2004). In contrast, a group of alcohol dependent military veterans diagnosed with schizophrenia (n=31) (Petrakis *et al.*, 2004b) drank less frequently than a large group (n=627) (Krystal *et al.*, 2001) of non-psychotic alcohol dependent military veterans (schizophrenic patients: drank on 39.0 ± 28.0% of the month prior to treatment; non-schizophrenic patients drank on 66.6 ± 29.0% of the 90 days prior to treatment).

Individuals with schizophrenia show alterations in their responses to nicotine, ethanol, and cannabis that may influence their substance abuse. For schizophrenic individuals, the favorable impact of nicotine ingestion upon cognitive function (Jacobsen *et al.*, 2004; Sacco *et al.*, 2005) and the worsening of cognitive deficits associated with nicotine withdrawal (George *et al.*, 2002) may promote the abuse of this substance. With chronic smoking, schizophrenic patients, but not healthy smokers, show increased NMDA receptor-related gene expression (Mexal *et al.*, 2005). This effect could address deficits in NMDA receptors associated with schizophrenia (Pilowsky *et al.*, 2006). Several studies describe abnormal regulation or structure of the α_7 subunit-containing (Leonard *et al.*, 2000; Freedman *et al.*, 2001) and high affinity ($\alpha_4\beta_2$ subunit-containing) nicotinic cholinergic receptors (Breese *et al.*, 2000). Surprisingly, to our knowledge, there are no systematic laboratory data regarding altered subjective responses to nicotine in

schizophrenic patients.

With alcohol and cannabis there is evidence of enhanced euphoric responses that may promote a heightened prevalence of abuse among schizophrenic patients. For example, a recent study found a dose-related increase in the euphoric effects of ethanol in stable and medicated schizophrenic patients (D.C. D'Souza, unpublished data). The facilitation of $GABA_A$ receptor function by ethanol may contribute to these effects (Krystal and Tabakoff, 2002). No enhancement of euphoria was reported in a similar population of schizophrenic patients compared to healthy subjects (D'Souza *et al.*, 2005), but retrospective reports suggest that cannabis may have anxiolytic and stimulatory effects in patients (Krystal *et al.*, 1999). It is not clear whether these euphoric effects reflect a stimulatory effect of THC at cannabinnoid receptors or whether they reflect an inhibitory action of another cannabinnoid, cannabidiol, at these same receptors.

However, schizophrenic patients also may be more sensitive to dysphoric effects of some abused substances. This trait might account for the fact that while individuals with schizophrenia abuse these substances more frequently than the general population, they abuse them with lower intensity. Ethanol has many actions in the brain. Ethanol actions at $GABA_A$ receptors are associated with low levels of intoxication. In contrast, the blockade of NMDA glutamate receptors by ethanol emerges as an important contributor to the discriminative stimulus effects of ethanol in animals and humans at levels associated with heavy drinking, generally above four standard ethanol drinks (Grant and Colombo, 1993; Krystal *et al.*, 1998; 2003c). Reductions in NMDA glutamate receptor function associated with schizophrenia may contribute to increased sensitivity to the cognitive effects of ethanol in schizophrenic patients (D'Souza *et al.*, unpublished data). This pattern contrasts with data collected in groups at risk for heavy drinking, who show reduced dysphoric responses to ethanol (Schuckit, 1994) and ketamine (Krystal *et al.*, 2003b). Their pattern is suggestive of enhanced NMDA glutamate receptor function. To the extent that reduced NMDA receptor function protects schizophrenic patients from heavy drinking, one might expect that a pharmacologic intervention that enhances NMDA receptor function might worsen drinking. As preliminary support of this hypothesis, a small pilot study now suggests that the addition of glycine to ongoing neuroleptic treatment either has no effect or even worsens drinking related outcomes compared to placebo in alcohol dependent schizophrenic patients who are receiving ongoing neuroleptic treatment (I. Petrakis, E. Ralevski, J. Krystal, unpublished data). These pilot data need to be replicated in larger clinical trials.

Similarly, schizophrenics may show dysphoria during THC ingestion due to its propensity to worsen psychosis, negative symptoms, cognitive impairments, and dysphoric mood in patients (D'Souza *et al.*, 2005). However, it is possible that substances in cannabis, such as cannabidiol, attenuate the full impact of THC in the context of marijuana ingestion.

IMPLICATIONS: FROM SUBSTANCE ABUSE VULNERABILITY TO SELF-MEDICATION

Self-Medication of Subjective Distress by Schizophrenic Patients: Uses of Abused Substances and Pharmacotherapy

There is relatively limited evidence to support a narrow self-medication hypothesis, *i.e.*, that patients self-administer abused substances in order to cope with psychosis or negative symptoms. As has been reviewed, this hypothesis is not supported by clear associations between the severity of symptoms and the level of abuse or evidence that the abused substances effectively suppress the targeted symptoms (Brunette *et al.*, 1997). As noted earlier in this review, nicotine may be one exception in that there is growing data related to its efficacy in improving attention and related cognitive functions.

However, schizophrenic patients are not different from the general population in using substances to cope with emotional distress, predominately anxiety and depression (Krystal and Raskin, 1970; Khantzian *et al.*, 1974; Dixon *et al.*, 1991; Brunette *et al.*, 1997; Khantzian, 1997). Prescribed antipsychotic medications, similarly, are tools that patients use to cope with their subjective distress. Adherence with prescribed medications is highest when patients recognize their need for medications and when the medications produce a desirable balance of positive and negative subjective effects (Freudenreich *et al.*, 2004; Sibitz *et al.*, 2005). If

patients view abused substances as superior alternatives to prescribed medications to cope with subjective distress, they would seem to be at risk for poor outcomes.

Synergy Among Substance Abuse Risk Mechanisms for Individuals with Schizophrenia

The extent of neurobiological understanding of substance abuse risk associated with schizophrenia is extremely limited. Despite progress in many areas, relatively few translational neuroscience approaches have been applied to the study of this issue. However, this paper has reviewed many factors that may contribute to the excess substance abuse vulnerability in schizophrenia patients compared to the general population. The research conducted to date supports a scenario that is consistent with our clinical experience. Schizophrenic patients may seek the euphoria and the reduction in dysphoria that abused substances offer. Disturbances in their processing of delayed rewards and punishments, altered responses to abused substances that increase their abuse liability, and a tendency for disadvantageous decision-making under risky conditions combine to promote impulsive and repeated self-administration of abused substances - a process that may lead to substance abuse and dependence. We now understand that disturbances in a widely distributed circuit that includes, but is not limited to, VMPFC, hippocampus, amygdala, and ventral striatum, contribute to the motivational disturbances and risky decision-making in primary substance abusers and patients with schizophrenia. Disturbances in glutamatergic, GABAergic, nicotinic, and dopaminergic function are implicated in the vulnerability to substance abuse and the treatment of substance abuse in schizophrenic patients. Ongoing advances in the understanding of substance abuse risk among schizophrenic patients increases the likelihood that we will develop more effective prevention and treatment approaches for these patients.

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