L1s. Reducing the risk for developmental factors that influence epigenetics (eg stress and nutrition) may limit L1 somatic mutation during CNS development.

Somatic mutation studies of neurodevelopmental disorders (autism, idiopathic epilepsy) may reveal brain-specific alleles that convey risk. Germlines may harbor only a fraction of the alleles of interest for CNS diseases.

FUNDING AND DISCLOSURE

Preparation of this paper was supported by R21 NS095756-01, 1R21MH101065, R21DA035607 to WHB. Mental Illness Research, Education and Clinical Center, VISN-4, David Oslin, MD, is PI. The authors declare no conflict of interest.

Glenn A Doyle[1] and Wade H Berrettini[1]

[1]Department of Psychiatry, Center for Neurobiology and Behavior, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
E-mail: wadeb@mail.med.upenn.edu

Bundo M, Toyoshima M, Okada Y, Akamatsu W, Ueda J, Nemoto-Miyauchi T *et al* (2014). Increased l1 retrotransposition in the neuronal genome in schizophrenia. *Neuron* **81**: 306–313.

Freed D, Stevens EL, Pevsner J (2014). Somatic mosaicism in the human genome. *Genes* **5**: 1064–1094.

Goodier JL, Cheung LE, Kazazian HH Jr. (2013). Mapping the LINE1 ORF1 protein interactome reveals associated inhibitors of human retrotransposition. *Nucleic Acids Res* **41**: 7401–7419.

Kaer K, Speek M (2013). Retroelements in human disease. *Gene* **518**: 231–241.

Okudaira N, Ishizaka Y, Nishio H (2014). Retrotransposition of long interspersed element 1 induced by methamphetamine or cocaine. *J Biol Chem* **289**: 25476–25485.

Upton KR, Gerhardt DJ, Jesuadian JS, Richardson SR, Sánchez-Luque FJ, Bodea GO *et al* (2015). Ubiquitous L1 mosaicism in hippocampal neurons. *Cell* **161**: 228–239.

Neuropsychopharmacology Reviews (2016) **41,** 386–387; doi:10.1038/npp.2015.302

Psychiatric Illnesses as Oscillatory Connectomopathies

Neural oscillations underlie critical computational and representational functions of the brain. Oscillatory activity extends from the millisecond cycles of an interneuron-pyramidal neuron microcircuit, to flows of information over hundreds of milliseconds in columnar mesocircuits, to the coordination of long-range brain macrocircuit interactions over seconds that support higher order cognitions (Mathalon and Sohal, 2015). These three regimes correspond roughly with three orders of magnitude of frequency ranges: 100 Hz (high gamma), 10 Hz (delta to low gamma), and <1 Hz (infraslow). Oscillations arise from and interact on a neuronal scaffold, whose intrinsic property is plasticity—both developmental and experience dependent. We propose that psychiatric illnesses are pathologies of the oscillatory connectome, in which critical representational processes generated within neuronal architecture and supported by oscillatory coupling are distorted.

We define the oscillatory connectome (OC) as the patterns of oscillatory coupling of neuronal populations under given conditions, physically conjoined with a specific axodendritic and glial architecture. The OC stores information and executes computations through plasticity in topology, synaptic strength, and membrane conductance (Sejnowski and Paulsen, 2006). It reflects the interplay between an individual's genome, exposome, developmental stage, and cognitive/behavioral repertoire.

OC pathologies frequently manifest at longer time scales across large cortical and subcortical neural populations (eg, abnormal prefrontal-subgenual network dynamics seen in depression during processing of emotionally evocative stimuli (Smart *et al*, 2015)). Pathology may also be observed at shorter time scales and within localized neuronal assemblies, such as impaired auditory representations in early psychosis that progress concomitant with volume reductions in Heschl's gyrus (Salisbury *et al*, 2007). OC pathologies appear to be probabilistically related to clinical psychiatric features.

Defining psychiatric illnesses as oscillatory connectomopathies has three immediate research implications:

(1) Structural and physiological assessments of the brain must be integrated, ideally combining detailed information on neural architecture with measures of oscillation patterns and their coupling across different frequency bands and brain regions.
(2) As genomics begins to elucidate molecular components of abnormal synaptic and microcircuit function, we must discover how such abnormalities contribute to meaningful variations in oscillatory meso- and macrocircuits. We predict that dysplasticity mechanisms will represent key common pathways—processes that affect neural architecture or communication over time in a manner that:
    (a) Impedes normal developmental and experience-dependent plasticity in both micro and mesoscale oscillatory dynamics (as is likely in schizophrenia and autism), or
    (b) Biases macroscale plasticity toward selective enhancement of maladaptive but highly salient representations (as happens in addictions, depression, PTSD).
(3) Significant innovations in psychiatric nosology and treatment development will require an understanding of neural oscillatory connectomics in health and disease. In social anxiety, resting state connectivity metrics (indirectly measuring the infraslow OC) and tractography of right inferior longitudinal fasciculus is five times better than symptom severity at predicting improvement after CBT (Whitfield-Gabrieli *et al*, 2015). In schizophrenia, intensive auditory training drives changes in oscillatory dynamics across auditory and prefrontal cortices that correlate with cognitive gains (Dale *et al*, 2015). 'RDoC' and 'successful target engagement'—the new buzzwords in psychiatric research—ultimately mean understanding and harnessing adaptive changes in the neural network oscillation patterns that give rise to human behavior.

FUNDING AND DISCLOSURE

Sophia Vinogradov is a site investigator on an SBIR grant to PositScience, Inc., a company with a financial interest in cognitive training software; she is also a consultant to Forum Pharmaceuticals. There are no competing financial interests in relation to the work described in this article. Dr Herman has no disclosures to report.

ACKNOWLEDGMENTS

Some of the work described in this report was supported by NIH grant MH68725 and by the San Francisco VA Medical Center, San Francisco, CA, USA.

Sophia Vinogradov[1,2] and Alexander Herman[1]

[1]Department of Psychiatry, University of California, San Francisco, CA, USA; [2]Mental Health Service, San Francisco VA Medical Center, San Francisco, CA, USA

E-mail: sophia.vinogradov@ucsf.edu

Dale CL, Brown EG, Fisher M, Herman AB, Dowling AF, Hinkley LB *et al* (2015). Auditory cortical plasticity drives training-induced cognitive changes in schizophrenia. *Schizophr Bull* (e-pub ahead of print; doi:10.1093/schbul/sbv087).

Mathalon DH, Sohal VS (2015). Neural oscillations and synchrony in brain dysfunction and neuropsychiatric disorders: it's about time. *JAMA Psychiatry* **72**: 840–844.

Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch Gen Psychiatry* **64**: 521–529.

Sejnowski T, Paulsen O (2006). Network oscilations: emerging computational principles. *J Neurosci* **26**: 1673–1676.

Smart OL, Tiruvadi VR, Mayberg HS (2015). Multimodal approaches to define network oscillations in depression. *Biol Psychiatry* **77**: 1061–1070.

Whitfield-Gabrieli S, Ghosh SS, Nieto-Castanon A, Saygin Z, Doehrmann O, Chai XJ *et al* (2015). Brain connectomics predict response to treatment in social anxiety disorder. *Mol Psychiatry* (e-pub ahead of print 11 August 2015; doi:10.1038/mp.2015.109).

Neuropsychopharmacology Reviews (2016) **41**, 387–388; doi:10.1038/npp.2015.308

The Cellular Sequelae of Early Stress: Focus on Aging and Mitochondria

That stress and trauma impact physiologic systems and promote psychiatric and other medical illness is now well accepted. Biologic aging is driven by molecular alterations at the cellular level, including telomere decline and mitochondrial DNA (mtDNA) mutations, promoting DNA damage, and mitochondrial dysfunction. These changes contribute to cellular senescence, apoptosis and cancer risk, signal increased inflammation, and ultimately contribute to organ dysfunction and risk for age-related conditions including diabetes and cardiovascular disease. Early or severe stress is associated with reductions in telomere length and maintenance, suggesting these exposures might accelerate the aging process (Ridout *et al*, 2015). New research supports the intriguing hypothesis that early stress may also affect mitochondrial function, further linking early stress and accelerated aging.

Mitochondria provide the main source of cellular energy through aerobic respiration and are integral to cellular signaling. Reactive oxygen species are a by-product of mitochondrial respiration that are not simply mediators of cellular damage but have vital roles in cellular signaling pathways (Picard *et al*, 2014). Aging is characterized by increased mitochondrial ROS production, declines in mitochondrial function, mtDNA mutation accumulation, and mitochondrial replication alterations. These changes contribute to metabolic and inflammatory system dysregulation and the development of age-related disorders, including diabetes, Alzheimer's disease, and cardiovascular disease (Picard *et al*, 2014).

New data suggests that stress and psychopathology are associated with mitochondrial changes similar to those seen with aging. Our group recently reported increased leukocyte mtDNA copy number in adults with a history of early life stress and with depressive, anxiety, and substance use disorders (Tyrka *et al*, 2015b). In the same subjects, telomere length was reduced and mtDNA and telomere length were correlated (Tyrka *et al*, 2015a). Similar findings were reported in saliva of subjects with early stress and depression (Cai *et al*, 2015) and, in animals exposed to chronic stress or depression models, mitochondrial activity is impaired in the hippocampus, thalamus, and cortex (Picard *et al*, 2014). mtDNA copy number is a gross measure of mitochondrial activity; increases may occur as a compensatory response to impaired mitochondrial function (Picard *et al*, 2014). These results suggest that early stress may contribute to mechanisms triggering such compensatory responses and that psychiatric disorders may represent a form of chronic stress.

New findings identify mechanistic pathways linking stress, glucocorticoid signaling, telomere dynamics, and mitochondrial proliferation and function. Telomerase, an enzyme that maintains telomere length and modulates cell signaling, gene expression, and DNA damage responses, also influences mitochondrial proliferation and function (Sahin and DePinho, 2012). Telomerase activity changes with stress and other conditions altering neuroendocrine function (Ridout *et al*, 2015). Glucocorticoid exposure, and associated inflammatory and oxidative stress pathway activation, is linked with telomere shortening and may be a mechanism through which early stress contributes to telomere decline (Ridout *et al*, 2015). Glucocorticoid signaling is also involved in mitochondrial replication (Cai *et al*, 2015) and can damage mitochondria via elevating glucose levels, promoting systemic inflammation, altering gene expression in proapoptotic pathways, and hastening cellular aging (Picard *et al*, 2014). Increased demands on mitochondria in brain regions impacted by early stress such as the hippocampus may increase ROS production and mtDNA damage, contributing to reduced energy production and proapoptotic signaling in these brain regions, which may result in changes in neurotransmitter signaling, neuronal cell function, and viability (Picard *et al*, 2014). Such potential mechanisms warrant further exploration and may constitute intervention targets to prevent stress-related aging and disease.