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# Olfactory bulb dysgenesis, mirror neuron system dysfunction, and autonomic dysregulation as the neural basis for autism

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SUMMARY

Autism is a disorder characterized by social withdrawal, impoverished language and empathy, and a profound inability to adopt another's viewpoint – a failure to construct a "theory of mind" for interpreting another person's thoughts and intentions. We previously showed that these symptoms might be explained, in part, by a paucity of mirror neurons. Prompted by an MRI report of an individual with autism, we now suggest that there may be, in addition, a congenital aplasia/dysplasia of the olfactory bulbs with consequent reduction of vasopressin and oxytocin receptor binding. There may also be sub-clinical temporal lobe epilepsy affecting the recently discovered third visual system that is rich in "empathy" related mirror neurons (MNS) and projects (via the TOP junction – just below the inferior parietal lobule) to limbic structures that regulate autonomic outflow. This causes deranged autonomic feedback, resulting in additional deficiencies in MNS with loss of emotional empathy and introspection.



Despite decades of research, the neural basis of autism spectrum disorders (ASD) remains unknown. A wide range of anatomical deficits have been observed (for a review, see Ref. [1]) and many psychological theories have been advanced, but little progress has been made in explaining the mental symptoms in terms of the specific functions of known anatomical structures. In 2000, we proposed "the mirror neuron theory" of autism and provided experimental support for the idea that a dysfunction of mirror neurons might underlie ASD [2]. In the frontal lobes (and IPL) of primates many neurons – "motor command neurons" – fire when the animal (or person) performs a skilled or semiskilled action (reaching for food, putting food in mouth, pulling a lever, etc.) [3]. Intriguingly, a subset of these cells – called mirror neurons – fire even when the person or primate merely watches someone else perform the same action; as if the neuron (or strictly, the network of which it is part) was using the visual input to adopt the other person's point of view in interpreting his impending action. Such neurons have been implicated – perhaps with excessive zeal! – in a wide range of phenomena including the origins of language, emotional empathy, the ability to infer the goals of others for predicting their behavior, "pretend play" in children (which requires you to temporarily "model" or mime yourself or a toy as another person) and imitation learning. Since these are the very abilities that are compromised in ASD, it seemed reasonable to suggest that mirror neuron dysfunction may be the primary cause of the symptoms. Although, there have been attempts in the past to pin down the cause of autism, ours was the first to explain the symptoms that are *specific* to autism (poverty of empathy, language, pretend play, etc.) in terms of the properties that are *unique* to a specific set of neurons. We then used electrophysiological signatures of mirror neuron activity to demonstrate such deficits [2], an observation that has now been confirmed in many large-scale studies by several groups including our own [4–7].

Previous studies into the neural basis of autism have found changes in many far-flung brain regions, but the changes do not, for the most part, explain the spectrum of symptoms that are specific to the disorder. Conversely, psychological theories (e.g. ASD is based on an inability to construct "a theory of other minds") come perilously close to being tautologies. Surely the two contrasting approaches should be seen as complementing each other – not mutually exclusive (no more than DNA and Mendel's laws are mutually exclusive). The mirror neuron theory may help bridge the two kinds of explanations: "reductionist" and "black box".

We recently postulated that recursive activity of the mirror neuron system may also be involved in some aspects of self awareness and introspection and these too, seem partially compromised in ASD, although the idea has not been tested rigorously. One might predict, for example, that high functioning ASD individuals will have special difficulty introspecting on and understanding "self" related attributes (such as self-conscious, self-effacing, self-promoting, self-aggrandizing, selfish, embarrassment, etc.) compared to their overall verbal IQ or their aptitude with other equally difficult abstract words and phrases (e.g. what does a "left leaning" politician mean? Why did King Solomon suggest dividing the baby into two? What is infinity?).

A second cluster of symptoms – unpredictable emotional outbursts, hypersensitivity and hyper-reactivity to trifling noises – is

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also seen in ASD, yet these symptoms are unexplained in terms of mirror neuron deficits. We had previously suggested [8] that these symptoms might in part be caused by childhood temporal lobe epilepsy (TLE; either clinically obvious or subclinical). TLE has been noted in as many as one–third of ASD subjects [8] and it seems possible that the repeated volleys of seizure activity may lead to indiscriminate "kindling" or strengthening (and possibly some effacement) of pathways connecting sensory systems to the amygdala, and between limbic structures and autonomic outflow [9]. This theory ("distorted salience landscape") would help explain why ASD subjects are often curiously indifferent to stimuli (e.g. eyes) that fascinate normal children and conversely why they over-react with emotional/autonomic outbursts to trifling sensory stimuli. Such deranged autonomic outflow could result in a correspondingly compromised autonomic feedback from viscera. Consistent with the James-Lange theory (developed in its most elegant form by Damasio [10]) the final result of this reduction in autonomic feedback would be a blunting of ones own experience and introspection of emotions and, consequently, a disabled "theory of other minds" mechanism (the interface between "self" related emotions and inferred emotions of others being provided by mirror neurons which, as we already noted, are compromised in ASD).

Thus, malfunction of the mirror neuron system and of autonomic regulation may help explain many of the symptoms of autism, but what causes such malfunction in the first place? And, are there other brain lesions – or transmitter imbalances – that contribute to the symptoms either directly or acting via the mirror neuron system?

Here, an additional anatomical structure may provide a clue. It has been known for decades that there are two parallel pathways that diverge from early visual centers (primary/secondary visual cortex, etc.), one called the *where* (*or how*) pathway – projecting to the parietal lobe responsible in part for controlling actions – and the second, called the *what* pathway, involved in both object recognition and the assignment of meaning and names to objects [11]. There is a third, more recently identified pathway, which projects from the visual centers to an area just under the inferior parietal lobule (IPL) [12]. We refer to it loosely as the "emotional pathway" or "ventro-dorsal pathway" (referring its anatomical location roughly in the temporo parieto occipital junction). This pathway is rich in mirror neurons – especially those involved in emotional empathy – and subsequently projects to limbic structures including anterior cingulate – concerned with attending to emotional salience. We postulate that subclinical TLE in childhood with consequent autonomic dysregulation and feedback monitoring of autonomic inflow, leads to a mirror neuron deficiency in this ventro-dorsal pathway. The net result would be a deficiency in introspecting on ones own emotions as well as empathizing with others; two of the symptoms of ASD. We suggest that this malfunctioning, self-perpetuating cycle of events involving the ventro-dorsal pathway and its multiple feedback loops – both central and peripheral – serves as the conduit in producing many of the dysfunctions characteristic to ASD. However, understanding these cycles of events underlying autism does not speak to the mechanism(s) of initial damage.

Our first hint of this primary deficit came in early 2008 when we were contacted by an individual with high functioning ASD, whose structural MRI revealed complete agenesis of his olfactory bulbs. Since we lost contact with the patient we could not do a full clinical work-up here at our institution. Prompted by this observation, we propose a new theory of autism that can be tested using large-scale brain imaging studies. In particular, we suggest that a dysgenesis (or complete agenesis) of the olfactory bulbs and projection zones in the brain may lead either directly or indirectly (through transmitter imbalances or by contributing to mirror neuron system malfunction) to some instances of autism spectrum disorders. Such dysgenesis may be the primary cause or a contributing cause. We will not discuss the much-debated environmental (e.g. vaccines, heavy-metal poisoning) and genetic alterations which in turn lead to the specific brain changes we postulate. Indeed the olfactory bulb dysgenesis and mirror neuron system malfunction may either be unrelated pleiotropic effects of the same genes or the former may actually lead to the latter.

Support for the olfactory bulb dysgenesis theory comes from several pieces of circumstantial evidence:

(1) The absence of olfactory bulbs observed in the single case mentioned earlier.
(2) Recent work has shown volumetric decreases in the olfactory bulbs correlate with their functional abilities in normal individuals (e.g. larger olfactory bulbs exhibit finer olfactory discrimination) [13]. The ability to discriminate between unique smells has been shown impaired in autism [14] which, as mentioned, relies on intact functioning of the olfactory bulbs. It can be assumed, therefore, that a reduction in size outside the range of normal variation (or total absence) of the olfactory bulbs should be observed in autism. This abnormality can be expected to generalize to deficits beyond olfactory discrimination, due to utilization of the olfactory bulbs in social and emotional processing, as we will discuss later.
(3) Previous research has shown both individuals with schizophrenia as well as their first-degree relatives display reduced olfactory bulb volumes [15,16]. As autism and schizophrenia have long been known to share clinical features – indeed, autism was once believed to be childhood schizophrenia – it can well be expected they will also share this phenotypical trait.
(4) Vasopressin and oxytocin have been regarded as "affiliation hormones" crucial to social functioning [17] and have received much attention as a potential mechanism for autism treatment. As a high density of oxytocin and vasopressin receptors is present throughout the olfactory bulbs, each of these neurotransmitters' action is dependent on this brain area's *proper* functioning. Any impairment of the olfactory bulbs during development would also compromise a key mechanism of action mediating these social behaviors.
(5) Consistent with this view, reduced levels of oxytocin have been observed in individuals with ASD [18,19] and intravenous oxytocin administered to adults with autism remediates both repetitive behaviors and speech comprehension [20,21].
(6) Excessive "mothering" behavior (noted by one of us; VSR with AV Srinivasan) in a TLE patient was accompanied by a seizure related surge in prolactin. Conversely, there was a reversible aversion to the infant (and reduction of prolactin) whenever carbamazepine was administered to control seizures. We postulate that the TLE seizures cascade in the hypothalamus/hypophysial axis causing prolactin release.
(7) The observation of excess plasma-based serotonin (hyperserotonemia) is one of the most well-replicated findings in autism. Over 25 studies have reported to this effect (for a review, see [22]), demonstrating that approximately 1/3 of individuals with autism exhibit on average a 50% increase in plasma-based serotonin. This increase in serotonin during development is generally thought to reduce the functioning of serotonin terminals in the brain due to negative feedback and desensitization. As oxytocin is metabolized from serotonin in the brain, hyperserotonemia has been shown in rats to have a similar desensitization effect on oxytocin receptors [23]. Further, McNamara showed that social behaviors based

on olfactory cues were also significantly reduced by serotonin-agonist administration, suggesting that hyperserotonemia during development may impair general functioning of the olfactory bulbs, in addition to desensitization of oxytocin receptors.

(8) The olfactory bulbs project to the limbic structures and indirectly via these structures to autonomic outflow. When present, an olfactory bulb malfunction could "propagate" through the system causing both the emotional/autonomic "storms" and outbursts and – via the mirror neuron system – producing a poverty of social affiliation and empathy (abilities that are both evolutionarily and anatomically linked to olfaction).

(9) Early anecdotal observations that high fever in a child can, surprisingly, ameliorate the symptoms of ASD temporarily. We have previously suggested [9] that this occurs because (as noted above) autonomic outbursts and associated emotional tantrums are mediated by hypothalamic nuclei. Such nuclei – given that they regulate sympathetic outflow – are also very likely to be involved in temperature regulation and fever. If so, fever might have a damping effect on nuclei involved in the autonomic storms (and associated hyperreactivity), thereby damping some of the ASD symptoms that cannot be explained by the mirror neuron system abnormalities.

The mirror neuron system, however, also permeates the limbic system (e.g. insula and anterior cingulate). Therefore, the olfactory bulb dysfunction and hypothalamic/autonomic abnormalities may also lead to loss of social empathy. The exact cause-effect sequences need to be disentangled here and it is best to remain agnostic at this point, given, especially that there likely to be many back and forth interaction between these structures. Nonetheless, these ideas may provide a novel conceptual framework for approaching the disorder. One straightforward prediction from this theory would be that individuals who have had trauma (or frontal lobe tumor) that destroy or compress on the olfactory bulb would show at least some autism like symptoms over and above what one would expect from simple frontal lobe pathology.

The olfactory bulb hypothesis also has important clinical implications. Based on the oxytocin reduction theory, researchers have made attempts administer the hormone intranasally. In our scheme, this would not be the most effective method since the hormone needs to be initially absorbed by the olfactory bulb before being transmitted to limbic structures. As a functional prediction from this theory, children before the age of 2 who will later develop autism should show decreased levels of oxytocin and the vasopressin in their system as a first warning sign. Accordingly, the onset might be permanently stayed by intravenous injections with oxytocin. While oxytocin does not enter the adult brain in significant quantities due to the blood–brain barrier, effective administrations should target cerebral spinal administrations or focus on oxytocin and vasopressin precursors.

To explore the validity of this theory, a systematic study is being undertaken by us comparing olfactory bulb volumes in individuals with autism with those of normal controls.

In summary, we propose that a combination of olfactory bulb dysgenesis causing (or accompanied by) dysregulation of oxytocin and vasopressin functioning, mirror neuron system deficits, and hypothalamic/autonomic dysregulation might help explain many of the seemingly unrelated symptoms in autism spectrum disorders. While the cause of autism is unlikely to be of single origin, the framework we have provided – and the bits of circumstantial evidence we have tried linking together – might provide a starting point for a more complete theory of this tragic disorder.

## Conflict of interest statement

None declared.

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