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Serotonin and dopamine receptors in motivational and cognitive disturbances of schizophrenia

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Negative symptoms (e.g., decreased spontaneity, social withdrawal, blunt affect) and disturbances of cognitive function (e.g., several types of memory, attention, processing speed, executive function, fluency) provide a major determinant of long-term outcome in patients with schizophrenia. Specifically, motivation deficits, a type of negative symptoms, have been attracting interest as (1) a moderator of cognitive performance in schizophrenia and related disorders, and (2) a modulating factor of cognitive enhancers/remediation. These considerations suggest the need to clarify neurobiological substrates regulating motivation. Genetic studies indicate a role for the monoamine systems in motivation and key cognitive domains. For example, polymorphism of genes encoding catecholamine-O-methyltransferase, an enzyme catabolizing dopamine (DA), affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion. On the other hand, motivation to maximize rewards has been shown to be influenced by other genes encoding DA-related substrates, such as DARPP-32 and DA-D_2 receptors. Serotonin (5-HT) receptors may also play a significant role in cognitive and motivational disabilities in psychoses and mood disorders. For example, mutant mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors. Taken together, genetic predisposition related to 5-HT receptors may mediate the diversity of incentive motivation that is impaired in patients receiving biological and/or psychosocial treatments. Thus, research into genetic and neurobiological measures of motivation, in association with 5-HT receptors, is likely to facilitate intervention into patients seeking better social consequences.

Keywords: serotonin, 5-HT receptors, motivation, cognition, schizophrenia, dopamine, negative symptoms, psychosis

INTRODUCTION

Disturbances of mental processes, including cognitive function (e.g., several types of memory, attention, processing speed, and executive function, fluency) and motivation characterize many of the psychiatric illnesses, such as schizophrenia, mood disorders, and substance abuse (Simpson et al., 2011; Choi et al., 2014; Sumiyoshi, in press). Recently, the development of biological (e.g., pharmacotherapy and brain stimulation) and psychosocial (e.g., cognitive rehabilitation) interventions is targeting social function/adaptation as an important outcome measure (Harvey et al., 2011; Leifker et al., 2011). In this context, negative symptoms (decreased spontaneity, social withdrawal, and blunt affect) and cognitive impairment provide a major determinant of long-term outcome. Specifically, motivation deficits have been attracting interest as a moderator of (1) cognitive performance in patients with schizophrenia and related disorders, and (2) beneficial influence of cognitive enhancers/remediation (Fervaha et al., 2014; Strauss et al., 2014). These considerations suggest the need to clarify neurobiological substrates regulating motivation for improving quality of life in a rational and effective manner.

We herein present a theory/hypothesis that the research into genetic and neurobiological measures of motivation, linked to serotonin (5-HT) receptors, would facilitate treatment of patients with schizophrenia or other psychiatric illnesses.

MOTIVATIONAL DISTURBANCES IN SCHIZOPHRENIA

Schizophrenia is characterized by a range of symptoms, e.g., positive symptoms (delusions, hallucinations, thought disorders), negative symptoms, mood symptoms, and cognitive impairment. Specifically, there is a suggestion that negative symptoms can be separated into two domains; (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia (Strauss et al., 2014). There is a general consensus that motivational disturbances may overlap some (e.g., anhedonia), but not all (e.g., blunt affect, alogia) aspects of negative symptoms. The former dimension has been considered to be of greater importance in terms of functional outcome, quality of life, and recovery from the disease (Strauss et al., 2014). Whether other aspects of symptomatology of schizophrenia (e.g., mood

symptoms) may substantially affect motivation in patients or vulnerable people remains to be determined (Schlosser et al., 2014).

DOPAMINE (DA) SYSTEMS GOVERNING MOTIVATION AND COGNITION

The neural basis for intrinsic motivation has been an issue of extensive research. For example, activity of the anterior striatum and prefrontal cortex (PFC), measured by the functional MRI, has been shown to be associated with intrinsic motivation (Murayama et al., 2010). This line of anatomical evidence is consistent with genetic studies indicating a role for the monoamine systems in cognition and motivation, as discussed below.

The Val158Met polymorphism of the genes encoding catecholamine-O-methyltransferase (COMT), an enzyme catabolizing DA, affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion (Egan et al., 2001). Thus, individuals with the val/val carriers in *COMT* show greater efficacy of the enzyme, leading to decreased DA levels in the PFC. The enzyme has also been suggested to mediate uncertainty-based exploration that is linked to DA levels in the PFC. For example, individuals with at least one met-allele show enhanced exploration compared to those with val/val genotype (Frank et al., 2007).

On the other hand, motivation to maximize rewards has been shown to be influenced by other DA-related genes expressed in the striatum/nucleus accumbens (NAc). Specifically, reward learning and negative reward avoidance are affected by genotypes of a polymorphism (rs907094. A/G) of the gene encoding DARPP-32 (a protein required for synaptic plasticity and reward learning mediated by DA-D_1 receptors) and the D_2 receptor (related to avoidance of negative outcomes), respectively (Frank et al., 2007; Klein et al., 2007). Thus, individuals with T/T genotype show greater expression of mRNA for the DARPP-32 gene, leading to greater performance to maximize rewards compared to C-allele carriers (reviewed in Frank et al., 2009). Similarly, T/T carriers of genes encoding D_2 receptors are associated with greater density of these receptors in the striatum and greater likelihood to maximize rewards (Hirvonen et al., 2004; Frank et al., 2007). A recent study (Simpson et al., 2013) reported that overexpression of D_3 receptors, a member of the D_2 receptor family, in the striatum selectively impaired incentive motivation, as measured by an operant task.

The mechanisms by which DA receptors govern motivation and cognitive functions may involve timing perception. For example, genetically-engineered mice overexpressing D2 receptors in the striatum have been shown to elicit impaired working memory, behavioral flexibility and sensorimotor gating, i.e., behavioral abnormalities reminiscent of schizophrenia (Kellendonk et al., 2006). These model animals also demonstrate reduced motivation, as well as alteration of interval timing organization, as measured by the operant timing task (Drew et al., 2007). Further studies indicate that the impaired timing in these mutant mice mediates the ability of decreased motivation to worsen cognitive functions, including working memory and attention (Ward et al., 2009). These lines of evidence suggest a strategy for the intervention into motivational disturbances, in terms of biological and/or tailor-made treatments.

Figure 1 summarizes a concept about how genes encoding these DA-related substrates contribute to cognitive and motivational behaviors.

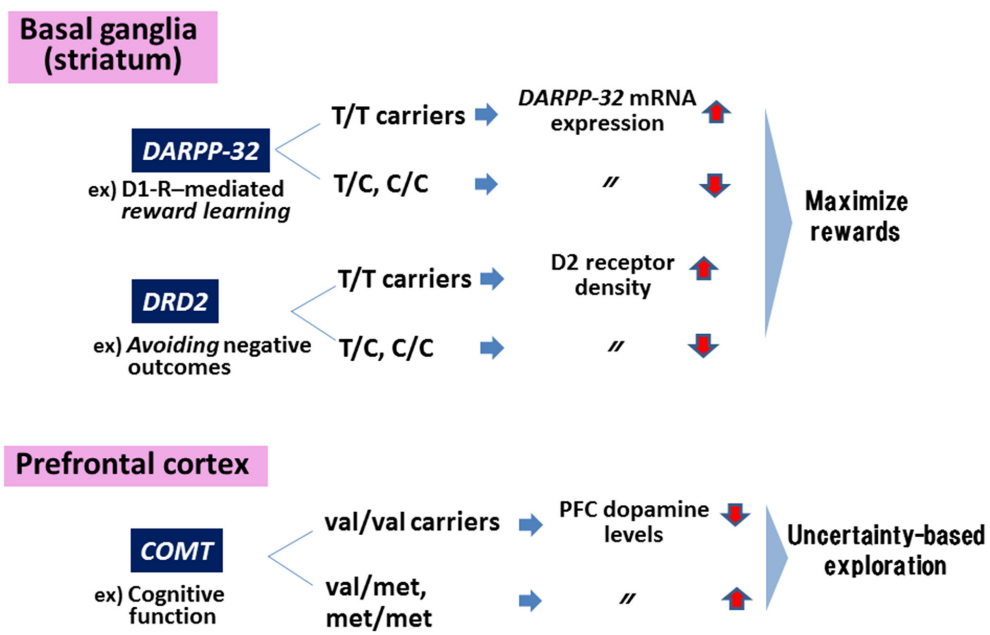

FIGURE 1 | Genes in the dopaminergic motivational system. Polymorphisms of genes encoding *DARPP-32* and dopamine (DA)-D_2 receptors *(DRD2)* affect behaviors to maximize rewards, while the polymorphism in *COMT* are associated with uncertainty-based exploration. Information in the Figure was extracted from Frank et al. (2009).

5-HT RECEPTOR SUBTYPES IN MOTIVATION-RELATED BEHAVIORS

5-HT receptors, e.g., 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} subtypes, may also play a role in cognitive and motivational disabilities in psychoses and mood disorders (Meltzer and Massey, 2011; Newman-Tancredi and Albert, 2012; Ohno et al., 2012). For example, several antipsychotic and antidepressant drugs have been suggested to ameliorate negative symptoms and mood disturbances, partly through actions on 5-HT_{1A} and 5-HT_{2A} receptors (Newman-Tancredi and Albert, 2012; Ohno et al., 2012; Sumiyoshi et al., 2013; Sumiyoshi, 2014). Clozapine, the prototype of atypical antipsychotic drugs, which is most effective in treating negative symptoms, may act as an inverse agonist on 5-HT_{2C} receptors (Meltzer and Massey, 2011).

Data from recent investigations support the contribution of 5-HT receptors to motivational behaviors. For example, mutant mice over-expressing D_2 receptors in the striatum, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors (Simpson et al., 2011). Furthermore, increased D_1, D_2 and 5-HT_{2C} receptors co-exist in mice mis-expressing ADAR2, an RNA-editing enzyme, and these animals elicit altered expression of reward-related mRNAs in the brain (Akubuiro et al., 2013). Collectively, these observations indicate the importance of some 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, in the pathophysiology and treatment of motivational disturbances associated with psychoses (**Figure 2**).

The role for 5-HT_{2C} receptors in psychiatric symptoms relevant to functional outcome is also supported by observations in mice whose 5-HT-synthesizing enzyme (tryptophan hydroxyxlase-2) was genetically engineered (Del'Guidice et al., 2014). Thus, treatment with the 5-HT_{2C} agonist CP809,101 ameliorated impairments in cognitive flexibility and reversal learning in these mutant animals (Del'Guidice et al., 2014).

As noted above, up-regulation of 5-HT_{2c} receptors in the striatum may be associated with a decrease in incentive motivation (Simpson et al., 2011). Further, 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also have been suggested to regulate motivation by modulating transmissions to NAc (Bubar et al., 2011) (**Figure 2**). It should be noted that a proportion of NAc-projecting VTA neurons may release both DA and GABA (Bubar et al., 2011). Altered balance in this complicated 5-HT_{2c} receptor-associated network is postulated to cause reward-related disorders, such as schizophrenia, depression, and addiction (Bubar et al., 2011).

Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}receptors, may directly or indirectly influence this neural system for motivational behaviors as well. For example, 5-HT_{1A} receptor gene promotor polymorphism (rs6295, C-1019G) has been associated with treatment effects on negative symptoms of schizophrenia (Reynolds et al., 2006). **Figure 2** illustrates a putative neural network mediating motivational behaviors in relation to 5-HT receptors, which, together with

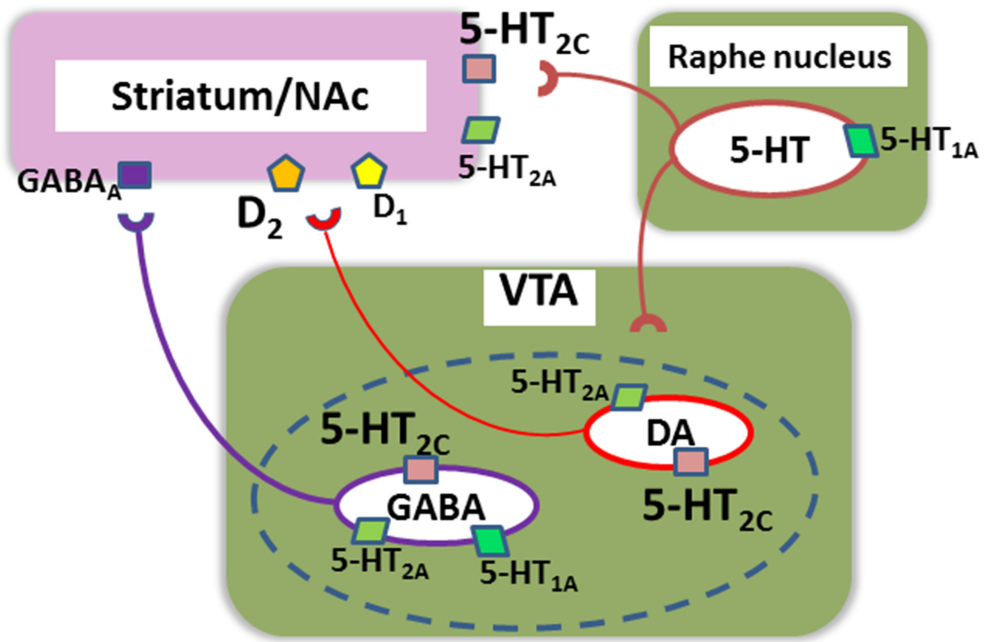

FIGURE 2 | A putative neural network mediating motivational behaviors in relation to serotonin (5-HT) receptors. (1) Up-regulation of 5-HT_{2c} receptors in the nucleus accumbens (NAc)/striatum may be associated with a decrease in incentive motivation in mutant mice over-expressing dopamine (DA)-D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). SB242084, a selective *ant*agonist at these receptors, increases incentive motivation in these model mice. (2) 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also affect motivation by modulating transmissions to NAc, including actions on D_1 and D_2 receptors (Bubar et al., 2011). The dotted line indicates that a proportion of NAc-projecting VTA neurons releases both DA and GABA (Bubar et al., 2011). (3) Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}, may also directly or indirectly regulate this neural system of motivational behaviors.

Figure 1 (upper part), may suggest the contribution of DA-5-HT interactions.

CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

Based on the discussions so far, drugs acting on some 5-HT receptor subtypes, particularly, 5-HT_{2C} receptors, are likely to improve motivational deficits in individuals with schizophrenia. For example, SB242084, a selective *ant*agonist at 5-HT_{2C} receptors, has been shown to increase incentive motivation in mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). By contrast, the 5-HT_{2C} receptor *ago*nist CP809,101 has been demonstrated to enhance performance on some cognitive tasks in mice with decreased 5-HT synthesis (Del'Guidice et al., 2014). These preclinical observations warrant clinical studies of the effect of agents for specific 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, on motivational and cognitive disturbances. Specifically, it is important to see if such putative pro-motivation drugs will lead to improvement of functional outcome affected by cognitive function on which such compounds might act in variable directions.

In view of a possible influence of motivation on cognitive training, it may be interesting to determine if augmentation with pro-motivation compounds, e.g., 5-HT_{2C} agents, would provide additional merits for cognitive and functional outcome in patients with schizophrenia. Also, whether genetic variations regarding 5-HT and/or DA receptors affect motivational response to treatment with existing pharmacological or psychosocial interventions deserves further study.

In summary, genetic predisposition related to 5-HT and DA receptors may mediate the diversity of incentive motivation that is impaired in patients with schizophrenia. This concept is expected to facilitate rational treatment with biological and/or psychosocial tools to improve social consequences for people with psychiatric illnesses.

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