AUTISM SAGE JOURNALS

EDITORIAL

DOPAMINE DYSREGULATION IN REWARD AND AUTISM SPECTRUM DISORDER (ASD): TO BE OR NOT TO BE?

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As the namesake lead character in William Shakespeare's masterpiece Hamlet, using timeless rhetoric, poses the question "to be or not to be", neuroscientists find themselves confronting difficult to fathom complexities while contemplating an expanding knowledge base relating autism and dopaminergic brain reward circuitry. A major challenge with any theory addressing the pathogenesis of autism is that this disorder is surpassingly complex. Autism may arise from any of over 1000 implicated genes, and at least in part derives from immunological effects, manifold environmental factors, and epigenetic insults, such as in utero exposure to the neuropsychiatric therapeutic, valproic acid (Marotta et al, 2020; Mandy & Lai, 2016; Mandic-Maravic et al, 2022; DiCarlo and Wallace, 2022, Neurosci and Behav Rev; Christensen et al, 2013). Moreover, signaling in the brain mesolimbic reward system is very intricate and nuanced, involving multiple cell types, interactions, connections, receptors, and neurotransmitters with complex effects (Smolders et al, 1997). Against this backdrop, while

much has been learned about autism and dopaminergic reward pathways, the specific role of dopaminergic reward effects in autism has spawned extensive debate. Here, in a reductionist vein, we consider the often mentioned possibility that in ASD an array of genetic and epigenetic events, and neurophysiological signaling circuits, converge to downstream, common dopaminergic pathways. This is a long and widely held perspective that may now need to be updated and re-affirmed, i.e., "to be or not to be", because of a renewed focus on GABA and glutamate, and emerging data showing mesolimbic GABAergic neurons directly projecting to core brain reward structures. Moreover, there is a growing awareness that the regulation of dopamine release during reward signaling involves multiple neurotransmitters and complex neural interactions in mesolimbic loci. These interactions modulate dopaminergic neurons and involve manifold, subtle interactions, for example the ability of transmitters to modulate their own release and the responses to other neurotransmitters. This may offer some insight into why the treatment of autism has proved so challenging. Nonetheless, dopamine is a dominant reward effector, and we believe that a dopaminergic ASD reward model taking into account successive and discrete stages, or levels, occupied by key players, e.g., genetic alterations, epigenetic effects, disrupted mesolimbic signaling, and so forth, may offer a beneficial conceptual framework to probe a clinically challenging disorder with a very varied and detailed natural history.

Autism Spectrum Disorder and the Dopaminergic Reward Pathway

Autism, or more properly, autism spectrum disorder (ASD), encompasses a heterogeneous set of conditions that have in common a core set of deficits in social skills and communication, and the expression of restricted, repetitive, stereotyped behaviors (Paval *Dev Neurosci* (2017) 39 (5): 355–360. , 2017; Zeidan et al, 2022; Dichter et al, 2012). ASD is diagnosed in 16.8 per 1,000 (one in 59) children aged 8 years (Baio et al, 2018, *Morb Mortal Wkly report Surveill Summ*. 67:1–23. 10.15585). While ASD disorders share the core manifestations described earlier in this review, the specifics and the extent to which each deficit is present varies between individuals along a spectrum, and in no small part, for this reason, the pathogenesis of ASD remains unresolved. In an effort to blend diverse strands of research to provide an integrated conceptual overview, Chevalier et al, 2012b (PMID: 22425667), theorized that autistic individuals exhibit poor social skills because they find social interactions less rewarding than their neurotypical peers. According to this perspective ASD can be regarded as an extreme case of reduced social motivation (Chevalier et al, 2012). Some authors suggest that the complex etiology of ASD converges on a singular pathway, while others suggest that it may be more appropriate to identify subgroups of ASD based various markers (DiCarlo & Wallace, 2022).

In any case, a widely held view of the neurobiology of ASD posits that the brain excitatory-inhibitory balance is (E/I balance) is disrupted in autistic subjects (Rubenstein&Merzenich, 2003; DiCarlo&Wallace, 2022). Extensive data indicates that there are deviations in the E/I balance in ASD which is affected by the main inhibitory brain neurotransmitter GABA, and the primary excitatory neurotransmitter, glutamate. ASD is associated with a high incidence of seizures, which result from hypersynchronous neuronal activity, indicative of an E/I imbalance. In addition, a key mesolimbic brain reward structure, the substantia nigra (SNc) is implicated in

dopaminergic reward pathways and is known to curtail seizure spread (Smolders et al, 1997). DiCarlo&Wallace (2022) in their excellent ASD review observe that dopamine modulates excitatory and inhibitory neurotransmitters as well as the neuronal response to this signaling. Moreover, multiple authors have suggested that akin to other neuropsychiatric syndromes that have core features, ASD has at its nucleus dysregulated dopamine signaling. This deficiency is still generally held to drive the disorder regardless of the exact nature of the parent condition and co-morbidities, as dopamine pathways constitute the primary constituent of the mesolimbic brain reward system (Pavalk, 2017; Gondré-Lewis et al. 2020; Blum et al., 2022). The primary dopaminergic reward pathways and centers reside in the mesolimbic system (MCL) which includes dopaminergic neurons in the ventral tegmental area (VTA) that project to the striatum, amygdala, hippocampus, prefrontal cortex and many other structures (Lewis et al, 2021). The ventral striatum is comprised of the nucleus accumbens (NAc), which plays a key role in reward processing and in evaluation and incentive-based learning behavior (Lewis et al, 2021; Paval 2017; Chevallier et al, 2012, Trends Cogn Sci 2012;16:231-239). Work in experimental ASD animal models has shown that activation of the VTA stimulates dopaminergic receptors which prompts social interaction, and imaging studies with humans have indicated that autistic subjects exhibit hypoactivation of structural elements within the dopamine dependent reward pathway (Gunaydin et al, Cell. 2014;157:1535–51. Stao et al, 2023; Molecular Psychiatry Dichter et al, 2012, Soc Cogn Affect Neurosci 2012;7:160-172; Siupekar et al, 2018, Brain Sep 1;141(9):2795-2805).

Dysregulated dopamine pathways and ASD may originate during the early development of the brain. Brain developmental differences have been identified in infants younger than 6 months that were later found to have ASD (Maestro et al, *J Am Acad Child Adolesc Psychiatry.* 2002;41:1239–1245).

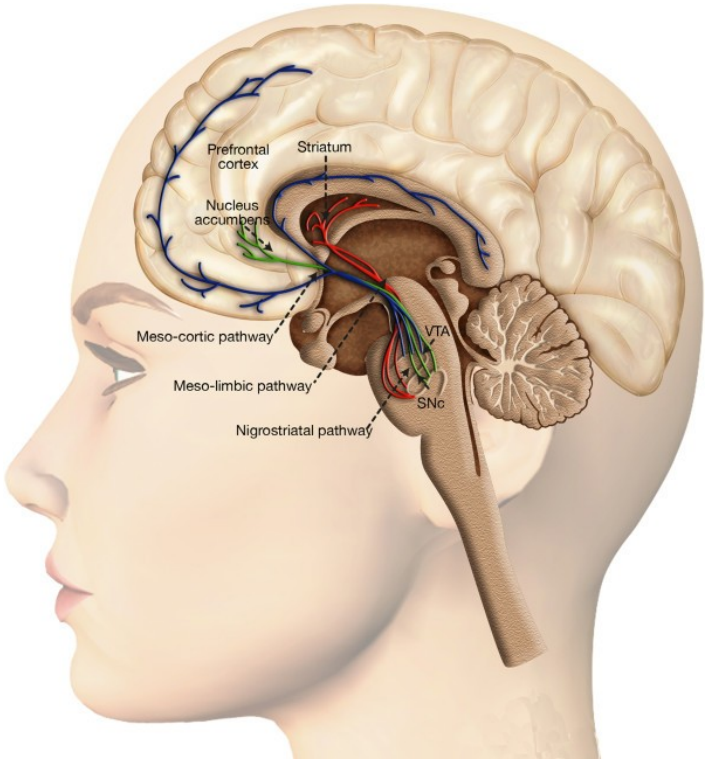
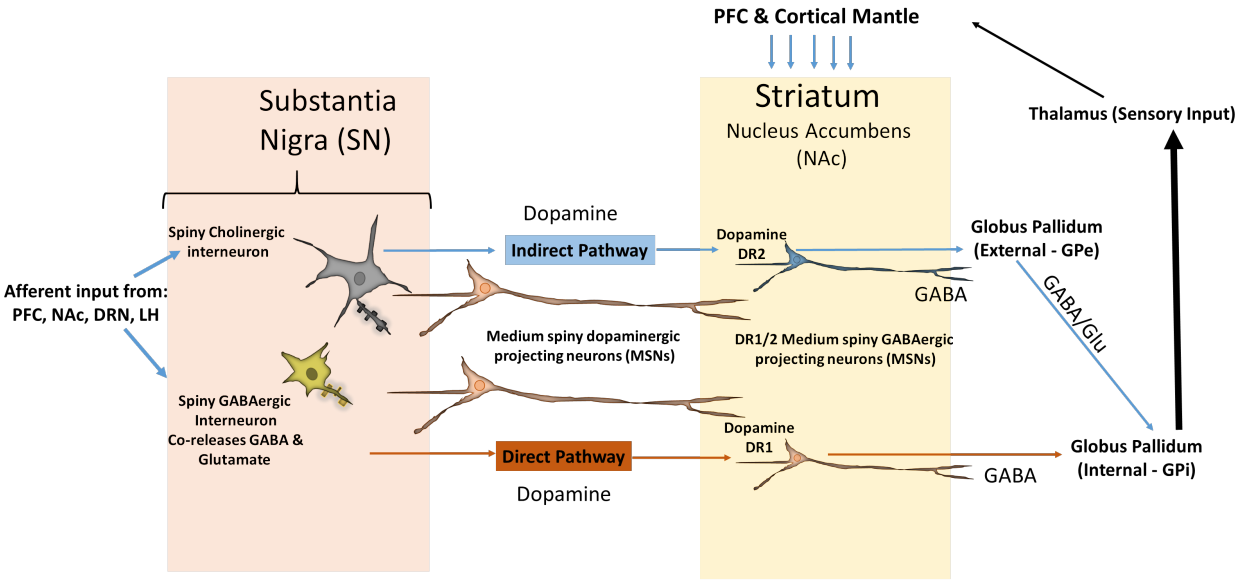


Figure 1. Dopaminergic system and reward processing. Dopaminergic neurons are located in the midbrain structures substantia nigra (SNc) and the ventral tegmental area (VTA). Their axons project to the striatum (caudate nucleus, putamen and ventral striatum including nucleus accumbens), and the dorsal and ventral prefrontal cortex. The mesolimbic dopamine pathway mediates the psychopharmacology of reward, whether that is a natural high or a drug-induced high, and is sometimes referred to as the pleasure center of the brain, with dopamine as the pleasure neurotransmitter. (From Arrias-Carron, et al, 2014, with permission).

Apoptotic caspases appear to crucially participate in the normal, orchestrated removal of excessive and non-functional synapses and the elimination of redundant cells, especially in the context of dopaminergic pathways. Importantly, in the striatum of mice lacking Capase-3, dopamine release was found to be significantly reduced, and the resultant hypodopaminergia induced repetitive stereotypies, impaired social interaction, and restrictive interests, all regarded as the core symptoms of ASD (García-Domínguez et al., 2020). The effects of dopamine release may vary according to prior exposure, for example drugs of abuse may acutely induce a significant dopamine surge, while chronic abuse has been observed to attenuate dopamine release (Peters et al., 2021). Deficiency of dopamine may leave subjects more vulnerable to stress, and ASD in adults is associated with rates of social anxiety as high as 28% (Loftus et al., 2023). A study by Phan et al (2021), suggests that adult exposure to stress could exacerbate behavioral and neuroanatomical phenotypes linked with developmental effects of genetic En2 deficiency in ASD. There is evidence indicating that dopamine may not be required for all kinds of reward (Cannon & Palmiter, 2003), and there are other neurotransmitters involved in ASD, including serotonin, N-acetyl aspartate, oxytocin and arginine vasopressin, melatonin, vitamin D, orexin, endogenous opioids, and acetylcholine (Marotta et al, 2020).

Direct and Indirect Mesolimbic Pathways and Modulation of Dopaminergic Neurons by Basal Ganglia Interneurons

Striatal interneurons regulate medium spiny projection neurons (MSNs) via inhibitory GABAergic signaling and excitatory glutamate signaling (Lewis et al, 2021; Gittis et al, 2010), while a minority are crucially important cholinergic interneurons that are linked to event salience (Berridge and Robinson, 1998; Lewis et al, 2021; Gittis and Keitzer, 2012). Cholinergic interneurons also decrease glutamate release via spiny acetylcholine (muscarinic) receptors and nicotinic receptors. Importantly, acetylcholine release in the striatum regulates striatal dopamine release and dopaminergic receptor neurons respond differentially depending on whether they bear M1 or M2 muscarinic receptors. Receiving neurons in the striatum, including the NAc, respond according to dopamine receptor subtype, DR1 or DR2 (**see Figure 2**). The neurons representing the main output of the striatum are medium spiny neurons that release γ-aminobutyric acid (GABA) and trigger two pathways; the direct pathway governed by dopamine D1 receptor (D1R) medium spiny neurons (dMSNs) and indirect pathway, driven by dopamine D2 receptor (D2R) expressing medium spiny neurons (iMSNs) (Lewis et al, 2021; Graveland and Difiglia, 1985). Dopaminergic neurons from the substantia nigra (SN) also project towards the dorsal striatum (DS), creating the nigrostriatal (NS) circuit which supports goal oriented motor activities (Paval, 2017; Haber SN, 2014 Neuroscience 2014;282C:248-257). The dorsal striatum is involved in action selection and initiation, and mediates valiance and magnitude (Lewis et al, 2021; Balleine et al, 2007; Burton et al, 2015; Lipton et al, 2019).



Adapted from C. Bouarab et al, Front Neural Circuits (2019),
J. Sonne et al (2022) StatPearl, Bjorklund & Dunnett, 2007 Trends in Neurosciences,
Deperrois et al, Front Neural Circuits, 2019, Loonen and Ivanova, 2013, CNS spectrums 18(1):15-20
Zinger et al, 2011, Parkinsons Disease
Grillner and Robertson, 2016, Curr Biol
Pretegiani&Optican, 2017, Front. Neurology

Figure 2. Simplified illustration of nigrostriatal pathways involving the substantia nigra (SN). Dopaminergic projecting neurons target striatal medium spiny neurons (MSNs) that express either dopamine D1 or D2 receptors and that release GABA at target sites. In addition there is input to the striatum, which consists of the NAc and other structures, from the cortical mantle. Striatal D1 neurons in the direct pathway project to the globus pallidum (GPi), which then sends inputs to the thalamus which in turn provides input to the cortex. The SN also targets striatal dopamine D2 receptor neurons that project to the GPe which then via GABAergic signaling targets the GPi, which in turn inputs to the thalamus and finally, the cortex.

The VTA/SN complex is a dopamine rich region with significant inputs and the SN operates via the nigrostriatal pathway while the VTA exerts its effects through the mesolimbic and mesocortical pathways (Kwon & Jang, 2014, Frontiers in Human Neuroscience). The VTA and SN appear to play complementary roles in learning and memory and they are both key reward system structures (Martig & Mizumnori, 2011, Learning and Memory). The primary targets and inputs of the VTA are shown in **Figure 3**. VTA dopaminergic projections to the NAc are involved in reward processing, salience, and motivation, while dopaminergic projections from the SN to the striatum, specifically from the substantia nigra pars compacta (SNc), referred to as the nigrostriatal pathway, is important in context-appropriate actions (Kosillo&Bateup, 2021). Howard et al, 2017; Watabe-Uchida et al, 2017; De Jong et al, 2019; Hamid et al, 2016, Mohebi et al, 2019). Kosillo&Bateup (2021) note that aberrant VTA mesolimbic dopaminergic pathways may diminish reward associated with social stimuli leading to a poverty of social skills and interactions, while mesocortical DA dysregulation may lead to deficits in sensory processing (Kosillo&Bateup, 2021, Front Neur Circ). Moreover, dysregulated nigrostriatal dopaminergic signaling may promote stereotyped movements and over reliance on habitual behaviors

((Kosillo&Bateup, 2021, Front Neur Circ), Front Neur Circ). Interestingly, Paval (2017 Dev Neutroscience) makes the point that either hyper- or hypo-dopaminergic signaling in key brain loci could trigger or aggravate the manifestations of ASD. Genetic studies have revealed sub-types of DA neurons and may facilitate common DA related ASD pathways resulting from genetic alterations (Kosillo&Bateup, 2021, Front Neur Circ; (Poulin et al., 2014; La Manno et al., 2016; Hook et al., 2018; Kramer et al., 2018; Saunders et al., 2018; Tiklová et al., 2019; Poulin et al., 2020).

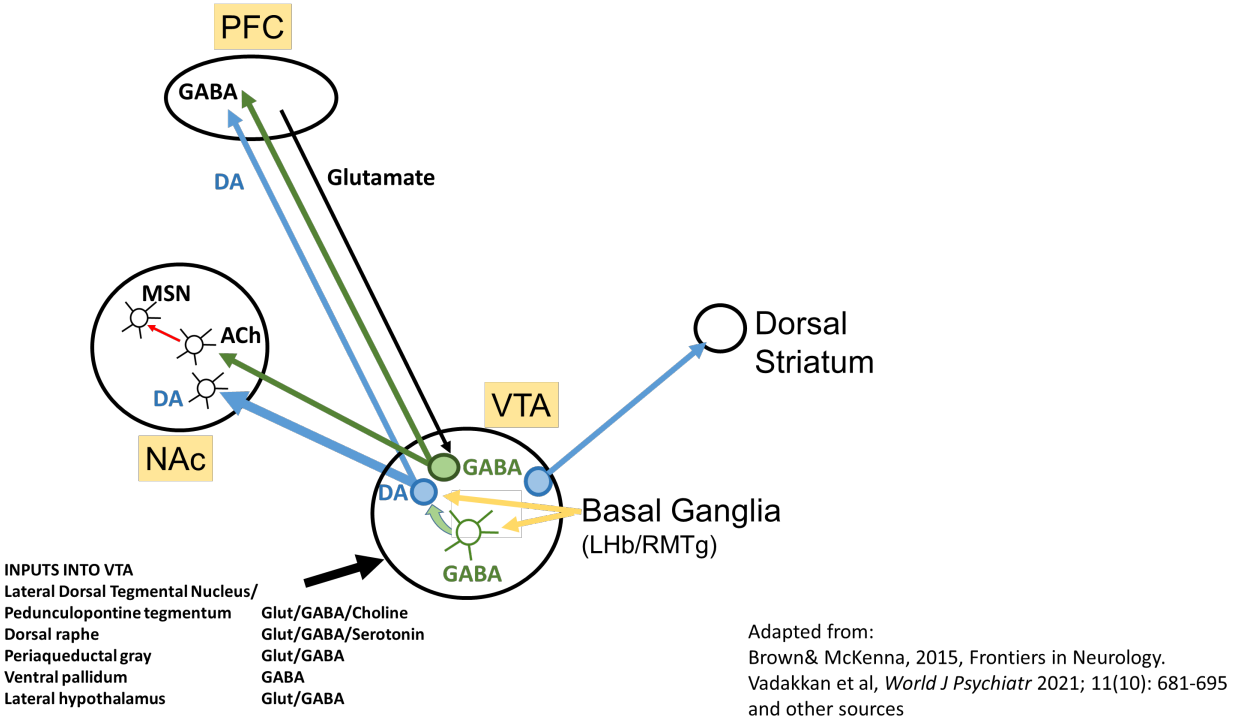


Figure 3. Simplified schematic depicting mesolimbic pathways associated with the VTA. Dopaminergic projecting neurons the prefrontal cortex and notably, the nucleus accumbens (NAc) which is a key mesolimbic reward structure. The VTA is a key reward structure richly endowed with dopaminergic projecting neurons, although is also houses GABAergic projections. The VTA receives inputs from the PFC and an array of other functional brain loci. As depicted, interneurons play a key role in transducing and modulating inputs to the VTA.

Dopamine and the Social Anhedonia of Autism

Under normal conditions dopamine maintains vital drives by providing reward and alleviating stress, Moreover, Barkus & Badcock (2019) point out, that people are highly social beings, yet humans with social anhedonia tend to display a reduced interest in or reward from social situations. This aligns with social issues observed in people diagnosed with ASD. Accordingly, Gold et al., (2018) also indicated that anhedonia could be due to derangements in mesolimbic dopaminergic pathways and their terminal fields (e.g., striatum, amygdala, and prefrontal

cortex) that seem to persist long after the traces of abused drugs causing anhedonia have been pharmacokinetically cleared. It has been postulated that anhedonia is not a distinct entity but is rather an epiphenomenon of hypodopaminergic states and traits arising from the interaction of both genetic traits and epigenetic states where the end result encompasses neurobiological alterations in response to negative environmental cues.

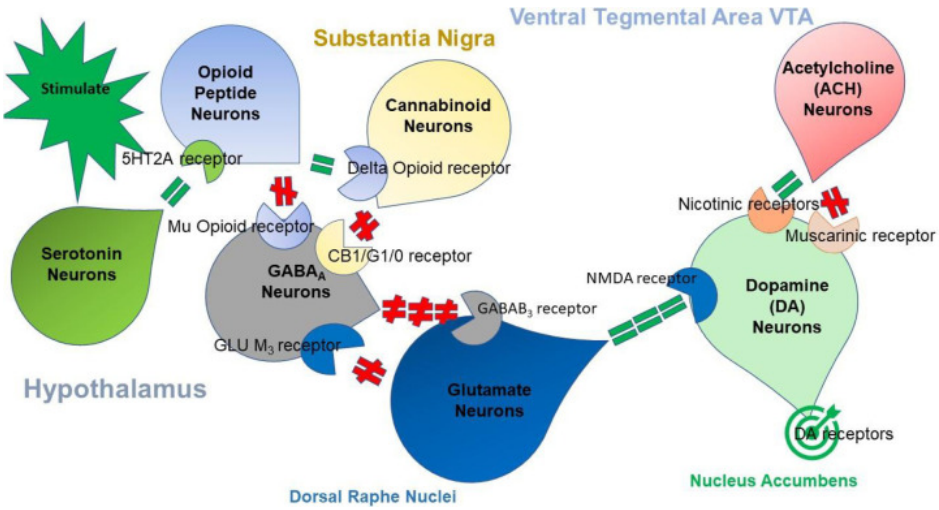


Figure 4. The brain reward cascade. The schematic drawing illustrates the interaction of at least seven major neurotransmitter-pathways involved in the Brain Reward Cascade (BRC). In the hypothalamus environmental stimulation results in the release of serotonin, which in turn via, for example, 5HT-2a receptors activate (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons, also in the hypothalamus. Then, in turn, the opioid peptides have two distinct effects, possibly via two different opioid receptors. Inhibition (red hash sign) through the mu-opioid receptor (possibly via encephalin projecting to GABA$_A$ neurons in the Substania Nigra (SN). Stimulation (green equal sign) of cannabinoid neurons is via beta–endorphin linked delta receptors, which in turn inhibit GABA$_A$ neurons at the SN. Activation of cannabinoid neurons via endogenous agonists, primarily 2-archydonoglcerol, can indirectly inhibit (red hash sign) GABA$_A$ neurons through activation of Gi/o-coupled muscarinic receptors in the SN. In the Dorsal Raphe Nuclei (DRN), glutamate neurons can then indirectly inhibit GABAA neurons in the SN through activation of GLU M3 receptors (red hash sign). GABA$_A$ neurons, when stimulated, will, in turn, powerfully (red hash signs) inhibit ventral tegmental area (VTA) glutaminergic drive via GABA-β3 neurons. It is also possible that stimulation of acetylcholine (ACH) neurons at the Nucleus Accumbens (NAc) can activate both muscarinic inhibitory (red hash) or nicotinic activating (green hash) receptors in dopamine neurons. Finally, Glutamate neurons in the VTA project to dopamine neurons through NMDA receptors (green equal sign) to preferentially release dopamine at the NAc shown as a bullseye, to elicit a euphoric, or a "wanting" response. The result is that when dopamine release is low, unhappiness is felt while general happiness depends on the dopamine homeostatic tonic set point (with permission Blum et al.)

In the above context, supporting the notion of dopaminergic pathways as a common denominator in social reward and ASD, there are several brain regions including the cortex, amygdala, cerebellum and basal ganglia that have been investigated as regions of interest in the context of ASD pathophysiology. In children Supekar and colleagues (2018) used high angular resolution diffusion-weighted imaging and functional MRI data to demonstrate that white matter tracts linking the NAc and VTA structural and functional aberrations in ASD children. (See Figure 3). In this study children with more severe social deficits had lower imaging density of NAc-VTA tracts. According to Kosillo & Bateup (2021) the midbrain dopamine system is at least one mediator of cellular and synaptic function in many ASD- brain regions via functionally and anatomically distinct dopaminergic neural circuit projections. Kosillo & Bateup (2021) suggested that dysfunctional dopaminergic pathways might contribute to the behavioral actualization of ASD, including changed reward value of social stimuli, altered motor stereotypies and sensorimotor processing.

The well-known dopamine depletion hypothesis related to abuse of psychoactive drugs such as cocaine and amphetamine (Dackis Gold,1985, Blum et al., 1977) has likely provided some impetus to similarly ascribe the dopamine hypothesis to ASD. It is noteworthy that human literature in general supports the involvement of modified dopamine transduction in ASD such as brain imaging, genetic, and pharmacologic studies.

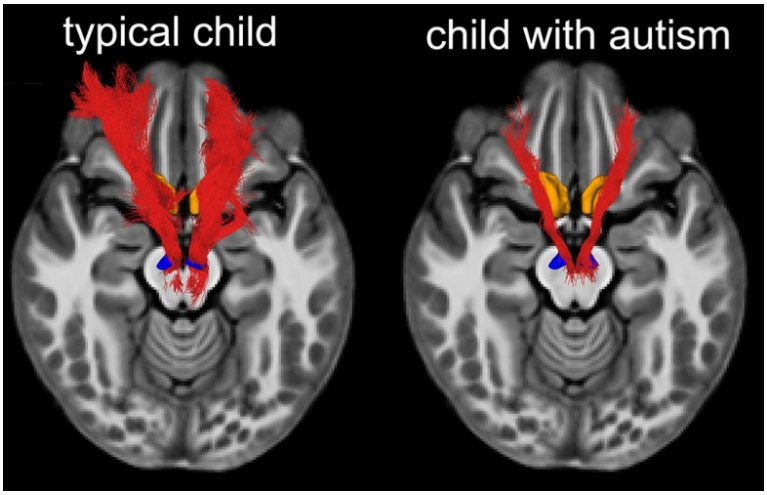


Figure 5. Reduced MR imaging signatures of NAc-VTA tracts in an ASD child compared to a typical, non-ASD child. Six control and six ASD subjects revealed that ASD subjects had lower density, and the reduction in density corresponded to increased severity of social deficits. Reproduced by permission of K. Supekar and E. Digitale, *Stanford Medicine*.

In any case the specific roles of reward system dopamine release have been extensively debated (Wang et al, 2020, J Neurophysiol•doi:10.1152/jn.00323.2020). In an attempt to resolve controversies regarding the causal contributions of mesolimbic dopamine (DA) systems to reward, some investigators have used three main competing explanatory categories: "liking," "learning," and "wanting" (Blum et al., 2012). Specifically, dopamine could mediate (a) the hedonic impact of reward, i.e., liking, (b) learned predictions about rewarding effects, learning, or (c) the pursuit of rewards by attributing incentive salience to reward-related stimuli, wanting. Along these lines especially as it relates to reward deficiency, we have suggested that the incentive salience or "wanting" hypothesis of dopamine activity is supported by a majority of

the evidence. Over a decade ago Chevallier and colleagues (2012, Trends in Cognit9ive Sciences) among others, proposed the concept that social interaction is a powerful process governing human behavior and that disruption of social motivational mechanisms may be a key mechanistic factor in ASD. These authors describe three processes; (1) social orienting which includes attention to faces and social signals and eye contact, (2) seeking – liking which refers to the incentive value, i.e., wanting and liking, of social reward stimuli, and (3) social maintaining which includes ingratiation strategies. They observe in this context that the orbitofrontal – striatum – amygdala circuit has been reported to be dysregulated in ASD. The response to facial social stimuli, social approval, and social rejection have been found to be abnormal (Bachevalier and Loveland, 2006, Neurosci. Biobehav. Rev; Schultz, et al, 2000, Arch. Gen. Psychiatry 57, 331–340; Scott et al, 2010 Autism Res. 3, 53–67; Masten CL et al, 2011, Dev. Cogn. Neurosci. 1, 260–270). The effects of dopamine may be subtle, for example Brandenburg et al (2020; Front Cell Neurosci) examined post-mortem brain tissues of ASD subjects and found normal expression of DA, GABA and 5-HT receptors in the dorsal striatum, but an increase of dopamine D2 receptor mRNA expression within individual medium spiny neurons that impact the globus paillidus externa (GPe), an integrative node in reward seeking.

The Role of GABA and Serotononin in ASD

GABA is the primary neurotransmitter in the brain that is responsible for inhibition, and a prominent hypothesis concerning the genesis of autism is that dysregulated GABAergic pathways disrupt the normal excitatory/inhibitory balance of the brain, which impairs social behaviors (Rubenstein & Merzenich, 2003, Genes, Brain and Behavior). GABA is derived from glutamate and magnetic resonance spectroscopy (MRS) has shown reduced striatal glutamate in mouse ASD models and in human adults with idiopathic ASD (Marotta et al, 2020; Horder et al, 2018). Robertson and colleagues (2016) noted that GABAergic transmission is dysregulated across heterogeneous murine models of autism, and mice with dysfunctional GABAergic neurons exhibit autistic features such as repetitive behaviors (Chao et al, 2010 Nature). Moreover, these authors also reported reduced GABAergic activity in the brains of human autistic subjects. In ASD children the plasma concentrations of GABA and glutamate differ from controls, and MRS has revealed that autistic individuals exhibited a comparatively higher ratio of excitatory glutamate to inhibitory GABA (Ford et al, 2017, PlosOne).

There is an extensive body of literature on GABAergic pathology in ASD, including the reduction of GABA binding sites, reduced expression of glutamic acid decarboxylase and thus lower conversion of glutamate to GABA, aberrant GABA receptor subtype expression, and increased glutamate activity (Fatemi et al, 2014; Shinohe et al, 2006). There are two classes of GABA receptors, $GABA_A$ and $GABA_B$ each with distinct functional roles, and Fatemi and co-workers reported downregulation of the $GABA_A$ receptor subunits $\alpha 6$, $\beta 2$, δ, ε, $\gamma 2$, $\varrho 2$, and θ, in samples from the superior frontal cortex of deceased autistic individuals, versus controls, suggesting a major impairment of GABA receptor subunits in the autistic subjects (Fatemi et al, 2014). Robertson and coworkers (2016) used MRI spectroscopy and visual images to assess the balance between excitation and inhibition in the visual cortex of autistic children. The authors

took advantage of a visual processing phenomenon called binocular rivalry, which allows one or the other eye to attain visual dominance as its cortical neuronal affiliates suppress the neuronal populations associated with the companion eye. This process is held to reflect inhibitory versus excitatory balance (Robertson, 2016; Said&Heeger, 2013). The authors found a linkage between binocular rivalry dynamics and GABA and glutamate concentrations in the visual cortex. They further observed that binocular rivalry was significantly slower in autistic individuals versus controls that were age and IQ matched, and found that the connection between GABA and binocular rivalry was absent in ASD subjects. The authors concluded that this autistic behavioral symptom could be a marker of GABAergic dysfunction in the autistic brain, and they noted that GABA may figure prominently in the developmental neurobiology of autism.

The participation of serotonin (5-HT) in ASD was first proposed in 1961 after it was found that a subpopulation of children with ASD has elevated blood 5-HT (Andersson, 2021, Mol Psychiatry; Shain&Freedman, 1961, J Pediatr). Anderson and co-workers (2021) recently reported that positron emission tomography (PET) revealed significantly lower 5-HT transporter availability in total gray matter and brainstem of ASD adults, and correlations between regional 5-HTT availability and social cognitive test performance. Dolen and colleagues (2013) examining the participation of oxytocin and 5-HT in mice, found that social reward required serotonergic inputs to the NAc via $5HT_{1b}$ receptors, and blockade of these receptors abolished social reward (Dolen et al, 2013, Nature). Calvacante et al (2017, Behav, Brain, Res) infused the insular cortex of rats with antagonists of $5\text{-}HT_{1A}$ serotonergic or D1/D5 dopaminergic receptors, and found that dopaminergic D1/D5, β-adrenergic, and $5\text{-}HT_{1A}$ receptor antagonists, but not glutaminergic, NMDA, histaminergic or H_2 receptor antagonists impaired the consolidation of social recognition memory.

Dopaminergic, GABAergic, and Serotonergic Antagonists/Agonists in ASD

Some beneficial effects of partial dopamine agonists have been observed in ASD but the side effects of pharmacotherapy are substantial and are limiting in both pediatric and adult ASD populations. Treatment with risperidone, aripiprazole, and olanzapine resulted in significant body mass index scores, with the greatest effect observed with olanzapine (Mandic-Maravic et al, 2021, front psychiatry; Haber, 2014, Neuroscience). Mandic-Maravic et al (2021) in their excellent review of D2/D3 partial agonists for ASD, note that dopamine D2 receptors densely populate the striatum, basal ganglia and prefrontal cortex, while dopamine D3 receptors mostly populate the NAc (Millan et al, 2020; Watson et al, 2016; Toma et al, 2013; LeClerc et al, 2015). Dopamine D2/D3 receptor partial agonists have lower activity at D2/D3 receptors than dopamine, so they are essentially antagonists (Girgis et al, 2016). Ariprazole is an FDA approved partial agonist has suppressed irritability, hyperactivity and stereotypies (Gross et al, 2013). Aripiprazole showed efficacy in terms of irritability, hyperactivity, noncompliance, and stereotypies in ASD Appiah-Kubi P, et al, *J Mol Recognit.* (2021). There are several agents that

are partial D2/D3 agonists and some that also agonize/antagonize various 5-HT receptor subtypes that have not been tested in ASD.

GABA modulators in ASD have been tested in relatively recent clinical trials and the data have proved inconclusive, limited by ASD heterogeneity and small study populations, insufficient follow-up, and variable inclusion criteria (Zhao et al, 2022, Front. Cell Dev. Biol., 07 February 2022). $GABA_B$ receptors are part of a complex array of signaling responses as they are metabotropic, i.e., responding to a range of ligands (Jembrek and Vlainic, 2015). A further complicating factor may also be signaling redundancy in reward pathways, as there are other neurotransmitters in addition to dopamine, such as endogenous opioids, acetylcholine, serotonin, adenosine, endocannabinoids, orexins, galanin and histamine that regulate the mesolimbic dopamine system (Arrias-Carrion, International Archives of Medicine, 2014). Zhao et al (2020) note that the most extensively studied GABA agent is baclofen, which agonizes $GABA_B$-R receptors, and which has reversed alterations in social behavior and stereotypies in mouse ASD models (Silverman et al, 2015). A $GABA_A$-R agonist suppressed multiple behavioral abnormalities including repetition in a genetic mouse ASD model (Cogram et al, 2019). Overall, there is insufficient data supporting the application of GABA modulators for ASD (Zhao et al, 2020).

Several drugs that are active at serotonergic (5-HT) receptors have been shown to improve ASD symptoms in human patients but as with dopamine receptor agonists their side effects are typically substantial (Lee et al, 2022). Cosi and co-workers tested F17464 a partial 5-HT_{1A}R agonist and human dopamine receptor subtype 3 antagonist which increases dopamine release, and found that it rescued impaired social interaction in valproate treated rats, a model of ASD (Lee et al, 2022; Cosi et al, 2021). Olanzapine is a 5-HT_{2A}R and D_2 dopamine receptor antagonist that induced significant improvements in terms of stereotyped behavior, social deficits, hyperactivity, irritability, and aggression in multiple human case studies (Lee et al, 2022, Int J. Mol. Sci). However, as noted above, this agent leads to substantial weight gain.

Genetic Alterations in ASD Converging to Common Genetic Pathways

The human oxytocin receptor gene occurs on chromosomes 3p25 and 3p26 and genome wide linkage studies have suggested that the oxytocin receptor gene is an ASD gene (Zhao, 2022; Kelemenova et al, 2010; Lee et al, 2012).

Supporting its symptomatic heterogeneity manifesting as a broad spectrum, multiple types of genetic abnormalities have been associated with ASDs [8]. These include a large number of single genes, a major subset of which encodes synaptic molecules. In addition, multiple genetic abnormalities, including various copy number variants (CNVs) produced by deletion or duplication of chromosomal fragments [9], are heavily implicated in the pathogenesis of ASD. Due to the complex genetic nature of the disorder and the difficulty associated with studying how each (or groups of) genetic abnormalities contribute to ASD symptomology, investigating mouse models that mimic the genetic and clinical features of ASD thus provides a promising avenue toward elucidating mechanisms of abnormal social behavior and potential therapeutic targets for treating this disorder. (stao et al, 2023; Molecular Psychiatry)

Recurrence within families and twin studies have implicated a strong genetic component to ASD (Bailey et al., 1995; Bolton et al., 1994; Constantino et al., 2010; Sumi et al., 2006). However, this disorder is not monogenic – there is not one gene responsible for all causes of autism. A growing number of genetic changes, including *de novo* single nucleotide variants (Iossifov et al., 2012; Neale et al., 2012; Sanders et al., 2012) as well as both *de novo* and transmitted copy number variants (CNVs) (Levy et al., 2011; Pinto et al., 2014, 2010; Sanders et al., 2015) have been identified in individuals with autism. Concordance rates and linkage studies suggest a multigenic inheritance pattern, although a subset of ASDs may have a monogenic etiology (Risch et al., 1999). Many have suggested that these seemingly disparate genetic risk factors ultimately converge on downstream mechanisms. (DiCarlo & Wallace, 2022, Neuroscience & Biobehavioral Reviews).

Neurofibromatosis type 1 (NF1) is a disorder that has a high prevalence of ASD, and mice lacking a single NF1 allele show deficits in long-term social learning and increased activation of mitogen-activated protein (MAP) kinase pathway in neurons from BLA and PFC [36]. These mice also display elevated GABA and glutamate neurotransmission and long-term potentiation in the BLA, and the social learning deficits are rescued by pharmacological blockade of p21 protein-activated kinase in the BLA [36].

Interplays between genetic and epigenetic mechanisms play an essential role in social functions and their deficits in ASD model mice [37]. A study has shown that Shank3 deficiency induces the histone deacetylase HDAC2 upregulation via a β-catenin–dependent mechanism, and its knockdown in the mPFC or treatment with the HDAC inhibitor romidepsin rescues the social deficits of heterozygous *Shank3*-deficient mice [38]. These findings underscore the likelihood of an epigenetic mechanism underlying social defects associated with Shank3 deficiency.

Interestingly, deletion or duplication of the human chromosome 22q11.2 is associated with behavioral traits and neuropsychiatric disorders, including autism spectrum disorders and schizophrenia. Moreover, phenotypes vary among people with identical deletions or duplications of 22q11.2 and which specific 22q11.2 genes contribute to these phenotypes. It is indeed important that human dopaminergic neurons are involved in a reward deficiency associated behavioral anti-reward phenotype. It is well established that the D2 macromolecule belongs to the G-Protein-coupled receptors. In humans' hybridization of lambda hD2G1 to an assignment to the q22-q23 junction of chromosome 11. However, the Taq A1 polymorphism resides in exon 8 of the ANKK1 gene (Neville et al., 2004). Of interest the DRD2 -A1 allele is located 300 kb 22q11: 113.41-113.48mb in the 3' flanking area. This takes on some importance in that Septin 5 (Sept5), a gene encoded in the approximately 200 kb region. It was found that Septin deficiency reduced associated active social interaction that could load onto the antisocial behavior observed in ASD (Suzuki, et al., 2009) It is further conceivable that the nearness of both the DRD2 A1 allele and Septin may interact and even form a defective haplotype.

Most recently, Genovese &, Butler (2023) using novel gene-protein interactions with pathway and molecular function analyses have discovered at least three functional pathway such chromatin modeling, Wnt, Notch and other transduction pathways as well as metabolic disturbances linked to neuronal growth and dendritic spine profiles. Of significant interest as mentioned earlier is that according to Ho et al. (2016) deletion or duplication of the human chromosome 22q11.2 is associated with behavioral traits and neuropsychiatric disorders as displayed in ASD (see FIGURE 2).

There are other studies that reveal specific genes related to ASD such as the Shank2 especially at C1 cells in the hippocampus has been associated with an overrepresentation of goal directed reward seeking behavior (Sato et al.,2020 ,2023).

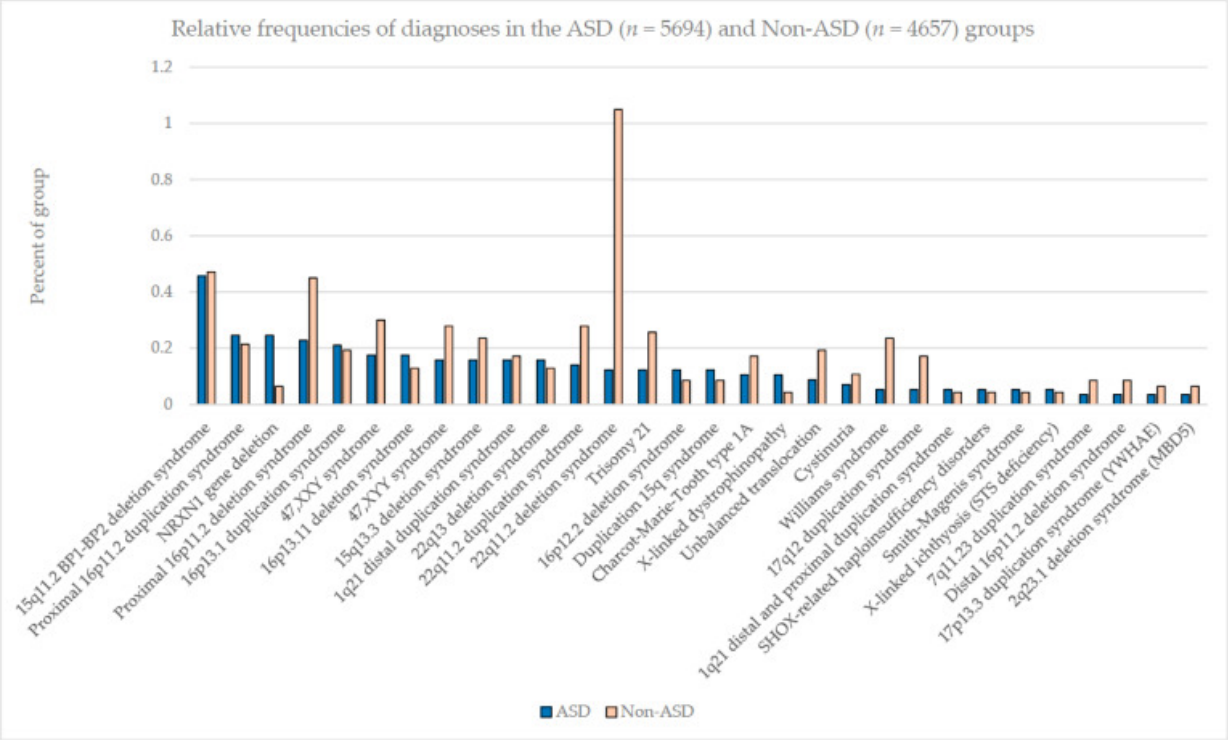


FIGURE 5

The relative frequencies of diagnoses in the combined ASD (n = 5694) and non-ASD (n = 4657) patient cohorts presenting for genetic services and laboratory testing using ultra-high-resolution chromosomal microarray analysis (reprinted with permission from Ho et al.

In summary, it is known that ASD as a genetic complex human disorder with high heritability as impacted by epigenetics, has seen an increased prevalence world-wide (Olusanya et al., 2023). Along these lines, it is agreed that ASD may be caused by a variety of different genetics such as rare genetic mutation; common copy number variants tied to duplication or deletion of stretches of chromosomal loci or even protein-disrupting single-nucleotide polymorphisms. Moreover, haploinsufficiency is one of the more common single-gene causes of ASD, that may account for 0.5% of cases. However, we should not ignore epigenetic mechanisms, especially DNA methylation similar to what is seen with alcoholism (Pandey et al., 2017) which could further result in environmental risk factors. It is our proposal that based on known human methylome as researched utilizing large GWAS as well as convergence to candidate genes including many neurotransmitter systems, second messengers and of cause finite pathways, that one launderable approach would be to genetic test ASD for gene-linked reward deficits as revealed in a series of studies utilizing the Genetic addiction Risk Severity (GARS)

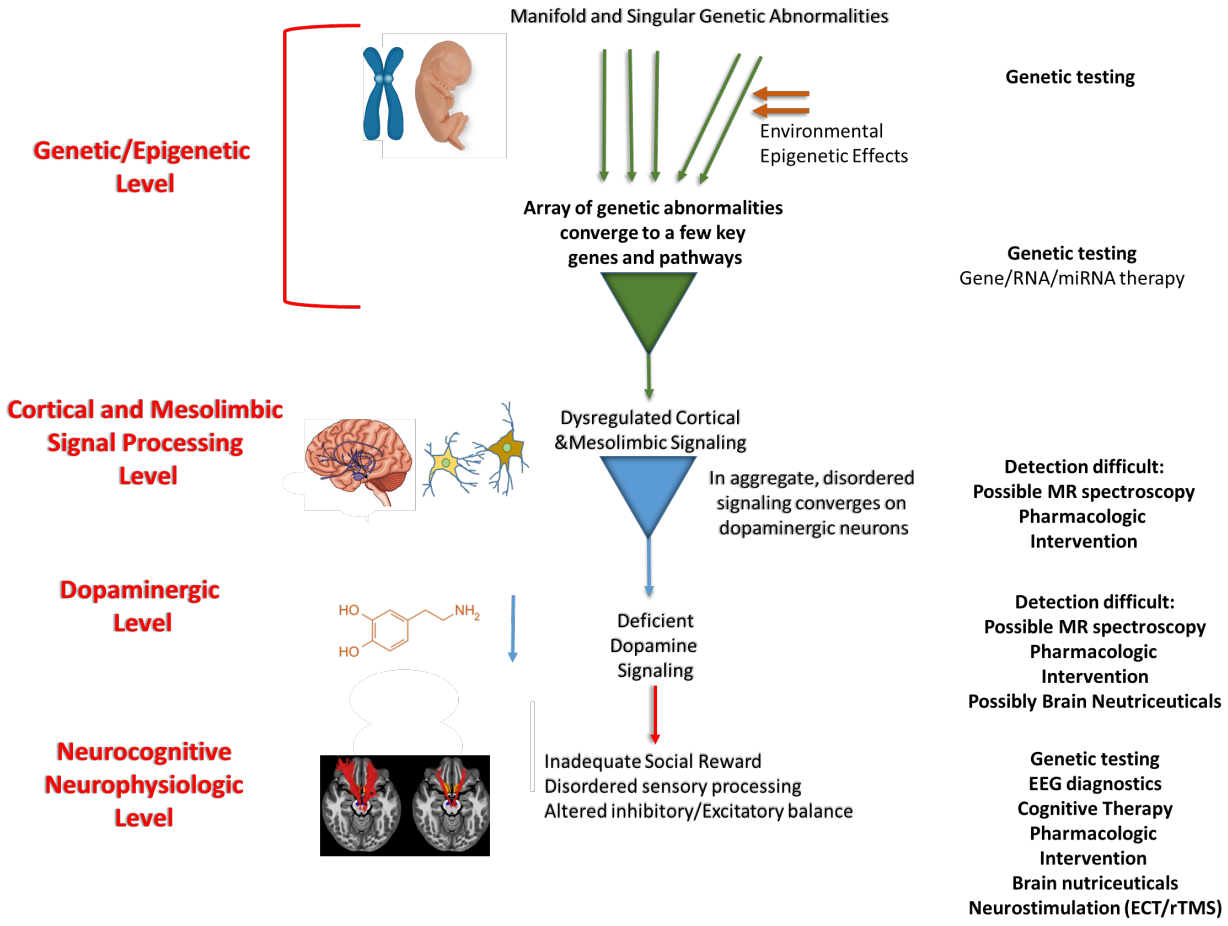


Figure 6. Provisional scheme illustrating stages or levels of dysregulated processes converging on dopaminergic pathways in ASD, and indicating various mechanistic levels and opportunities for therapeutic intervention. A plethora of ASD related genetic abnormalities converge on specific genes that influence complex cortical, and especially, mesolimbic signaling pathways that involve multiple neurotransmitters and endorphins. These pathways include neurons, glial cells, and various interneurons, which collectively converge on dopaminergic neurons that project to key mesolimbic and cortical reward sites. Finally, at the neurocognitive level, disordered social reward and sensory processing result in the psychobehavioral manifestations of ASD. Each mechanistic level may offer possibilities for specific types of diagnostics and somewhat distinct therapeutic interventions. Pharmacologic interventions may be complicated by the blood brain barrier (BBB).

test (Blum et al, 2022a,b, 2019, 2018, 2021,2023a,b, Moran et al., 2021,Fried et al., 2020, Dennen et al., 2022, Thanos et al., 2023, Vereczkei et al., 2022). In this regard, since it is indeed parsimonious to perform genetic testing prior to treatment, if possible, to identify for example, presence of reward gene polymorphisms (i.e., D1-D5, DAT1, COMT, MOAA, 5HTLPR, MOR, GABABR3), which will provide important specific

information regarding genetic dysfunction. Equally important would be the incorporation of even testing for histone methylation as well help understand environmental and possibly psychologically based insults. We are also proposing that coupled with genetic testing the incorporation of PrTMS will enhance clinical outcomes (Makale et al., 2023a,b).

To assist the readership concerning our proposal we developed a schematic for comprehensive purposes (see figure3).


DOPAMINE DYSREGULATION IN REWARD AND AUTISM SPECTRUM DISORDER (ASD):
TO BE OR NOT TO BE?
The Dopamine is prominent neurotransmitter implicated in reward mechanisms, mainly its dopamine D2 receptor. Importantly, while Dopamine is essential in this regard, it is the net effect of at least seven neurotransmitter systems that interact at the mesolimbic brain region that induces "reward".
Dopamine
Liking
Learning
Wanting
The hedonic impact of Reward
Learned predictions about rewarding effects
The pursuit of rewards by attributing incentive salience to reward-related stimuli – the wanting hypothesis of dopamine activity is supported by a majority of evidence
Dopamine is released from the nucleus accumbens and interacts with at least five dopamine receptors. Its major target projection is the striatum (The ventral region of the nucleus accumbens, which consists of Dopamine D1 & D2 receptor expressing spiny projection neurons.
Deletion or duplication of chromosome 22q11.2., Hybridization of lambda hD2G1 to an assignment of the q22-q23 junction of Chromosome 11, The importance of DRD2-A1 allele located in close of the 22q11 and the deficiency of Septin 5 gene associated with ASD antisocial behavior support the dopamine depletion hypothesis in ASD and might contribute to the behavioral actualization, including changed reward value of social stimuli, Anhedonia, altered motor stereotypies and sensorimotor processing.
Genetic & Epigenetic insults onto the dopamine & other neurotransmitter genes results in an impaired signaling. Dopamine dysfunction, causes individuals to have a high risk for multiple addictive, impulsive and compulsive behavioral propensities, including Autism Spectrum disorders (ASD).

Conclusion

Psychiatric disorders, including ASD, should be diagnosed based on their genetically regulated pathophysiology and this will indeed increase the power of even novel treatments like personalized repetitive transcranial magnetic stimulation (PrTMS) and other important non-pharmacological-non-addictive and safe modalities.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AUTHOR CONTRIBUTION:

KB and MTM developed the initial draft of the article. AB developed figure 3. KS, KTM, PKT, MM, MSG, IE, CD made comments and edited and approved the manuscript.

CONFLICT OF INTEREST

KB is the inventor and patent holder of gars and pro-dopamine regulators, KB is a paid consultant of the sunder foundation and Peaklogic, and MTM are paid consultant of Peaklogic.

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