In the study of neuropsychiatric and developmental disorders, the pursuit of biomarkers is key. Biomarkers may have roles in (earlier) diagnosis, prognosis, patient stratification, treatment selection and response monitoring. To achieve these aims, however, "markers" should have a plausible biological basis and hence a major aim is "putting the 'bio' into biomarkers". As the possibilities of imaging and electrophysiologic "markers" develop, this requirement for biological basis tends to warrant a multimodal approach (both within MRI and across imaging modalities). The present talk will discuss the emergence of electrophysiological signatures of autism spectrum disorders (recorded using magnetoencephalography, MEG) along with their clinical significance (in terms of correlating with behavioral and neuropsychological assessments). In several hundred children on the autism spectrum, results indicate key neural timing delays of the order of 10ms, that might mediate atypical neural connectivity and consequent function (Roberts et al., Aut. Res 2010). Later responses (e.g. the magnetic mismatch field, MMF) manifest with greater delays, proportional to the degree of clinical language impairment, for example (Roberts et al., Biol. Psych 2011). The biological underpinning of these markers is investigated using powerful multimodal MR approaches, incorporating diffusion tensor imaging (DTI) and HARDI (e.g. Berman et al., AJNR 2013), primarily of the thalamocortical projections of the auditory pathway – associations between white matter microstructure and cortical electrophysiology will be reported (see Roberts et al., Neuroreport 2009; Roberts et al., Brain Res. 2013). Similarly the clinical correlate of language impairment in ASD is explored in diffusion imaging studies of the arcuate fasciculus (e.g. Nagae et al., AJNR 2012; Roberts et al., AJNR

2014) in which axial diffusivity appears associated with “ASD” and radial diffusivity with “language impairment”, effectively deconstructing the biological and clinical confounds observed in “mean diffusivity” elevation. However, impaired conduction velocity may only represent part of the explanation for atypical electrophysiology. Not only is cortical timing affected in ASD, but also the integrity of cortical local circuitry, revealed in the phase synchrony of gamma band oscillations (see Gandal et al., Biol. Psych 2010; Edgar et al., J. Aut. Dev. Disorder 2013). The putative basis for these “oscillopathies” may lie in an imbalance of excitation and inhibition (E/I) at the synaptic neurotransmitter level (Rubenstein and Merzenich, 2003). Evidence supporting this is reported in a cohort of children with ASD in whom levels of the inhibitory neurotransmitter gamma-amino-butyric acid, GABA, are shown to be depleted in auditory cortex compared to age-matched controls (see Gaetz et al., Neuroimage 2013), while GABA levels have previously been associated with MEG-determined oscillatory activity (e.g. Muthukumuruswarmy et al., PNAS 2009; Gaetz et al., Neuroimage 2011). Thus both white matter maturational and synaptic transmission anomalies are investigated as contributing to the observed neural timing delays. Further support for these underlying mechanisms can be gleaned from preclinical translational work using similar electrophysiological signatures to validate and then probe mouse models of aspects of autism (e.g. Gandal et al., Biol. Psych 2010; Saunders et al., Aut. Res. 2013; Gandal et al., Genes Brain Nehav. 2012; Saunders et al., Behav. Brain Res 2012). Finally, the responsiveness of these electrophysiologic phenotypes to pharmaceutical manipulation motivates a new

wave of candidate treatments for human ASD, which can be stratified and evaluated using the above described multi-modal biomarker approach.