REVIEW ARTICLE

EVOKING SUBCLINICAL HYPOMANIA AS A POTENTIAL AUTISM TREATMENT - A HYPOTHESIS BASED ON AN UP-TO-DATE LITERATURE REVIEW

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Abstract

The growing number of children diagnosed with autism spectrum disorder (ASD) urges the scientific community to find a simple and cost-effective solution to this problem. Before 1990, the general population prevalence for autism was considered steady at 4–5/10,000 (1/2,000–1/2,500). However, recent studies on children in the United States have reported an ASD diagnosis in 1/91 3-17 year olds and 1/110 8 year olds.

A comprehensive literature review of over 700 articles on neurotransmitter levels and brain performance in autism and other psychiatric conditions was conducted to finally include 83 studies. The results of the search led us to the conclusion that autism is a state of the brain performance opposite in many aspects to mania (in particular hypomania), both behaviourally (in particular autism being characterized by social deficits and hypomania by hypersociability), neurochemically (e.g. low brain vasopressin, high cortisol in autism vs. high brain vasopressin, low cortisol in mania) and by activity of key brain areas (e.g. mirror neuron system, amygdala).

We hypothesize that instead of targeting separate neurotransmitter systems in autism, the focus should be on 'moving and locking' the brain into a subclinical hypomanic state when required. When in a subclinical hypomanic state, a patient's sociability (the key and most debilitating symptom of autism) should be massively improved. We have designed experiments which would test the above hypothesis.

Keywords: autism, mania, hypomania, mirror neuron system (MNS), amygdala

1. Background

'The growing number of children being diagnosed with autism has raised enormous concern from parents, physicians, and scientists fearing that some environmental toxins have emerged to cause an autism epidemic. Before 1990, the general population prevalence for autism was considered steady at 4–5/10,000 (1/2,000–

1/2,500). Recent studies in the United States reported the diagnosis of autism spectrum disorder (ASD) in 1/91 3- to 17-year olds and 1/110 8-year-old children [1].'

'Children with classic autism are unable to 'read' other people, ignoring them and often strenuously avoiding eye contact. Reciprocal communication, through speech, gestures, or facial expressions, is impaired. **Children with autism fail to develop friendships with peers and siblings. In school, they often stand and watch other children from a distance. Some children respond to social overtures but take little social initiative, whereas others seek interaction but have little sense of how to proceed toward normal friendships** [1].'

ICD-10 defines **childhood autism (Kanner's syndrome)** as follows: 'A type of pervasive developmental disorder that is defined by: (a) the presence of abnormal or impaired development that is manifest before the age of three years, and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behaviour. In addition to these specific diagnostic features, a range of other non-specific problems are common, such as phobias, sleeping and eating disturbances, temper tantrums, and (self-directed) aggression [2].'

Asperger's syndrome is classed as a milder form of autism and defined as: 'A disorder of uncertain nosological validity, characterized by the same type of qualitative abnormalities of reciprocal social interaction that typify autism, together with a restricted, stereotyped, repetitive repertoire of interests and activities. It differs from autism primarily in the fact that there is no general delay or retardation in language or in cognitive development. This disorder is often associated with marked clumsiness. There is a strong tendency for the abnormalities to persist into adolescence and adult life. Psychotic episodes occasionally occur in early adult life [2].'

New diagnostic criteria have been proposed for ICD-11 beta draft due to be published in 2018, merging Kanner's syndrome, Asperger's syndrome and Pervasive Developmental Disorder – Not Otherwise Specified under one umbrella of Autism Spectrum Disorder. However, due to cited articles being published at different times and the ongoing debate whether that merger was a right one, we refer to the diagnostic criteria used in the original studies we cited [3].

In ICD-11 beta, 'Autism spectrum disorder is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests. The onset of the disorder occurs during the developmental period, typically in early childhood, but symptoms may not fully manifest until later, when social demands exceed limited capacities. Deficits are sufficiently severe to cause impairment in personal, familial, social, educational, occupational or other important areas of functioning and are usually a pervasive feature of the individual's functioning observable in all settings, although they may vary according to social, educational, or other context. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities [4].'

On the other hand, ICD-10 defines **hypomania** (a milder form of mania) as 'a disorder characterized by a persistent mild elevation of mood, increased energy and activity, usually marked feelings of well-being and both physical and mental efficiency. Increased sociability,

talkativeness, over-familiarity, increased sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection. Irritability, conceit, and boorish behaviour may take the place of the more usual euphoric sociability. The disturbances of mood and behaviour are not accompanied by hallucinations or delusions [2].'

We present references on how main neurotransmitters (acetylcholine, noradrenaline, cortisol, dopamine, histamine, NMDA ligands, opioids, oxytocin, serotonin, testosterone, vasopressin) have opposing (low/high compared to controls) levels in autism and mania. The fact that there is opposing activity of the mirror neuron network (low in autism, high in mania), different emotional biases (towards negative emotions in autism and towards positive emotions in mania), opposing amygdala activation in autism and mania (high to neutral and sad faces in autism, low to sad and high to happy faces in mania) supports our hypothesis that evoking a subclinical hypomanic episode using commercially available pharmacological agents in adolescents and adults with autism (in particular mild autistics / Asperger's syndrome patients) would help these individuals in improving their social skills, the key and most debilitating symptom of autism. We compare autism to mania, and in particular to hypomania, because hypomania is characterized by hypersociability and can be evoked by commercially available medications [6, 7, 16, 17]. We hypothesize that hypomania can be evoked in autistics as well, therefore evoking it would alleviate autism symptoms.

2. Review Method

The massive search was carried out using search engines **Pubmed, Scopus, Google Scholar** with the use of search keywords (neurotransmitter name OR brain part name) AND (autism OR mania / manic) for each combination (e.g. vasopressin + autism; vasopressin + mania; amygdala + autism; amygdala + mania). The study DID NOT involve people, human tissues, medical records or death certificates even retrospectively, therefore no approval from the bioethical commission was needed. The search resulted in over 700 articles, of which 83 most relevant are cited below. The review is non-systematic as a systematic one would have had a very high volume, and a very high volume is not necessary to present our idea. We selected the most representative articles to include in this publication based on quality of the publication and the research centre the study was conducted at. Mania is not so heavily researched. Aside from a few studies (e.g. mirror neuron activity, cortisol levels), the articles are usually case reports of hospitalized patients after being initiated on certain medication. The results of the search provided us with sufficient arguments to hypothesize that autism is the opposite state of the brain performance to mania in many aspects, in particular hypersociability, therefore triggering a subclinical hypomanic state should abolish autism symptoms for the duration of hypomanic state and the idea of conducting the experiment in attempt to test the hypothesis is justified in our opinion.

3. Review results

3.1. Neurotransmitters

Neurotransmitters, also known as chemical messengers, are endogenous chemicals that transmit signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft,

where they are received by receptors on the target cells.

Neurotransmitters are used by brain cells (neurons) to 'communicate' with each other.

Below we present comparison of available data about levels of main neurotransmitters in the brain and central nervous system in both autism and mania.

3.1.1. Acetylcholine

Binding of nicotine agonist epibatidine to granule cells and Purkinje cells is significantly reduced in autistics [5], whereas activation of nicotinic receptors either directly through their agonists, e.g. varenicline [6], or indirectly by increasing the level of acetylcholine by acetyl-cholinesterase blockade (donepezil) can induce a manic episode [7]. Nicotinic agonists (mecamylamine) and acetyl-cholinesterase inhibitor galantamine have anti-autistic properties in humans [8, 9].

3.1.2. Adrenergic system

The levels of acute noradrenaline were found elevated in autistics, however, various studies have demonstrated decreased noradrenaline over a 24-hour period in autistics using urinary 3-methoxy-4-hydroxyphenethylene glycol (MHPG), a metabolite of noradrenaline [10], and have also shown decreased levels of salivary α-amylase [11] which is an indicator of noradrenergic tone. Interestingly, it has been found that autism symptoms diminish during fever which is believed to be due to increased activity of the locus coeruleus, a major noradrenergic nucleus in brain during febrile episodes [12]. Atomoxetine (selective noradrenaline re-uptake inhibitor) [13] and venlafaxine (serotonin-noradrenaline re-uptake inhibitor) both have been found to alleviate the autism symptoms including social deficits (venlafaxine) [14]. On the other hand, increased levels of a major noradrenaline metabolite (MHPG) were found in CSF fluid of patients with acute mania and the levels correlated with severity of the episode (YMRS score) [15]. Atomoxetine (noradrenaline re-uptake inhibitor) [16], and venlafaxine (serotonin/noradrenaline re-uptake inhibitor) [17] are known to induce manic switch. The efficacy of clonidine in mania (α-2 agonist lowering noradrenaline levels) [18] is well documented.

3.1.3. Cortisol

In a number of studies, elevated cortisol levels have been found in plasma of autistic children and they correlated positively with the severity of autism symptoms [19, 20], whereas during the first ever manic episode in drug naive patients cortisol levels were significantly lower compared to controls and correlated negatively with severity of manic episode [21].

3.1.4. Dopamine

There is conflicting evidence in regards to HVA concentration in CSF autistics with some studies presenting evidence of increased concentration, while others reporting similar levels in autistics and controls [22]. In an interesting research, an eye blink rate (a reliable indicator of dopamine level in prefrontal cortex) was positively correlated with the theory of mind performance in autistics [23]. In BTBR mice (model of autism) dopamine re-uptake inhibition failed to elicit mesolimbic and striatal reward responses and also significant psychomotor activation. Furthermore, pre-synaptic and post-synaptic activity of D2 receptors was significantly impaired in BTBR mice with D1 receptors-mediated response left intact [24]. Fluorine-18-labelled fluorodopa accumulation in the anterior medial prefrontal cortex was 39 % lowered compared to controls, suggesting lowered dopamine activity in that part of

brain in autistics [25]. Atypical antipsychotics: olanzapine [26] and aripirazole [27] have been found to be effective in ameliorating autism symptoms. They are thought to increase cortical dopamine release through partial dopamine agonism (aripiprazole), direct 5-HT1A receptor agonism (risperidone) or indirect 5-HT1A receptor stimulation once 5-HT2A receptors are blocked (olanzapine, clozapine) [28].

Contrary to autistics, manic subjects displayed increased homovanillic acid concentrations in cerebrospinal fluid compared to controls [29]. Many drugs with dopamine-related mechanism of action (levodopa, dopamine receptor agonists like ropinirole and pramipexole) are known to induce mania [30, 31]. Surprisingly, atypical antipsychotics which are D2-receptor antagonists have been reported to induce manic symptoms (olanzapine, risperidone, aripiprazole) [28, 32-34], hypothetically through the mechanism mentioned above [28].

3.1.5. Histamine

Histamine receptor antagonists (H1 - niaprazine [35] and H2 - famotidine [36]) have demonstrated promising clinical improvements in autistics, however, they have also been reported to induce manic symptoms (H1 - pheniramine [37]), H2 - famotidine [38]).

3.1.6. NMDA receptors

D-cycloserine, an NMDA receptor agonist has been found to be effective in ameliorating autism symptoms in both laboratory animals and humans [39]. Combined concentration of glutamate and glutamine (naturally occurring NMDA receptor agonist in brain) in the basal ganglia was lowered in autistics compared to controls and the reduction was significantly correlated with social impairment [40].

On the other hand, plasma levels of both glutamate and glycine (which have co-agonist sites at the NMDA receptor) were increased during manic episodes [41]. Furthermore, glutamine levels were significantly increased in the dorsolateral prefrontal cortex during the manic phase [42]. Memantine, an NMDA receptor antagonist has been found effective in treatment of manic episodes [43].

3.1.7. Opioids

Patients taking morphine for long time display similar characteristics to autistic patients including a reduced need for social contact and insistence on sameness [44]. It has been found that β-endorphin levels in the CSF and plasma of people with autism are higher compared to controls [45]. Naltrexone, a μ-opioid receptor antagonist, has been found to be effective in improving social withdrawal, irritability, hyperactivity and self-injurious behaviour in people with autism [46].

On the other hand, numerous studies report the development of manic episodes after the withdrawal of opioids [47].

3.1.8. Oxytocin

In a recent study, oxytocin nasal spray led to significant improvements in social responsivity in autistic children [48]. Moreover, MDMA/Ecstasy, a drug with known pro-social effect correlating with oxytocin release, has been reported to exert pro-social effects in autistics as well [49].

On the other hand, serum oxytocin levels were found to be increased in bipolar patients with an active manic phase when compared to depressive and remission groups [50].

3.1.9. Serotonin

Low brain serotonin concentration (as per 5-Hydroxyindoleacetic acid (5-HIAA) levels in the CSF) has been associated with pervasive developmental disorder – not otherwise specified (PDD-NOS) [51]. Various antidepressants exerting their action through increasing brain levels of serotonin like: mirtazapine [52], clomipramine [53], and especially selective serotonin re-uptake inhibitors (SSRI) like fluoxetine [54] and sertraline [55] have been found to be helpful in alleviating autism symptoms.

On the other hand, numerous anti-depressants have been reported to induce mania. These include mirtazapine [56] and in particular paroxetine (SSRI) [57].

3.1.10. Testosterone

High concentrations of testosterone in autistics were found during the prenatal period and early childhood [58], however, during adolescence male patients with autism had significantly lower serum testosterone compared to controls [59]. On the other hand, it is well known, that anabolic steroid abusers (testosterone analogues) often develop mania or hypomania as a result of taking doses up to 100-fold in excess of therapeutic ones [60].

3.1.11. Vasopressin

Blood arginine vasopressin concentrations (which correlated to CSF concentrations) significantly and positively predicted the theory of mind performance in autistics, but failed to do so in non-autistic patients [61]. Moreover, treatment with transcutaneous electrical accupoint stimu-lation of children with autism resulted in increased blood vasopressin and at the same time alleviated some of the behavioural issues associated with autism [62].

Contrary to this, manic patients were found to have significantly higher vasopressin in the CSF compared to other psychiatric patients [63]. Also, basal plasma vasopressin-neurophysin was significantly higher in the patients with manic schizophrenia compared to other patients [64].

3.2. Mirror neuron network activity

A mirror neuron is a neuron that fires both when an animal acts and when the animal observes the same action performed by another [65, 66, 67]. Thus, the neuron "mirrors" the behaviour of the other, as though the observer were itself acting. Such neurons have been directly observed in primate species [68]. In humans, brain activity consistent with that of mirror neurons has been found in the pre-motor cortex, the supplementary motor area, the primary somatosensory cortex and the inferior parietal cortex [69].

A number of studies confirmed lowered mirror neuron network activity, a group of neurons responsible for the ability to understand and imitate others' behaviours, in patients with autism. For example, EEG assessments did not show significant μ wave suppression (thus, did not show mirror neuron network activity) during observed hand movements in autistics [70]. Also, the transcranial magnetic stimulation study gave similar results with reduced mirror neuron network excitability during observation of transitive hand gestures in autistics. Interestingly, this correlated negatively with self-reported social impairments (the lower mirror neuron activity, the greater the impairment) [71].

On the other hand, during manic states in drug naive patients (manic patients are known to be overfamiliar and have increased sociability) the mirror neuron network activity positively correlated with the severity of manic symptoms as established by Young Mania Rating Scale [72].

3.3. Emotional bias

The autistic patients displayed hyper-vigilance towards faces displaying disgust [73]. Also, adults with ASD occasionally misinterpreted happy faces as neutral and attributed negativity to neutral faces in another study [74].

Contrarily, patients in active manic states showed worse recognition of fear and disgust than controls and showed inverse correlation of YMRS score with recognition of sadness [75]. In another study, patients with mania had attenuated subjective rating of sad facial expressions with attenuated activity of corresponding brain areas [76].

3.4. Amygdala activity

The amygdala is one of two almond-shaped groups of nuclei located deeply and medially within the temporal lobes of the brain in complex vertebrates, including humans. It has been shown in research to perform a primary role in the processing of memory, decision-making, and emotional reactions. The amygdalae are considered a part of the limbic system [77].

It was found that youth with ASD had decreased amygdala habituation to sad and neutral faces compared with controls. Moreover, decreased amygdala habituation correlated with autism severity as measured by the Social Responsiveness Scale [78]. Also, autistics relative to control group showed greater activation in the amygdala, particularly to sad faces [79]. This was confirmed in another study where the ASD group reported greater social anxiety which was associated with increased activation in the right amygdala compared to controls [80].

On the other hand, it was found that during manic episodes, patients had attenuated sensitivity to sad facial expressions and this was associated with attenuated amygdala response to these sad faces [81]. Also, compared to healthy individuals, hypomanic or manic patients showed higher valence ratings in positive pictures and associated larger blood-oxygen level-dependent responses in the left amygdala during positive versus neutral picture viewing. This correlated with Young Mania Rating Scale scores and with euphoria as opposed to irritable symptom presentation [82].

4. Conclusions

As presented above, mania in many aspects (levels of neurotransmitters, performance of key areas of the brain and most importantly, the social behaviour) is the opposite state of brain performance to autism. Therefore, we claim that instead of focusing on targeting pharmacologically separate neurotrans-mitter systems independently, evoking subclinical hypomanic state in autistic individuals should invert many autism symptoms, in particular increase sociability (e.g. activate mirror neuron system and change the performance of amygdala as a result of changed levels of neuro-transmitters) for the duration of subclinical hypomanic state. According to us, the focus should be placed on the overall state and the performance of the whole brain rather than on separate neurotransmitters.

As many medications known to induce mania exist, the induction of subclinical hypomania should be a matter of finding a tolerated medication or their combination in a right dose for each patient. We suspect that the reason these medications work is simple - they shift the brain state towards mania.

Interestingly, some case reports have documented the abolition of symptoms of Parkinson's disease during a manic episode. Parkinson's disease is linked with mental health disorders and affects motor skills in a similar but not the same way as autism [83].

We compared autism to mania and in particular to hypomania because hypomania is characterized by hypersociability and can be evoked by commercially available medications (several reports in the literature exist – cited in this publication). We hypothesize that hypomania can be evoked in autistics as well, therefore evoking it in autistics would alleviate autism symptoms.

We also hypothesize that this approach should be the most effective in mild autism, in particular among adolescents and adults with Asperger's syndrome and would allow them to develop social skills and confidence in social situations. We assume that gaining that experience would rewire the brain in such a way that pharmacology would no longer be necessary just like a driving instructor is no longer needed after several hours behind the wheel of the car.

We would like to test this hypothesis in experiments designed by us.

5. Limitations and recommendations for future studies

Autism spectrum disorder is a heterogenous group of similar disorders caused by genetic, environmental and social factors. The pharmacological studies on autistics are limited and cohorts of patients used are usually small. With regards to mania, there is a limited number of studies on the pharmacology of mania and there are often reports of patients who developed manic symptoms after being started on a certain medication.

Due to the methodology used, some studies give positive results and some neutral (see mirror neurons).

Our aim is to conduct experiments to check whether subclinical hypomanic states can be evoked on purpose in autistics and whether during these states the main symptoms of autism are fully abolished. We have designed a series of trials in order to assess whether our hypothesis is correct or not.

Competing interests:

The authors declare that they have no competing interests.

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Table 1. Comparison of various aspects of autism and mania.

Neurotransmitter / Performance of brain areas	Autism	Mania
Acetylcholine	•There is evidence that nicotinic signalling is lowered in autism [5], •Nicotinic agonist mecamylamine [8] and acetylcholinesterase inhibitor galantamine have anti-autistic properties [9]	•Activation of nicotinic receptors either directly through their agonist varenicline [6] or •Indirectly by increasing the level of acetylcholine by acetylcholinesterase blockade can induce manic episodes [7]
Adrenergic system	•The levels of acute noradrenaline were found to be elevated in autistic, however studies have demonstrated decreased noradrenaline over a 24-hour period in autism [10], •This includes the lowered level of salivary alpha-amylase [11] which is an indicator of noradrenergic tone •Autism symptoms diminish during fever due to increased activity of the locus coeruleus, a major noradrenergic nucleus in brain during febrile episode [12] •Atomoxetine (selective noradrenaline re-uptake inhibitor) [13] and venlafaxine (serotonin-noradrenaline re-uptake inhibitor) both have been found to alleviate the autism symptoms [14]	•Increased levels of major noradrenaline metabolite (MHPG) were found in the CSF of patients with acute mania and the levels correlated with the severity of the episode (YMRS score) [15] •Atomoxetine (noradrenaline re-uptake inhibitor) [16] and venlafaxine (noradrenaline re-uptake inhibitor) are known to be able to induce manic switch [17] •The efficacy of clonidine (alpha-2 agonist lowering noradrenaline levels) [18] in treatment of acute mania has been confirmed
Cortisol	•In a number of studies enhanced cortisol levels have been found in the plasma of autistic children and they correlated positively with the severity of autism symptoms [19, 20]	•During the first ever manic episode in drug naive patients, cortisol levels were significantly lower compared to controls and correlated negatively with severity of manic episode [21]
Dopamine	•There is conflicting evidence with regards to homovanillic acid concentration in	•Manic subjects displayed increased homovanillic acid concentrations in the CSF

Dopamine	cerebrospinal fluid in autistics, some evidence in favour of increased concentration, whereas others show similar levels as controls [22] •Eye blink rate (a reliable indicator of dopamine in prefrontal cortex) was positively correlated with the theory of mind performance in autistics [23] •In BTBR mice (model of autism) dopamine re-uptake inhibition failed to elicit mesolimbic and striatal reward response and significant psychomotor activation as well. Furthermore, presynaptic and postsynaptic activity of D2 receptors was significantly impaired in BTBR mice with D1 receptors-mediated response left intact in BTBR mice [24] •Fluorine-18-labelled fluorodopa accumulation in the anterior medial prefrontal cortex accumulation was 39% lowered compared to controls suggesting lowered dopamine activity in that part of brain in autistics [25] •Atypical antipsychotics: olanzapine [26] and aripirazole [27] have been found to be effective in ameliorating autism symptoms. They are thought to increase cortical dopamine release through partial dopamine agonism (aripiprazole), or indirect 5-HT1A receptor stimulation once 5-HT2A receptors are blocked (olanzapine) [28]	compared to controls [29] •Many drugs with dopamine-related mechanism of action (levodopa, dopamine receptor agonists like bromocriptine, cabergoline and pramipexole) are known to induce mania [30, 31] •Surprisingly, atypical antipsychotics which are D2-receptor antagonists have been reported to induce manic symptoms (olanzapine, clozapine, risperidone, aripiprazole) [32, 33, 34]. This interesting effect is thought to be evoked through the mechanism mentioned above (indirect dopamine release in cortical tissue through 5-HT1A receptor stimulation due to 5-HT2A receptor blockade) [28]
Histamine	•Histamine receptor antagonists (H1 - niaprazine [35] and H2 - famotidine [36] have demonstrated promising clinical improvements in autistics	•Antihistamines can induce manic symptoms (H1 - pheniramine [37] and famotidine [38])
NMDA	•D-cycloserine, NMDA receptor agonist has been found effective in ameliorating	•Plasma levels of both glutamate and glycine (it has co-agonist site at the NMDA receptor)

NMDA	autism symptoms in humans [39] •Combined concentration of glutamate and glutamine (naturally occurring NMDA receptor agonist in brain) in basal ganglia was lowered in autistics compared to controls and the reduction was significantly correlated with social impairment [40]	were increased during manic episode [41] •Glutamine levels were significantly increased in the dorsolateral prefrontal cortex during the manic phase [42] •Memantine, an NMDA receptor antagonist, has been found effective in treatment of manic episodes [43]
Opioids	•Patients taking morphine for long time display similar characteristics to autistic patients including: reduced need for social contact and insistence on sameness [44] •β-endorphin levels in the CSF and plasma of people with autism are higher compared to controls [45] •Naltrexone, μ-opioid receptor antagonist has been found to be effective in improving social withdrawal, irritability, hyperactivity and self-injurious behaviour in people with autism [46]	•On the other hand, numerous reports exist in the literature about developing manic episodes after the withdrawal of opioids [47]
Oxytocin	•Oxytocin nasal spray led to significant improvements in social responsivity in autistic children [48] •MDMA/Ecstasy, a drug with known prosocial effects correlated with oxytocin release, has been found to exert prosocial effects in autistics as well [49]	•Serum oxytocin levels were found to be increased in bipolar patients with active manic phase compared to depressive and remission groups [50]
Serotonin	•Low brain serotonin concentration (as per 5-HIAA levels in the CSF) has been associated with PDD-NOS [51] •Various antidepressants which exert their action through increasing brain levels of serotonin: mirtazapine [52], clomipramine [53] and in particular fluoxetine [54] and sertraline [55] which are selective serotonin reuptake inhibitors have been found helpful	•Numerous antidepressants have been reported to induce mania. These include mirtazapine [56] and in particular paroxetine (SSRI) [57]

Serotonin	in alleviating autism symptoms	
Testosterone	•High concentrations of testosterone in autistics were found during prenatal period and early childhood [58] •During adolescence, male patients with autism had significantly lower serum testosterone compared to controls [59]	•Anabolic steroid abusers (testosterone analogues) often develop mania or hypomania as a result of taking doses up to 100-fold [60]
Vasopressin	•Blood arginine vasopressin concentrations (which are correlated to the CSF concentrations) significantly and positively predicted the theory of mind performance in autistics, but failed to do so in non-autistic patients [61] •Treatment with transcutaneous electrical accupoint stimulation of children with autism resulted in increased blood vasopressin and at the same time alleviating some of the behavioural issues associated with autism [62]	•Manic patients were found to have significantly higher vasopressin in the CSF compared to other psychiatric patients [63] •Also basal plasma vasopressin-neurophysin was significantly higher in the patients with manic schizophrenia compared to other patients [64]
Mirror neuron network activity	•A number of studies confirm lowered mirror neuron network activity, a group of neurons responsible for the ability to understand and imitate others' behaviours, in patients with autism. For example: •EEG assessment did not show significant μ wave suppression (did not show mirror neuron network activity) during observed hand movements in autistics [70] •The transcranial magnetic stimulation study gave similar results with reduced mirror neuron network excitability during observation of transitive hand gestures in autistics. Interestingly, this correlated negatively with self-reported social impairments (the lower mirror neuron activity, the greater the impairment) [71]	•During manic states in drug naive patients (manic patients are known to be overfamiliar and have increased sociability), the mirror neuron network activity positively correlated with severity of manic symptoms as established by Young Mania Rating Scale [72]

Emotional bias	•The autistic patients displayed hypervigilance towards faces displaying disgust [73] •Adults with ASD occasionally misinterpreted happy faces as neutral and attributed negativity to neutral faces in another study [74]	•Patients in active manic states showed worse recognition of fear and disgust than controls and showed inverse correlation of YMRS scores with recognition of sadness [75] •Patients with mania had attenuated subjective rating of sad facial expressions with attenuated activity of corresponding brain areas [76]
Amygdala activity	•It was found that youth with ASD had decreased amygdala habituation to sad and neutral faces compared with controls. Moreover, decreased amygdala habituation correlated with autism severity as measured by the Social Responsiveness Scale [78] •Autistics relative to control group showed greater activation in the amygdala, particularly to sad faces [79] •The ASD group reported greater social anxiety which was associated with increased activation in the right amygdala compared to controls [80]	•During manic episodes, patients had attenuated sensitivity to sad facial expressions and this was associated with attenuated amygdala response to these sad faces [81] •Compared to healthy individuals, hypomanic or manic patients showed higher valence ratings in positive pictures and associated larger blood-oxygen level-dependent responses in the left amygdala during positive versus neutral picture viewing and this correlated with Young Mania Rating Scale scores and with euphoric as opposed to irritable symptom presentation [82]

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