the National Center for Responsible Gaming, Forest Laboratories, Ortho-McNeil, Oy-Contral Pharma/Biotie Therapies, GlaxoSmithKline, and Psyadon Pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders, and other health topics; has consulted for gambling and legal entities on issues related to impulse-control disorders; provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has been an editor for journal sections and journals; has given academic lectures in grand rounds, CME events, and other clinical and scientific venues; and has generated books or book chapters for publishers of mental health texts. The remaining authors declare no conflict of interest.

DISCLAIMER

The content of this manuscript does not necessarily reflect the views of the funding agencies and reflect the views of the authors.

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Somatic DNA Variation in Brain as a Source of Risk for CNS Diseases

Somatic mutation during brain development leads to CNS disorders. A missense mutation in *GNAQ* (R183Q) occurs in affected tissues of persons with Sturge–Weber disease, with a frequency in diseased brain and skin ranging from 3 to 36% (Freed *et al*, 2014). In hemimegalencephaly, somatic mutations in *AKT3* were found in 8–35% of cells in the affected tissues (Freed *et al*, 2014). Somatic mutation in *PSEN1* (P436Q) at a frequency of 18% in frontal cortex caused early-onset Alzheimer's disease (Freed *et al*, 2014). One form of somatic mutation that can contribute to CNS disease risk is mediated by long interspersed nuclear element 1 (L1) retrotransposons (Kaer and Speek, 2013). L1s are 6 kb sequences that spread in the human genome by a copy and paste mechanism, and constitute 17% of the human genome (Upton *et al*, 2015). The frequency of *de novo* L1 retrotranspositions in normal brain is controversial (Upton *et al*, 2015). Most retrotransposition-competent L1s are prevented from retrotransposition by epigenetic mechanisms or interactions with inhibitory proteins (Goodier *et al*, 2013).

Whole genome sequencing of genomic DNA from dorsolateral prefrontal cortex (dlPFC) and liver of three persons with schizophrenia revealed increased *de novo* L1s in specific gene ontologies (GOs; see Table 1; Bundo *et al*, 2014). Using L1-based amplification of dlPFC neuronal DNA from 26 schizophrenia samples and 26 control samples, we confirmed an excess of L1 retrotransposons in genes within these GOs in schizophrenic, but not in control tissues. There was a fourfold increase of *de novo* L1s in 'synapse part' genes (over the random expectation) in our data. Of the 18 genes with putative *de novo* L1s in our 'synapse part' GO list, 9 were also detected by Bundo *et al*, 2014: *DNM2*, *DNM3*, *DLGAP1*, *GRID2*, *GRIN2A*, *HOMER1*, *GPHN*, *SYNE1*, and *SYN3*. These genes are 'of interest' in schizophrenia research because they support data showing associations with GWAS or animal models of schizophrenia.

TABLE 1 Gene Ontology Terms with Significant Gene Disruption by *de novo* LINE1 Elements

GO term	*p*-value (Bundo *et al*, 2014)	*p*-value (Doyle *et al*,[a])
Plasma membrane part	1.5×10^{-5}	7×10^{-4} [b]
Synapse part	4.4×10^{-5}	8×10^{-4}

[a]Unpublished observation. [b]All *p*-values Bonferroni corrected.

Methamphetamine and cocaine increased *de novo* L1s in neuronal cells *in vitro* (Okudaira *et al*, 2014). Thus, we conducted an L1 study of medial PFC neuronal DNA from 30 persons with cocaine addiction and controls. Strong evidence ($p \approx 10^{-6\wedge}$) for L1-mediated gene disruption was found in phosphate metabolism and kinase pathways, which were not significant among controls (Doyle *et al*, unpublished observation).

The evidence that somatic brain mutation causes brain disease warrants studies of a range of neuropsychiatric disorders (including rodent models) for similar risk-increasing somatic alleles. As somatic mutation does not convey heritable risk, it may be a mechanism to explain some of the environmental risk for neuropsychiatric diseases. There may be disease-specific L1-mediated gene disruption in certain GOs, such as has been found in schizophrenia and cocaine addiction. New drug development might be directed toward gene pathways disrupted by

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.

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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.