diagnoses, including autism, Addison's disease, moniliasis, and diabetes mellitus. The next older brother had hypoparathyroidism, Addison's disease, moniliasis, and alopecia totalis. The oldest son was symptom-free. The mother had ulcerative colitis, the father had 'chronic athlete's foot', and a paternal uncle had diabetes mellitus. Consistent with these observations, we showed that first- and second-degree relatives of children with an ASD have a higher number of autoimmune disorders than family members of healthy children (Sweeten *et al*, 2003). In a recent post-mortem study of 13 males with autism and 9 control cases, microglia appeared markedly activated in 5 of 13 cases with autism, including 2 of 3 under the age of 6 years, and marginally activated in an additional 4 of 13 cases (Morgan *et al*, 2010), suggesting ongoing inflammatory processes in brain.

Observations in humans are supported by experiments in laboratory animals. As one example, Martin *et al* (2008) exposed pregnant rhesus monkeys to human IgG collected from mothers of children diagnosed with ASDs, while controls received IgG collected from mothers of normally developing children. Those offspring that were gestationally exposed to IgG class antibodies from mothers of children with ASDs consistently demonstrated increases in stereotypies and hyperactivity. These findings suggest that some ASD-like behaviors can be triggered by environmental (non-genetic) manipulations.

The notion that environmental factors contribute to ASD prevalence continues to evolve. Once-influential theories suggesting links among exposure to vaccines containing attenuated virus or toxins, conditions such as inflammatory bowel disease, and ASDs have fallen from favor since the retraction of a key study (Wakefield *et al*, 1998). It is important to emphasize, however, that the major reason for retraction was poor scientific method rather than theoretical flaws. Although ASDs are currently within the realm of psychiatrists and neurologists, it is becoming clear that at least some subtypes represent whole-body

disorders, offering exciting new possibilities for therapy.

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DISCLOSURE

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Cognitive Training for Psychiatric Disorders

Psychiatric disorders are associated with impairments in neural system activity and connectivity across distributed networks that underlie cognition and social-emotional processes. Increasing evidence indicates that these neural system dysfunctions are

not immutably fixed, but instead may be amenable to well-designed cognitive training interventions that target restoration of neural system operations (Browning *et al*, 2012; Klingberg *et al*, 2005; Subramaniam *et al*, 2012). An explicitly 'systems neuroplasticity'-based approach to cognitive training is founded on the premise that during successful skill learning, disproportionately larger and better-coordinated neuronal populations represent the salient inputs and action outputs of the trained skill, resulting in an increased feed-forward signal strength from sensory regions as well as greater task-relevant feedback-inhibitory control from the prefrontal cortex to enhance representations of relevant stimuli, and to enable more efficient and accurate associative memory processes (Vinogradov *et al*, 2012).

Effective cognitive training must target the underlying neural impairments associated with a specific pathophysiology. For children with ADD, for example, Klingberg *et al* 2005 found that computerized visual working memory (WM) exercises drove improvements in non-trained visuospatial and executive tasks, indicating generalization of training. This group also found that WM training improved WM capacity, which was correlated with neural changes in D1 receptor density, indicating increased dopaminergic release during training (Klingberg, 2010; McNab *et al*, 2009). Browning *et al* (2012) investigated attentional bias modification (ABM) training in remitted patients with depression, and found that ABM reduced residual depressive symptoms and normalized the cortisol awakening response, suggesting that it may be a 'cognitive vaccine' that reduces the neurobehavioral risk for future depression episodes.

Our group recently performed a double-blind randomized controlled trial of a set of computerized exercises that focused on early auditory and visual processing, WM and basic social cognition (*vs* computer games control condition) in individuals with schizophrenia. Our rationale was that schizophrenia is characterized by deficits in both early pre-attentive perceptual

Figure 1. Whole-brain fMRI analysis of reality-monitoring activity reveals signal increase within: (a) the medial prefrontal cortex (mPFC) in 15 healthy comparison (HC) subjects, (b) the posterior cingulate cortex, rather than the mPFC, in patients with schizophrenia (SZ) prior to computerized cognitive training, and (c) the mPFC in only the group of SZ patients who completed 80 h of active computerized cognitive training (SZ-AT), which is similar to the neural activation patterns observed in the HC sample (see Subramaniam *et al*, 2012).

processes as well as higher-order attention and WM operations (Vinogradov *et al*, 2012). We found that the schizophrenia participants who received the targeted training showed behavioral improvements on (untrained) neuropsychological measures of verbal memory and on reality-monitoring tasks, thus indicating generalization of training effects. Further, after the intervention, neural activation patterns during reality monitoring, which were abnormal in these patients at baseline, began to resemble the patterns observed in healthy participants (Figures 1a and c), and predicted better social functioning 6 months later (Subramaniam *et al*, 2012).

Together, these emerging data suggest that people with a range of neuropsychiatric illnesses can benefit from targeted cognitive training; that this type of training can ‘restore’ aspects of behavior and neural system functioning; and that this training can be generalized to enduring improvements in real-world functioning (Browning *et al*, 2012; Klingberg *et al*, 2005; Subramaniam *et al*, 2012). Future studies must examine the specific intervention methods that promote maximal cognitive and neural system

‘restoration’ in the neuropsychiatrically impaired brain—likely by combining targeted cognitive training approaches with cognitive enhancing medications and neuromodulation techniques such as transcranial direct current stimulation.

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Psychoactive ‘Bath Salts’: Compounds, Mechanisms, and Toxicities

Recently, there has been an alarming increase in the abuse of so-called ‘bath