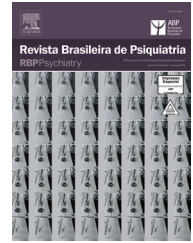




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EDITORIAL

More than two dozen “autisms”

Autism is a condition that typically includes problems with social interaction and communication and a sharply restricted range of activities and interests. Some of the diagnostic categories in the current diagnostic classification systems, including the Diagnostic and Statistical Manual - IV (DSM-IV), include the following: autistic disorder, Asperger's disorder, and pervasive developmental disorders not otherwise specified (PDD-NOS). The proposed changes in the next version of the DSM (DSM-5) are based on two dimensions: (1) social and communication impairments as one domain and (2) restrictive and repetitive behaviors as another domain. This decision is based on field trials. The proposed DSM-5 criteria would remove a number of the diagnostic categories in current use, including autistic disorder, Asperger's disorder and PDD-NOS, and combine them under the term autism spectrum disorder (ASD).

In spite of the progress in the psychiatric diagnoses of ASD, genetic studies have been disappointing. Although several candidate genes have been described in the literature, no consistencies in replication studies have been found. More advanced technologies, such as genome-wide scans, and large sample sizes have not improved our knowledge about ASD etiologies. In addition, the recent data from copy number variations (CNVs), micro-RNAs, and epigenetic studies suggest that trying to identify a single autism gene could be unproductive. Currently, many aspects of the genetic factors that predispose someone to develop ASD remain a puzzle.

How can we solve this puzzle? One way would be to suggest that a single diagnostic entity of ASD does not exist and that we have been observing the functional outcomes of several brain circuits working in concert. In other words, a boy with communication impairment, stereotyped behavior and social isolation but with clear affectionate behaviors directed toward his parents most likely has a more functional affiliative behavior system than communicative and motor management systems. Hundreds of different combinations could be built considering the brain circuits supporting social skills, communication, and patterns of behavior.

However, our puzzle has many pieces to be considered. As we continue to explore the activity of specific brain circuits in individuals with ASD over the course of development, we might consider patterns in phylogeny and ontogeny. Reptiles have a basic range of behaviors (most of them restrictive and ritualistic, with strong genetic determinism). Birds have more developed affiliative behaviors, social interaction, and basic communication systems with more gene-environment interaction and parental imprinting. Primitive mammals manifest robust affiliative behaviors, social skills, and communication systems. Primates have added planning and anticipation skills able to modify the environment, reflecting an improvement in executive functions and limited genetic determinism due to gene-environment interactions and brain flexibility.

The ontogeny of human beings shows the same pattern of development based on brain function maturation. Babies have a set of genetically determined behaviors located in specific brain circuits that can also be found in our mammalian ancestors. By interacting with their parents and other human beings, these infants alter the developmental course of these circuits so that they typically develop more complex social behaviors (and more complex circuitries). In sum, as a species, we depend on these ancient affiliative circuits and then build on this base so that the complex communication system observed in our species can reach its full potential.

However, phylogeny shows us that neural development is neither homogenous nor normally distributed. Principles of communication can be observed in organisms as primitive as bacteria. I also think of the complex communication skills observed in the amazing studies on Alex, the gray parrot. Primitive mammalian behavior, such as jaguars hunting gazelles, present theory of mind skills based on the anticipation of intentional biological movement. Ontogeny follows the same rule, and based on this, we can understand the different presentations of social brains and ASD.

Let us now explore gestalt perception as part of the central coherence function. Here, I have been fascinated by the role that the connexin protein plays in the formation of gap junctions in the frontal lobe and how that might

provide insights into the functionality of the “social brain” and the ASD endophenotype. The ability to have gestalt perception seems to be related to the presence of gamma oscillation patterns on EEG, as observed in the frontal lobe of infants approximately eight months of age. In contrast, gamma oscillation is related to the expression of connexin and adhesion molecules responsible for electric synapses. Based on this, we can expect a dysfunction in gestalt perception as a consequence of the disruption of connexin gene expression or even expression disruption in the connexin-folding process. Interestingly, connexin depends on calcium to be folded or functional, and it could be misfolded in high calcium concentration environments, such as may be found in the frontal lobe cortices of ASD brains. In a certain way, this example can help us to understand why candidate gene studies are sometimes not informative because the dysfunction can be localized downstream in the protein-folding process. In addition to these different steps in the workflow of the molecular bases of neuronal circuitries, we can assume that the functionality of gestalt perception also has a gradient from the entire comprehension of a certain event to the perception and understanding of sub-components of an image. In terms of functionality, the quality of gestalt perception depends on the way the information is combined from different circuitries, and the actions derived from this perception depend on the complexity of the executive function networks. Thus, an individual can have well-performed gestalt perception, but the type of executive functions and frontal lobe projection networks might limit the actions that can be taken from gestalt perception. As a hypothesis, this includes the need for interneurons to work properly for these circuits to achieve optimal executive functions.

One of the sub-domains of social behavior is modulated by circuitries that express affiliative behavior. Its influence is more related to affective binding, preoccupations with the presence of the “other,” modulated by the oxytocin system. Some ASD individuals have better functional affiliative behavior, expressing more affective connection with their parents.

However, if these ASD individuals have compromised gestalt perception (perhaps due to electrical synapses working slower due to an impairment in intra-cellular calcium), we observe social interaction impairments. They may express feelings by touching, hugs, or kisses but not more complex social interaction acts, such as the pleasure in sharing a chat, listening to a story, or even being admired in words. However, we can consider that the affiliative behavior system and the gestalt system are working fine, but the anticipation of the impact of some behaviors during social interaction are not working properly due to a failure in the executive function and its frontal projections.

For further information concerning specific points mentioned by Professor Marcos T. Mercadante, readers are invited to consult various websites, including those associated with Wikipedia, on the following topics:

DSM-5 proposed changes:

<http://www.dsm5.org>

Alex, the gray parrot:

[http://en.wikipedia.org/wiki/Alex_\(parrot\)](http://en.wikipedia.org/wiki/Alex_(parrot))

Theory of Mind:

http://en.wikipedia.org/wiki/Theory_of_mind

Gestalt perception:

http://en.wikipedia.org/wiki/Gestalt_psychology

Connexins and the formation of gap junctions:

<http://en.wikipedia.org/wiki/Connexin>

Gamma wave oscillations:

http://en.wikipedia.org/wiki/Gamma_wave

Oxytocin system:

<http://en.wikipedia.org/wiki/Oxytocin>

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