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Question 2 How can I understand what is happening?

Aspirational Goal: Discover how alterations in brain development and brain function lead to ASD in order to inform the development of effective targeted interventions that improve quality of life for persons with ASD.

Introduction:

Over the course of last decade there is considerable new knowledge related to :

a) the role of genetic contributions to the risk of developing ASD that has enabled a greater understanding of:
    a. mechanisms by which highly penetrant mutations disturb brain development and brain function in the syndromic forms of ASD.
    b. how the many common genetic variants that affect the risk of ASD converge on disordered synaptic dysfunction as a common mechanism
b) differences in brain development in persons with ASD as compared to typical development
c) nature and prevalence of comorbidities in persons with ASD

In almost all cases however our knowledge is incomplete and significant gaps in science have stymied attempts to develop therapies to improve QOL for those suffering with ASD.

What do we know?

1) Our understanding of what is happening in the brain to cause ASD and its varying symptoms is informed in large part by studies of the implicated gene effects in cellular or animal models. These genetic findings are the subject of Question 3.

a) The function of the normal and mutated protein in syndromic forms of ASD, TSC, Retts, Phelan McDermott, SCN1, Fragile X
b) The function of genes implicated by large GWAS studies-

2) Brain imaging technologies to examine brain structure and function in humans has identified differences in brain development and brain connectivity in persons with ASD.

a) brain overgrowth during a specific period in development

Work is ongoing to link these to the core features of ASD:

a) difficulties in social interaction

b) difficulties in verbal and non verbal communication
c) repetitive behaviors

As well as with other neurological manifestations such as:

a) anxiety
b) intellectual disability
c) epilepsy
d) difficulties with motor control
e) difficulties with attention
f) sleep disorders
g) sensory processing
h) special skills in some persons with autism, ie math, visual, memory

3) Studies of persons with ASD has led to a greater appreciation of the contribution that comorbidities make to a decreased QOL for persons with ASD.

GI dysfunction,
Increased frequency of infections

<u>What do we need?</u>

1) Greater knowledge of brain development through longitudinal imaging studies using standardized acquisition parameters to enable comparability across studies and with robust data sharing policies to enable expert analysis of the data by a variety of computational scientists.
    a. Beginning in utero and throughout the first two years of life in persons at high risk of developing ASD.
    b. At time of diagnosis and in the years following ASD diagnosis
    c. MRI techniques to examine brain development are now more powerful. The 'baby connectome" project will establish norms in typically developing infants and toddlers to compare with data from young children with signs of ASD.
    d. Search for adaptive brain changes in response to a developmental disturbance. These adaptive changes may be beneficial or incur net harm. Search for adaptive changes in brain activity/structure that predict response to interventions (CBT).

2) Greater knowledge of the structural and molecular changes in ASD brain. Studies of post mortem brain tissue to uncover developmental abnormalities in brain structure as well as activation of cellular responses especially by the immune system.
    a. BRAIN Initiative has as its goal the development of a census of cell types and would be important to compare it with the census of cell types in ASD brain.
    b. There is a need to understand the role of the immune system in ASD. RNA studies in ASD brain have identified changes in the brain's

immune system. Immune cells in the brain have been recently shown to have a major role in shaping the connections between neurons in development as well as in neurodegeneration.

c. Chromatin remodeling
d. Somatic mutations in brain have **now** been found to occur much more commonly than previously thought. What is their role in ASD?
e. Search for adaptive changes that may be attempts at compensation for a developmental disturbance, either beneficial or with net harm.

3) Greater knowledge of the brain circuit abnormalities implicated in ASD in animal models which can **now** be explored in detail using techniques to map neural connections, record from large number of neurons during a behavioral task, precisely turn on or turn off specific types of neurons to understand the nature of the brain circuit abnormalities caused by biologic mechanisms tied to ASD, ie. genetic mutations, immune challenge,
    a. Attempt to understand the synaptic dysfunction implicated by the GWAS studies.
    b. Attempt to understand what changes are reversible
    c. Explore these models for the effects of XX vs. XY, sex hormones
    d. Explore how abnormal sensory input and processing affects neurodevelopment

4) Greater knowledge of the neural effects of genes implicated in ASD. Studies can **now** be performed in cells from persons with syndromic and potentially non -syndromic autism which have been reprogramed to IPSCs and then differentiated into neural cells or even neural tissue. These can then be compared to genetically corrected identical cells (syndromic ASD) or to cells or tissues derived from typical developing controls.
    a. Establish a differentiating phenotype in neurons, glia
        i. Synaptic dysfunction, firing properties, epileptogenesis, etc.
    b. Explore development and cellular differentiation in brain organoids
    c. Explore these models for effects of XX vs. XY, sex hormones

5) More inclusive and more in depth knowledge of the difficulties experienced by persons with ASD is needed to better define and quantify important aspects of the disorder. Phenotyping studies can **now** employ non-invasive monitoring of speech (automatic language processing), motor activity, eye tracking, interactions with others and the environment.

    a. To better understand the course of the disorder and its variability
        i. Characterize and quantify effect of comorbidities in persons with ASD.
            1. Bowel function, abd pain, sleep patterns, wandering, emotional swings.
        ii. Identify phenotypic subtypes to link to genetic differences

iii. Develop algorithms to predict course of the disorder. (precision medicine)
iv. Develop clinical measures that would be useful in intervention trials
v. Better understand the changes across the lifespan including transition to adulthood and aging.

Barriers to research:

1) There is a need for innovative single center studies to continue, but there is now a greater need to prospectively plan to standardize data elements, data acquisition parameters to enable greater comparability between studies and the establishment of large, high quality databases of genetic, phenotypic and imaging data.
2) As brain development in ASD occurs over many years there is a need for longitudinal studies; and less need for small cross sectional studies.
3) Validated animal models.
    a. Relevant biology
    b. Relevant behaviors?
    c. NHP—marmoset is now target for new genetic tools currently confined to mouse.
4) We have little knowledge of the environmental influences that must be out there
    a. In utero
    b. Infancy
5) We have little knowledge of how to design therapeutic interventions to improve brain function.
6) Few targets for therapeutic development.

Policy issues:

a. Inclusion of persons on autism spectrum in research plans and messaging
b. Quality of life needs to be tracked across the lifespan
c. Need to address replicability of findings by
    i. followup validation studies,
    ii. prospective guidelines for ASD research
        1. standardization of data acquisition
        2. prospectively planned data sharing
        3. standardization of behavioral measures
d. Need to move to larger team studies for certain types of research
    i. Longitudinal patient studies
e. Attract more diverse workforce
    i. Engineering, machine learning, monitoring device engineers, bioinformatics, etc.