The Social Brain Network and Autism

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ABSTRACT

Available research data in Autism suggests the role of a network of brain areas, often known as the 'social brain'. Recent studies highlight the role of genetic mutations as underlying patho-mechanism in Autism. This mini review, discusses the basic concepts behind social brain networks, theory of mind and genetic factors associated with Autism. It critically evaluates and explores the relationship between the behavioral outcomes and genetic factors providing a conceptual framework for understanding of autism.

KEYWORDS: Autism, Behavioral Genetics, Brain Networks

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Introduction

It is hypothesized that the deficits in social cognition and related cognitive functions in Autism results from reduced synchronization between these key brain regions during different social and emotional tasks: recent research suggests autism to be a 'neural connectivity disorder'.

These interconnected neural systems can be understood through the relationship between functionally relevant anatomic areas and neurochemical pathways, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems. It has been suggested that autism emerges from a developmental cascade in which a fundamental deficit in attention to social stimuli beginning as early as infancy leads to impaired interactions with primary caregivers. This results in abnormal development of social cognition, which in turn adversely affects later behavioral and functional domains such as language development which are dependent on these early processes.

A common neuroanatomical theme in autism is over-connectivity in closely related areas and decreased connectivity in longer circuitry needing large scale integration. Disordered development of grey and white matter in autistic individuals has been demonstrated in the frontal and temporal cortices, where selective increase in late developing white matter and narrow mini columns in frontal and temporal cortex has been associated with early accelerated postnatal head growth.[1]Studies have found fewer, abnormally small and densely packed neurons especially in lateral nucleus of the thalamus and the Purkinje cells of the cerebellum.[2] The corpus callosum and major inter-hemispheric connection tracts are smaller than non-autistic, age- and gender-matched individuals.

Social brain network in autism

Neuropsychiatric and neuropsychological evaluations in Autism have revealed selective dysfunction of 'social cognition', with sparing of motor, perceptual and basic cognitive skills. Social cognition includes a range of skills and functions required for successful interpersonal interaction, mediated by a 'Social Brain Network', consisting brain regions that are dysfunctional in autism: Fusiform face area (perception of personal identity), inferior frontal gyrus (facial expression imitation), posterior superior temporal sulcus (perception of facial expressions and eye gaze tasks), superior frontal gyrus (theory of mind, i.e., taking another person's perspective) and the amygdala (emotion processing).[3-5]

Theory of mind in autism

One theory of autism proposes that the core deficit is an inability to metalize and infer the state of mind of another person, or "Theory of Mind" (TOM).[6] Autistic individuals perform poorly on typical ToM tasks, which involve guessing what a character is thinking based on a vignette presented in words or pictorially. Difficulty in metalizing leads to being unable to share or express emotions as they cannot anticipate thoughts and actions of others or even understand that others have their own intentions, feelings and points of view is been inferred from the study. Communication is a way of influencing others to construct a picture of the world similar to ones own, but in autism, individuals cannot conceive that others have inner worlds. They can master complex technical operations but cannot learn from verbal instructions and environmental clues, act on hints or understand humor or irony.

ToM deficits in autism have been linked to abnormal patterns of hypo activation in superior temporal gyrus, superior temporal sulcus, and basal temporal areas and hyper activation in Brodmann's area 9/10, compared to healthy subjects who performed well on ToM tasks. Furthermore, it has been demonstrated that the amygdala and left medial prefrontal cortex, which are core regions in healthy subjects were not involved at all in autistic subjects.[7] While reduced amygdala and medial PFC function has also been associated with difficulty in attributing emotional states to others.[8]

Mirror neuron system in autism

The Mirror Neuron System, which is postulated to underlie the ability to mimic, learn and understand the actions of others [9] has also been implicated in autism.[10] Mirror neurons are those in the ventral motor regions that fire when subjects observe actions performed by con-specifics, particularly when the subject has to mimic or learn that action. Although mirror neuron dysfunction has been proposed in autism behavioral paradigms, but has not revealed differences between autistic and non-autistic children in imitating and understanding hand gestures.[11] It has been proposed that lack of empathy, or the difficulty to 'feel what you feel' is linked to mirror neuron system dysfunction, but the evidence is sparse.

Genetic factors in autism

The programming of various brain networks is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems. Studies have reported that there are approximately 103 disease genes, 44 genomic loci are associated with autism.[12] A recent review of genetic studies of autism identified three basic phenotype/genotype combinations:[13]

- Autism plus phenotype consisting of Autism Spectrum Disorders (ASD) caused by rare, single-gene mutations; for e.g., fragile X in 5-10% in Autism Plus.
- Broad autism phenotype caused by genetic variations in single or multiple genes. These variations are common and are present in the general population, but result in varying clinical phenotypes when they cross a certain threshold through complex gene-gene and gene-environment interactions.
- A severe and specific phenotype caused by 'de-novo' mutations in the patient or transmitted through asymptomatic carriers of such mutation.

Table I. Disease genes and genetic disorders reported in individual with ASD

Gene	Locus	Mutations/ CNVs	Encoded protein/gene function	Clinical features	References
NTNG1	1p13.3	mutations	Protein acting as axon guidance cues during nervous system development	Schizophrenia, ASDs	(14)
CLCN6	1p36.22	mutations	Member of voltage-dependent chloride channel in the nervous system	ASDs	(15)
NRXN1	2p16.3	mutations, CNVs	Cell adhesion molecule and a receptor in the nervous system, formation and maintenance of synaptic junctions	ASDs, schizophrenia, epilepsy, ADHD, ID, speech delay, hyperactivity, depression, learning difficulties	(16-20)
TBR1	2q24.2	mutations	Transcription factor required for normal brain development	Schizophrenia, ASDs	(21)
SCN2A	2q24.3	mutations	Sodium channel, voltage-gated, type II, alpha subunit	ASDs epilepsy	(22, 23)
SCN1A	2q24.3	mutations	Sodium channel, voltage-gated, type I, alpha subunit	ASDs epilepsy	(12, 24)
CNTN4	3p32.2	mutations	Axonal-associated cell adhesion molecule	ASDs	(25)
FOXP1	3p13	mutations	Transcription factor	ID, ASDs	(12, 24)
TBL1XR1	3q26.32	mutations	Transcription activation	ASDs	(21)
CDH10	5p14.2	mutations	Neuronal cell-adhesion molecule	ASDs	(26)
CDH9	5p14.1	mutations	Neuronal cell-adhesion molecule	ASDs	(26)
SLIT3	5q34q35.1	mutations	Axonal guidance regulator	Depression, schizophrenia, ASDs	(21)
SYNGAP1	6p21.32	mutations, CNVs	Development of cognition and proper synapse function	ID, ASDs	(27)
AHI1	6q23.3	mutations	Cerebellar and cortical development in humans	Joubert syndrome	(12, 25)
HOXA1	7p15.3	mutations	Transcription factor	ASDs	(12)
RELN	7q22.1	deletions	Cell positioning and neuronal migration during brain development	ASDs	(28)
CNTNAP2	7q36.1	mutations, CNVs	Cell adhesion molecule and receptor in the nervous system	Focal cortical dysplasia, ASDs, ID, epilepsy, schizophrenia, bipolar disorder	(12)
DLGAP2	8p23.3	CNVs	Molecular organization of synapses and neuronal cell signaling	ASDs	(27)
CHD7	8q12.2	mutations, deletions	Chromatin remodeling	CHARGE syndrome, ASDs	(12)
RIPK2	8q21.3	mutations	Interacts with p38 kinase	ASDs	(15)
UNC13B	9p13.3	mutations	Synaptic vesicle maturation in a subset of excitatory/glutamatergic synapses	ASDs	(15)
ABCA1	9q31.1	mutations	Neuronal structure and function	Bipolar disorder, schizophrenia, ASDs	(15)
LAMC3	9q34.12	mutations	Laminin, plays a role in forming the convolution of the cerebral cortex	ASDs, ID	(24)
TSC1	9q34.13	mutations	Regulation of protein synthesis in a wide range of cell types including neurons	Tuberous sclerosis, ASDs	(29)

Gene	Locus	Mutations/ CNVs	Encoded protein/gene function	Clinical features	References
ANK3	10q21.2	mutations	Protein that link the integral membrane proteins to the underlying spectrin-actin cytoskeleton	Bipolar disorder, ASDs	(15)
PTEN	10q23.3	mutations	Modulating cell cycle, inhibition of the AKT signaling pathway	Cowden syndrome, ASDs, macro-cephaly	(25, 30-32)
DHCR7	11q13.2	mutations	7-Dehydrocholesterol Reductase	Smith-Lemli-Opitz syndrome, ASDs	(12, 33)
	q13.5				
SHANK2	11q13.3	mutations, deletions	Structural and functional organization of the dendritic spine and synaptic junction	Schizophrenia, ASDs, ID	(34)
HTR3A	11q23.2	mutations	5-hydroxytryptamine (serotonin) receptor 3A	ASDs	(24)
GRIN2B	12p13.1	mutations	Glutamate receptor ionotropic, NMDA 2B	ASDs, ADHD, schizophrenia	(21, 24)
CACNA1C	12p13.3	mutations	Calcium channel, voltage-dependent, L type, alpha 1C subunit	Timothy syndrome, ASDs	(12, 25)
CHD8	14q11.2	mutations	Chromatin remodeling	ASDs, macrocephaly	(21, 22)
TSC2	16p13.3	mutations	Regulation of protein synthesis in a wide range of cell types including neurons	Tuberous sclerosis	(25, 29)
NF1	17q11.2	mutations	Stimulates the GTPase activity of Ras signaling pathway	Neurofibromatosis, ASDs	(12)
KATNAL2	18q21.1	mutations	Microtubule-severing ATPase activity	ASDs	(22, 23)
DYRK1A	21q22.13	mutations, CNVs	Plays a role in a signaling pathway regu-lating cell proliferation	Majority of phenotypic features in Down syndrome, ASDs, ID, micro-cephaly	(21, 35)
SHANK3	22q13.33	mutations, deletions	Structural and functional organization of the dendritic spine and synaptic junction	Phelan-McDermid syndrome, ASDs, schizophrenia	(29, 36-38)
PTCHD1	Xp22.11	mutations, CNVs	Synaptic functioning	ASDs, ID	(27, 39)
NLGN4	Xp22.31 p22.32	mutations, CNVs	Neuronal cell surface protein involved in the formation and remodeling of central nervous system synapses	ASDs, ID	(28, 40-42)
PHF8	Xp11.22	mutations	Cell cycle progression, rDNA transcription and brain development	ASDs, ID	(43)
HUWE1	Xp11.22	mutations	Neural differentiation and proliferation	ASDs, ID	(43)
NLGN3	Xq13.1	mutations, CNVs	Neuronal cell surface protein, involved in the formation and function of synapses	ASDs, ID	(28, 29)
FMR1	Xq27.3	mutations	Translation repressor	Fragile X syndrome, ID, ASDs	(25, 32)
MECP2	Xq28	mutations, CNVs	Chromosomal protein that binds to methylated DNA, neuron maturation, negative regulation of neuron apop-totic process, cerebellum development, regulation of postsynaptic membrane potential, regulation of transcription	Re& syndrome, ASDs, ID	(25, 32)
SLC6A8	Xq28	mutations	Creatine transporter	Creatine deficiency syndrome, ID, ASDs	(12)
TMLHE	Xq28	mutations	Enzyme in the carnitine biosynthesis pathway	ASDs	(43, 44)

When is a gene mutation pathogenic

For a mutation to be pathogenic in autism, it should involve neurodevelopmental genes that regulate neuronal development, migration, circuitry formation and synapse function. Some candidate molecules are NGLs (neuronal cell adhesion molecules) NRX/CBLN/GluD2 complex (synapse organizer), LRRs (transmembrane proteins), SHANK3 (multiple ankyrin repeat domains), which are all involved in synaptogenesis. This is mediated via signaling molecular pathways through ubiquitin, mammalian target of rapamycin(mTOR), kinase and adenosine phosphorylation pathway. Mutation of genes leads to cascade of events linking

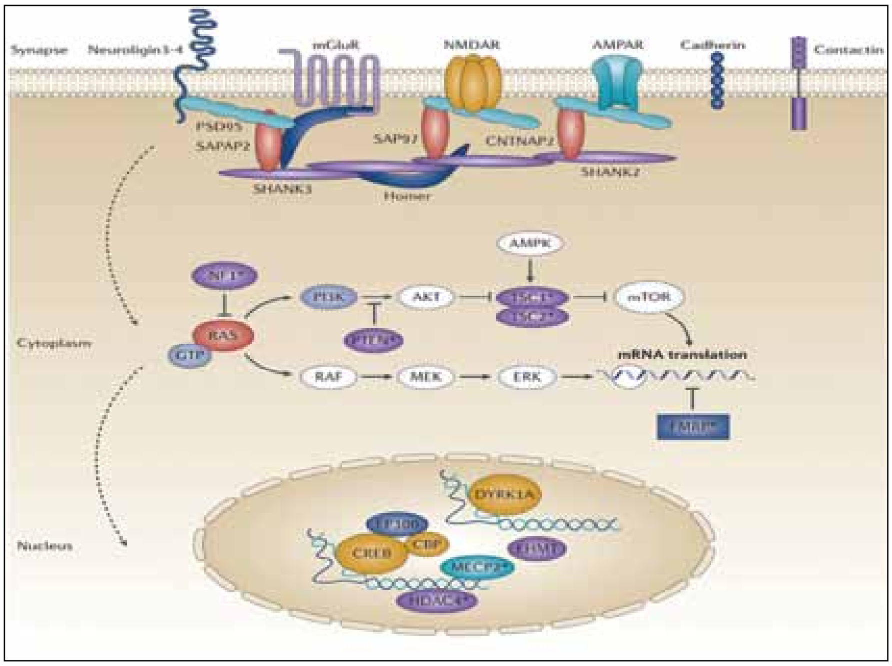

Fig. 1: Proteins with genetic variants associated with autism spectrum disorder (ASD) (excluding those in white ovals) are clustered in specific intracellular processes. In colour, proteins with genetic variants associated with ASD; in white, proteins not directly associated with ASD. From Ghosh et al., Nat Rev Drug Discov. 2013;12(10):777-90. Reprinted with permission.

transcription (e.g. MECP2 transcriptional regulator), translation (fragile X mental retardation related protein FMRP; translational regulator) and specific synaptic proteins important for maintenance of excitation/inhibition (E/I) ratio during synapse formation. The disruption of E/l ratio results in alternated in a) structure of synaptic connections, b) molecular assembly of synapses c) functional synaptogenesis.[45] E/I ratio imbalance also leads to high glutamatergic& low GABAergic activity and shift to excitatory hyper transmission states, leading to the development of a circuit which is hyperexcitable; i.e., a non-tunable circuit with poor differentiation and stability. (Fig 1.)[46]

Mutations of genes regulating neuronal migration may result in abnormal organization of cortical mini-columns and poor synchronization between neural regions, such as the hippocampus and prefrontal cortex, which is fundamental for learning and memory.[47]

Conceptual framework for autism: from behavior to genes

The putative underlying mechanism of local over-connectivity and long-range over connectivity is supported by the following cognitive deficits:

- Repetition of domain-specific routines in the absence of domain general executive integration; for e.g., echolalia but no functional spontaneous speech.
- Deficit in long-range communication between parallel specialized sub-circuits, such as the amygdalae and fusiform face area, contributing to impaired emotion perception.
- No cortical global workspace for integration of past and present experience.
- Lack of learning by trial and error through social experience indicates domain general executive integration and generalizability.

Therefore, in autism, an initial domain specific deficit results in secondary lack of normal social experience. Dependence on local domain specific networks leads to cognitive rigidity. The link of modular deficit to mirror phenomena leads to repetitive behaviors in the absence of functional imitation.

Disturbed patterns of neuronal activity underlying specific types of behavior could be correlated with specific genetic alleles thus linking gene to brain development to behavior.

Conclusion

Learning is genetically programmed but environmental activity dependent. This bi-directional interface offers an opportunity for intervention. Through modeling, observational and imitation learning in the preschool years that enhance social -emotional and social-cognitive development can build stronger circuitry.

Genetically mediated deficits and consequent functional impairments involve activity-dependent synapse development, which depend on postnatal learning and experience. Understanding these neurobiological underpinnings can lead to the design of interventions that accommodate the way the brains of children with autism function and may lead to the promotion of more flexible thinking and learning. Furthermore, since genetically mediated deficits and consequent functional impairments involve activity-dependent synapse development that depends on postnatal learning and experience, early intervention can prevent or reduce the risk of these deficits cascading into a trajectory toward full expression of the disorder. Such a model implies the importance of intervening early to prevent downstream effects, and is supported by studies showing greater efficacy with early intervention programs which seek to counteract this early deficit and normalize the development of social and communicative capacities through provision of heavily enriched social stimuli by therapists and caregivers. This offers an opportunity to interrupt the sequence of events that would otherwise have resulted in an abnormal developmental trajectory, but instead promote interactions that normalizes basic brain responses to social stimuli and alter the course of development by exploiting the neuronal maturation and brain plasticity in the early years of life.

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