Question 2 Draft Updates for the IACC 2011 Strategic Plan
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How can I understand what is happening?

What is new in this research area and what have we learned this past year?

Multiple studies in 2010 provided insight into neural mechanisms underlying autism spectrum disorders. These included:

- Structural imaging studies showing neural, white matter, and connectivity differences including underlying similar white matter aberrations in children with autism and their unaffected siblings (Barnea-Goraly, Lotspeich, & Reiss, 2010); decreased inter-hemispheric functional connectivity (Anderson, Druzgali, Froejlichs et al., 2010); alterations in frontal lobe white matter tracts and the corpus callosum in young children (Kumar, Sundaram, Livaswamy et al., 2010); increased random brain oscillations (Lai, Lombardo, Chakrabarti et al., 2010); and increased microglial activation and increased microglial density in the dorsolateral prefrontal cortex (Morgan, Chana, Pardo et al., 2010). One study of post-mortem brain tissue showed there were abnormalities in axons in the white matter of several brain regions (Zikopoulos & Barbas, 2010). Another study of post-mortem tissue suggested the potential role of vertical viral transmission as a pathogenic mechanism in autism (Lintas, altieri, Lombardi, Sacco, & Persico, 2010).

- Studies showing abnormalities in underlying brain structures including amygdala and hippocampal enlargement (Groen, Teluji, Buitelaar, & Tendolkar, 2010); differences in basal ganglia shape that predict social, communication, and motor dysfunction (Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010); and structure of the posterior temporal sulcus, which is related to autism traits in the general population (von dem Hagen, Nummermann, Yu, Engell, Ewbank, & Calder, 2010).

- Studies showing abnormalities in underlying neural circuits including those involved in face processing by means of the fusiform-amygdala system (Dziobek, Bahnemann, Convit, & Heekeren, 2010); atypical eye gaze, visual orienting, and visual perception (Akechi, Senju, Kikuchi, Tojo, Osanai, & Hasegawa, 2010; Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010; Loth Gomez, & Happe, 2010; New, Schultz, Wolf, Niehaus, Klin, German, & Scholl, 2010); and biological motion processing (Brieber, Herpetz-Dahlmann, Fink, Kamp-Becker, Remschmidt, & Konrad, 2010; Dinstein, Thomas, Humphreys, Minshew, Behrmann, & Heeger, 2010; Koh, Milne, & Dobkins, 2010). An additional study of biological motion perception in typically developing individuals, affected individuals, and their unaffected siblings suggested that biological motion perception may represent an attractive neural endophenotype of autism (Kaiser et al., 2010).

- A study showing that elevated urinary porphyrin levels, which indicated its disordered metabolism in children with autism (Woods et al., 2010).

Over the past year, IACC has nominated several studies that represent advances in what is known about the etiology of ASD with respect to neuropathology, symptoms, and cellular metabolism/ signaling. Schumann et al., (2010) published results of the first longitudinal study of early brain growth in toddlers aged 1.5 to 5. They found evidence of cerebral gray and white matter overgrowth in all regions by age 2.5. After correcting for age and gender, they found almost all brain regions developed at an abnormal rate in ASD. This quadratic trend was more pronounced in girls with ASD. Buie et al., (2010) issued a consensus report about evaluation, diagnosis, and treatment of gastrointestinal disorders in children with ASDs in the Journal *Pediatrics.* While the panel concluded that it was too early to make evidence-based recommendations, the consensus expert opinion was that individuals with ASDs deserve the same

Comment [OARC1]: Add Pelphrey reference

thoroughness and standard of care as all patients, and that problem behaviors in ASD may stem from gastrointestinal problems. Ibrahim et. al (Pediatrics 2009) tracked children in Olmsted County Minnesota and reported that the frequency of gastrointestinal symptoms was not different as compared to typically developing children. Mostafa, El-Hadidi, Hewedi, & Abdou (2010) examined oxidative stress in Egyptian children with autism. They found oxidative stress in close to 90% of these children and that this was related to an index of autoimmunity. They suggest that oxidative stress may play a role in autoimmunity, and that this represents a potential treatment target. Atladottir et. al. (2009) analyzed data from 690 thousand Danish children and reported that families with history of autoimmune disorders, rheumatoid arthritis, type 1 diabetes or celiac disease, are more likely to have ASD. Palmieri and Persico (2010) reviewed the literature and suggested that extant energy metabolism deficits in ASDs are not systematically related to specific genomic or genomic defects. Palmieri et al. (2010), examined gray matter from post-mortem brains of individuals with ASD and found increased levels of oxidized mitochondrial proteins in over half of subjects that was related to high calcium levels. They concluded that interactions between the mitochondrial aspartate/glutamate carrier gene and altered calcium homeostasis may play a role in autism.

Committee members also have pointed to the new focus on metabolic and immune system interactions through studies of mitochondria, oxidative stress, and viral infections; the potential utility of high throughput metabolomics approaches; findings of resolution of autism symptoms with fever; the intensified development of mouse models of autism (Silverman, Lord, & Crawley, 2010).

What gap areas have emerged since last year?

The Committee highlighted the newly emerging area of metabolomics, which in well controlled studies may provide a way to examine genotype-phenotype relationships. The Committee also recommended that we be cognizant of recommendations from other fields to identify “endophenotypes” in autism. Endophenotypes are partial/constituent phenotypes that may be more highly linked to specific genetic causes which may not be appreciated in studies which combine all symptom profiles. Endophenotypes may also aggregate in families and be amenable to deep sequencing genetic studies to identify genetic underpinnings. Endophenotypes also can be common to multiple neurodevelopmental disorders and offer leverage for understanding similarities and differences between different forms of developmental psychopathology.

Public comment points to the need for continued study of regressive autism, and females with ASD. New concerns were raised about the relationship between ASD and epilepsy, liver, and other diseases. It is also was recommended that we examine inflammation in expectant mothers and apraxia of speech and their relationship to ASD.

Several “implementation” related issues were raised by the Committee. These include the need to add rapidly emerging findings related to cell metabolism, signaling, neuroimaging, genetics, epigenetics, and co-existing medical conditions into existing databases designed to phenotype the “autisms.” Finally, the committee recommended that we continue to emphasize the rapid translation of our findings to clinical practice.

What new research opportunities and research objectives have emerged?

The following were recommended as changes to Research Opportunities and Objectives:

Research opportunities:

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- Revision of the first opportunity, second bullet point to read: "Multi-disciplinary assessments of brain imaging, metabolic and immunity markers, microbiomics, metabolomics, electrophysiology, and behavior."
- Studies to investigate metabolic pathway perturbations that affect immune function, and methylation in ASD.
- Reword research opportunity 7 to focus just on regressive autism
- Rework Short Term Objective-A to include concept of fever.
- Rework Short Term Objective-E to include the concept of wandering;

Comment [OARC2]: And all regression, not solely language regression; add mention of oxidative stress

Comment [OARC3]: And safety issues

What Progress is Being Made in Fulfilling Objectives?

As exemplified by the progress in the literature and funding as documented by the Portfolio Analysis, autism research is proceeding at a brisk pace. There are many promising studies of the neural correlates of autism-related symptoms that have not been classified. Also exciting are the number of young investigators and new investigators from other fields entering autism research as well as the strength of mentoring programs.

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