Dopamine ADHD/OCD theories: Is glutamine part of the story?

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Received: June 29, 2015
Published online: July 13, 2015

The role of cortico-striato-thalamo-cortical circuitry in a number of childhood presentations is reviewed. The comparative role of dopaminergic vs glutamatergic functions in conditions presenting with obsessive, cognitive, motor and/or autistic symptoms is examined. While dopaminergic dysfunctions appear to be more restricted to motor and cognitive symptomatology, glutamatergic mechanisms appear to have broader functions as illustrated by anti-NMDA encephalitis, negative affect and hallucinatory phenomena.

Keywords: PANDAS; anti-NMDA encephalitis; dopamine, glutamine; striatum


Introduction

The relation of cortico-striato-thalamo-cortical circuits (CTSC) to childhood psychopathology is better understood as a number of clinical presentations have been found to originate in dysfunctions of this circuitry. Conditions such as NMDA receptor encephalitis, and paediatric autoimmune neuropsychiatric disorder (PANDAS), are thought to result from immune reactivity while ADHD, autistic and schizophrenic flatness as well as catatonia may all represent dysfunctions of the above underlying circuits. With the advent of DSM-5, comorbid diagnoses of autism and ADHD are permitted. However the question of shared underlying pathology in severe comorbid presentations remains poorly understood. On the one hand Shorter and Wachtel[¹] have argued for “recognition of a mixed form of catatonia, autism and psychosis”, while on the other side of the argument, Happe, Ronald & Plomin [²] have argued for “behavioural fractionation of social impairment, communication difficulties and rigid repetitive behaviours” influenced by non-overlapping genes. An examination of comparative presentations may provide insights into the pathology of these conditions. An understanding of the role of cortico-striato-thalamo-cortical circuitry in mixed vs restricted presentations should help with the broader question of treatment of comorbid child psychiatric phenomena.

CTSC circuits

Haber [³] has reviewed the place of dopamine in the cortico-basal ganglia circuit. The author points out that the “interface between functional domains within the striatum is between cortico-striatal, striato-nigro-striatal and the lateral habenula projection to the midbrain. Midbrain projections from the ventral striatum project to both the ventral tegmental area (VTA) and ventro-medial substantia nigra pars compacta (SNc). Projections from the VTA medial/SN project back to the ventral striatum and laterally to dorsal striatum, forming a feed-forward loop or spiral, which continues through the striato-nigral-striatal projections which
impact on cognitive and motor striatal areas via midbrain dopamine”. According to Haber “the ventral striatal efferent projection to the midbrain extends beyond the tight ventral striatal/dorsal tier/ventral striatal circuit, terminating lateral and ventral to the dorsal tier into the striatal area that receives input from the dorsal PFC”. Projections from the PFC are thus able to “influence cells that project to motor control areas of the striatum, limiting the influence of the motor striatum to a relatively small region, and providing a mechanism by which motivation and cognition can influence motor decision-making processes and appropriate responses to environmental cues”. The author concludes that the complexity of the striato-nigral system is a key factor in developing appropriate responses to environmental cues and adaptive behaviour.

**Obsessive Compulsive (PANDAS) disorder**

Kaira and Swedo [4] outlined patterns of comorbidity and related neuroimaging studies in children with obsessive-compulsive disorder. They pointed out that two decades of research had indicated that childhood OCD is also thought to be associated with dysfunction of cortico-striato-thalamo-cortical circuitry (Swedo, Rapoport, Leonard, Lenane & Cheslow) [5]. The authors postulated a model in which “increased glutamatergic signals from the frontal cortex lead to increased excitation in the striatum (caudate and putamen), which then increases inhibitory GABA signal to the globus pallidus interna (GPI) and the substantia nigra pars reticulata (SNr), which then decreases the inhibitory output via GABA from the GPI and SNr to the thalamus, resulting in thalamic excitatory glutamatergic output to the frontal cortex”. It was suggested that this positive feedback could lead to repetitive thoughts (obsessions) and actions (compulsions). On the other hand an “indirect external loop composed of globus pallidus externa (GPe) and subthalamic nucleus is postulated to contribute to a steady state of excitation/inhibition. This increased glutamatergic signal from the thalamus to the frontal cortex interactions between striatum and GPe can lead to a lack of inhibition of the thalamus (which sends more signals to the cortex), or if the striatum is dysfunctional it does not inhibit GPe, leading to a lack of inhibition of the subthalamic nucleus, decreased excitation of GPI/SNr and again decreased inhibition of the thalamus, which sends more glutamatergic signals to the cortex”.

Swedo, Rapoport, Leonard, Lenane & Cheslow [5] described a subgroup of patients with childhood onset OCD, secondary to streptococcal infections known as paediatric autoimmune neuropsychiatric disorder (PANDAS), with 5 clinical features: OCD, and/or tic disorder, abrupt onset, a relapsing-remitting course as well as choreiform movements. The pathogenesis of OCD symptoms in the PANDAS subgroup was hypothesized by the authors to result from “basal ganglia dysfunction produced by antibodies cross-reactive between group A β-hemolytic streptococci (GABHS) epitopes and the caudate. Monoclonal antibodies are thought to cross-react with neurons of the caudate, putamen and globus pallidus. Regional autoimmune reactors are suggested by the demonstration that monoclonal antibodies specific for mammalian lysoganglioside and N-acetyl-B-glucosamine, an epitope of group A streptococci”. According to Kaira and Swedo [4] introduction of these antibodies into basal ganglia of rats has been shown to produce stereotypies such as “wood-chip eating, self-gnawing, biting, licking and grooming, paw to mouth movements, vacuous chewing and head and paw shaking”.

**Anti-NMDA encephalitis**

Bowes, Levy, Lawson, Mandalis, Mohan & Weickert [6] have documented a case report of a successfully treated 15-year-old girl, diagnosed with Anti-NMDA Receptor Encephalitis who manifested a sequence of delirium, with agitation and hallucinations, seizures and oro-bucco-lingual and body dyskinesias, and finally catatonia and increased autonomic instability. The authors have hypothesised an initial increase in cortical excitability, progressing to delirium and seizures and accompanied by a fronto-striatal motor syndrome, culminating in catatonia. The progression of symptoms in anti-NMDA encephalitis from a possible affective psychosis to seizures, dyskinesia and catatonia indicated that immunological investigations should be carried out at an early stage, particularly as NMDA encephalitis is treatable and early treatment is likely to be important for prevention of progression to autonomic and respiratory failure. It raised the question of when immunological investigations should be carried out, particularly as early treatment may be important for prevention of residual neurological impairment. A recent meta-analysis of the association between N-methyl-D-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder found that “individuals with schizophrenia or schizoaffective, bipolar, or major depressive disorders are collectively about three times more likely to have elevated NMDAR antibody titres compared with healthy controls, though considerable methodological and statistical heterogeneity exists”.

**Catatonia**

A revival of interest in the ‘etiopathogenesis’ of catatonia (Dhossche, Stoppelbein Rout [7]), particularly in the context of a better understanding of the pathology of Anti-NMDA (Anti-N-methyl-D-aspartate) Receptor Encephalitis (Dalmau,
Lancaster, Martinez-Hernandez, Rosenfeld & Balice-Gordon R [8]; Dalmau, Tuzun, Wu , Masjuan, Rossi, Voloschin et al [9]

may cast some light on the phenomenology of both catatonia and psychosis, as well as the motor symptoms often observed in the course of this condition (and also observed as side effects of stimulant medications in some children) (Levy [10]; Levy, Wimalaweera, Moul, Brennan & Dadds [11]).

Dhossche and Wachtel [12] suggested that catatonia, originally described by Kahlbaum [13] as a “unique clinical presentation of motor, vocal and behavioural abnormalities”, might be “hidden in plain sight among different psychiatric disorders” in children. They detailed symptoms of catatonia, including rigidity, posturing, waxy flexibility, stupor, unresponsiveness, negativism, echopraxia, echolalia verbigeration, mutism, stereotypic and repetitive movements, aggressive behaviors and autonomic and thermoregulatory instability. They described a number of cases including a 9-year old boy with postulated late-onset autism, loss of language and severe regression and also a 13-year-old boy with a 3-month history of bizarre behaviours, decreased speech, aggression and agitation as well as episodes of hypersonomolence. The association of verbal, motor and autonomic symptoms is reminiscent of “NMDA catatonia” [12].

Treatments for these severe cases included benzodiazepam, and/or bilateral electroconvulsive treatment. On the other hand a 12-year old girl admitted to hospital with major psychiatric symptoms and autonomic instability was treated with prednisolone but after 6 weeks cerebrospinal fluid investigation revealed G-antibody reactivity with hippocampal neutrophil, as well as serum antibodies to the anti-N-methyl-D-aspartate receptor. Plasmophoresis with 8 sessions over 13 days resulted in almost full recovery with only minimal dysfunction in short-term memory. Benzodiazepines are believed to act as “positive allosteric modulators on the gamma amino butyric acid (GABA)-A receptor. GABA is the most common neurotransmitter in the central nervous system, found in high concentrations in the cortex and limbic system. GABA is inhibitory in nature and thus reduces the excitability of neurons and produces a calming effect on the brain” [11].

Autistic flatness: Motor or affective effects?

Levy and Dadds [14] extended the tonic-phasic dopamine hypothesis, by showing predictive findings in relation to the minor allele of the D1 receptor that indicated a disrupted balance of D1/D2 functions in cortico-thalamic-striatal circuits, in which the minor allele of the D1 receptor predicted negative motor side effects, in particular the clinically-observed phenotype of ‘zombie-like’ symptoms observed by parents and researchers including ‘stares’, ‘zombie-like state’ and ‘rigidity’. In the present context, the zombie-like side effect can be likened to a minor form of catatonic presentations. If this is the case, then the underlying etiopathogenesis of catatonia, negative symptoms of schizophrenia, and autistic flatness may all be related to striatal dopaminergic motor circuits. On the other hand, the more widespread cortical actions of glutamine versus localised dopaminergic effects also draws attention to a cortical glutamatergic role in negative symptomatology.

In relation to stimulant side effects Levy, Wimalaweera, Moul, Brennan & Dadds, Dadds [11] found that D1 allelic status (rs4532) predicted “zombie-like” side-effects from stimulant medication for ADHD. Previous research had shown that the minor allele of rs4532 is more common in ADHD probands and predicted response and side-effects to drug treatment in schizophrenia, albeit associated with the DA antagonistic action of anti-psychotics rather than the agonistic action of stimulants (Bobb, Addington, Sidransky et al [15], Lai, Mo, Chen, Wang, Chen, Liao DL et al [16], Potkin, Basile, Jin, Masellis,Badri, Keator D et al [17]). SNP rs4532 is located in the 5’ UTR exon of the DRD1 gene and while its functional relevance is unclear, it may have affected DRD1 expression (Huang, Ma, Payne, Beuten, Dupont & Li [18]).

Positive vs negative symptoms

Noetzel, Jones & Conn [19] have pointed out that while current treatments of schizophrenia primarily address positive symptoms, there is left a large unmet need in the treatment of negative and cognitive symptoms. According to the authors, there is evidence suggesting that targeting aberrant glutamatergic signaling might provide an approach to treating all three symptom clusters. A review of dopamine-glutamate interactions in relation to schizophrenia (Javitt [20]) drew attention to a potential role for glutamatergic mechanisms in schizophrenia, following earlier observations that phencyclidine (PCP) and ketamine induced psychotic symptoms and neurocognitive disturbances similar to those of schizophrenia by blocking neuro-transmission of NMDA-type glutamate receptors. According to Javitt, evidence had accumulated supporting a role for NMDA hypofunction in the pathophysiology of schizophrenia as an alternative to the extant dopamine theories. While dopaminergic models have emphasized circumscribed brain pathways, glutamatergic models predicted widespread cortical and subcortical effects.
Javitt\textsuperscript{[20]} attributed differences in effects of amphetamine vs ketamine to differential actions of dopamine vs glutamine at striatal receptors, where NMDA and dopamine D2 receptors have been found to produce opposite effects. When symptomatic actions of ketamine and amphetamine were studied in the same volunteer subjects, amphetamine induced only “positive” schizophrenia-like symptoms, while ketamine induced both positive and negative symptoms in equal proportions. Similarly, amphetamine induced only conceptual disorganization, while ketamine induced difficulties in abstract thinking, mannerisms and poor attention. NMDA receptors are found to produce net stimulation, and D2 receptors net inhibition. “Thus in striatum, NMDA antagonists and dopamine agonists produce similar inhibition of GABAergic outflow, the first by decreasing excitation and the second by increasing inhibition” (Javitt\textsuperscript{[20]}). Javitt also described complex cortical interactions between D1 and NMDA receptors, in which “both D1 and D2 receptors are part of interactive cascades that may potentially modulate glutamatergic function, allowing the striatum to act as a “valve” for motor, affective and cognitive effects”.

**Dopaminergic/glutamatergic phenomena**

Tseng & O’Donnell\textsuperscript{[21]} studied the modulatory actions of D1 and D2 receptors on NMDA and AMPA glutamate receptors of PFC pyramidal neurons in brain slices obtained from developmentally mature rats. They found that D1 and D2 agonists had opposite effects on PFC pyramidal neuron excitability. “Bath applications of NMDA, AMPA and the D1 agonist SKF38393 induced concentration-dependant excitability increases, whereas bath application of the D2 receptor agonist quinpirole reduced concentration-dependant excitability”. According to the investigators, “the modulatory D1 action on AMPA responses is complex, with evidence supporting both positive and negative interactions”, but they were not able to demonstrate a D1-AMPA net interaction. On the other hand, they showed D2 attenuation of NMDA effects. The interaction was blocked by bicuculline or picrotoxine, suggesting that the D2 inhibitory effect on NMDA response required GABA receptors. They commented that inhibitory D2 effects on pyramidal cell excitability might constitute an important cellular mechanism for selection of relevant information in the PFC. On the other hand, D1 enhancement of NMDA responses in PFC pyramidal cell excitability could provide a cellular mechanism by which DA sustained prolonged depolarization, acting as a state- dependant stabilizer of the appropriate neural ensembles. Thus, according to Tseng and O’Donnell, (2004), “during conditions eliciting DA cell burst firing (ie salient stimuli) the phasic DA increase in the PFC activates D1 and D2 receptors, while the inhibitory D2 effect on AMPA-mediated responses might increase signal to noise ratio by attenuating weak signals”. Combined activation of D1, D2, GABA and glutamate receptors would thus allow a “gating and filtering phenomenon. Disruption of these interactions in the PFC might contribute to abnormal neuron firing and yield the cognitive effects observed in schizophrenia and related neuropsychiatric syndromes”.

In the present context, the Javitt\textsuperscript{[20]} conclusion that “as opposed to dopaminergic agonists, NMDA antagonists produce negative and cognitive symptoms of schizophrenia, along with positive symptoms”, whereas the former produce positive symptoms only, provides clues as to possible convergence and dissociation of dopaminergic/glutamatergic phenomena, where striatal dopamine D2 predominance controls motor and possibly affective symptoms, while NMDA/glutamine blockade may produce both ‘excitatory’ or ‘negative’ cognitive and affective states, depending on receptor conditions.

Javitt, Hashim, Sershen\textsuperscript{[22]} reviewed the role of NMDA receptors in the modulation of striatal dopamine release in vitro, and of glycine transport inhibitors (GTI’s) as potential psychotherapeutic agents in schizophrenia. They found that “striatal dopamine levels are increased not only by DA agonists such as amphetamine, but also by NMDA antagonists such as phencyclidine and ketamine”. The authors concluded that the ability of NMDA agonists such as glycine to ameliorate persistent positive as well as negative psychotic symptoms in schizophrenia most likely reflected effects on striatal NMDA/DA interactions.

**Functional selectivity**

Mailman & Murthy\textsuperscript{[23]} have discussed the concept of “functional selectivity”, that describes drugs that cause markedly different signaling through a single receptor, including full agonist effects at one pathway and antagonist effects at a second. In terms of dopaminergic effects, it is well-known that dopamine agonists treating ADHD can give rise to therapeutic effects on the one hand and side effects such as tics, or rigidity on the other hand. While these effects have been postulated to be mediated at cortical vs subcortical receptors (Levy\textsuperscript{[10]}, Levy and Dadds\textsuperscript{[24]}) it is possible that functional selectivity at important receptor sites is also a factor. For example, Mailman and Murthy\textsuperscript{[22]} have described animal studies in which aripiprazole acts as a pure D2 antagonist in a system with extremely low dopamine tone (lesioned dopamine-depleted striatum), while in situations of high extracellular dopamine concentrations (mesolimbic areas involved in positive symptoms), partial agonist properties of aripiprazole are thought to cause partial antagonism of dopamine, with clinical benefit, whereas in
situations where dopamine concentrations are low (impaired working memory or prolactin release), the drug can occupy additional receptors and cause partial activation. These differential effects suggest that aripiprazole “works as a functionally selective D2 ligand, where its intrinsic activity varies markedly, depending on the signaling environment of the D2 receptor” (Mailman and Murthy [23]). Thus in situations of low dopamine tone and ‘negative affectivity’ there may be a role for its partial agonist effects.

Mailman and Murthy [23] described the actions of three generations of antipsychotic drugs in terms of receptor actions. First generation antipsychotics like haloperidol are effective for positive symptoms of schizophrenia, but often induce extrapyramidal and neuroendocrine effects, believed to be mediated via the D2 receptor. Second generation antipsychotics (“atypicals”) such as clozapine are thought to have modest affinity for D2 and D1 receptors, but have affinity for serotonin, histamine, muscarinic and 2-adrenergic receptors. On the other hand, risperidone (often used for child behaviour problems) is a high affinity 5-HT2A and D2 antagonist, but is relatively devoid of anticholinergic, α-adrenergic and histamine H1 activity. Third generation antipsychotics are described by the authors as “partial agonists or something more?” Full D2 agonists are thought to have a biphasic action at D2 receptors, where low doses give rise to inhibition at autoreceptors, while postsynaptic activation at higher doses gives rise to stimulation. It was thus believed that the “right” balance of these effects was required.

Mailman and Murthy [23] have suggested that antipsychotic drugs could be classified as “antipsychotics-dopamine antagonists (1st generation); antipsychotics-dopamine-serotonin antagonists (some 2nd generation); antipsychotics-multi-targeted (other 2nd generation; and antipsychotics-dopamine functionally selective (3rd generation)”. They also suggested that future pharmacological classes might include: “antipsychotic-serotonin 5-HT2A functionally selective; antipsychotics-dopamine D1 agonists; antipsychotics-glutamate metabotropic allosteric modulators”.

Conclusion

The basal ganglia appear to have important control functions that result in childhood psychopathology when these synaptic mechanisms are disrupted. Thus while PANDAS appears to affect glutamatergic control of GABA output to the thalamus, anti-NMDA Receptor Encephalitis appears to reflect more broad effects on motor cortical and autonomic functions. Findings in relation to differential dopaminergic vs glutamatergic effects are of interest in relation to affective symptoms, where dopaminergic circuits appear have circumscribed motor and affective functions, while glutamatergic mechanisms appear to be more widespread at cortical and subcortical levels. Unfortunately for psychopharmacology, most current antipsychotics (and antidepressants) do not have pure effects. For example the often used risperidone has receptor binding effects at 5-HT, dopamine, adrenergic and histamine receptors, with potential for dystonic dopaminergic side effects. So far ketamine an ionotropic NMDA blocker has been shown to have short-term antidepressant effects but metabotropic allosteric glutamatergic agents are still at the development stage (Kavalali & Monteggia [24]). If safe agents with predominant glutamatergic effects are developed, the new ‘Ritalin’ for blunted affect, may be on the horizon, but the wider spectrum of glutamatergic actions may make this difficult.

References

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