well as at a distal promoter of *SYN3* (613 bp) (Miklem and Hillier, 2012, see Figure 1). To date there is no evidence in the literature of altered DNA methylation at synapsins in mood disorders, although one study of a single schizophrenia patient suggests potentially variably methylated sites in the distal CpG island of *SYN3* (Murphy *et al*, 2008). Interestingly, the CpG islands at *SYN1* and *SYN2* are immediately preceded by regions of enriched H3K4me3 in mood disorders (Cruceanu *et al*, 2012, see Figure 1). The same is not true for *SYN3*, and considering this gene's distinct expression profile and potential implication throughout neurogenesis (Pieribone *et al*, 2002), perhaps different mechanisms regulate *SYN3*. The figure illustrates our current knowledge of the synapsin genes' structure, as well as the epigenetic mechanisms that have been identified in psychiatric disorders to date.

In conclusion, brain expression differences seen in synapsin genes in mood disorders may be explained in part by differences in H3K4me3. These results need additional and independent confirmation. Moreover, considering that promoter DNA methylation can modulate gene expression and lead to neuropsychiatric phenotypes, a study of DNA methylation patterns at the synapsin promoters is warranted. On the basis of growing evidence suggesting that epigenetic mechanisms may be involved in altered regulation of synapsins in mood disorders, it would be of interest to study these genes as potential therapeutic targets or biomarkers of treatment response. Evidence is starting to emerge pointing to epigenetic marks as potential biomarkers of treatment response. For instance, for brain-derived neurotrophic factor (*BDNF*), (Lopez *et al*, 2010) showed that promoter H3K27me3 levels could serve as a biomarker of response to citalopram in MDD, and (D'Addario *et al*, 2012) found distinct DNA methylation patterns at the *BDNF* promoter in BD patients depending on mood-stabilizer and antidepressant therapy. Although no such evidence has yet emerged for synapsins, a recent study showed that lithium, one of the most commonly prescribed drugs for BD, can modulate *SYN2* expression in neuronal cell types (Cruceanu *et al*, 2012). Thus, an investigation of synapsin epigenetics in the brain compared with the periphery would be an interesting next step in elucidating their potential to serve as biomarkers for mood disorders or their treatment.

ACKNOWLEDGEMENTS

This work was supported by the Canadian Institute of Health Research (CIHR) grant MOP64410 to GT, MA, and GAR, and CIHR grant MOP119430 to GT.

Cristiana Cruceanu[1], Erika Freemantle[1], Martin Alda[2], Guy A Rouleau[3] and Gustavo Turecki[1]

[1]McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada; [2]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; [3]Centre of Excellence in Neuromics, CHUM Research Center and the Department of Medicine, University of Montreal, Montreal, QC, Canada
E-mail: gustavo.turecki@mcgill.ca

DISCLOSURE
The authors declare no conflict of interest.

DISCLAIMER
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Cesca F, Baldelli P, Valtorta F, Benfenati F (2010). The synapsins: key actors of synapse function and plasticity. *Prog Neurobiol* **91**: 313–348.

Cruceanu C, Alda M, Grof P, Rouleau GA, Turecki G (2012). Synapsin II is involved in the molecular pathway of lithium treatment in bipolar disorder. *PloS one* **7**: e32680.

Cruceanu C, Alda M, Nagy C, Freemantle E, Rouleau GA, Turecki G (2012). H3K4 tri-methylation in synapsin genes leads to different expression patterns in bipolar disorder and major depression. *Int J Neuropsychopharmacol* **9**: 1–11.

D'Addario C, Dell'Osso B, Palazzo MC, Benatti B, Lietti L, Cattaneo E *et al* (2012). Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. *Neuropsychopharmacology* **37**: 1647–1655.

Jiang Y, Langley B, Lubin FD, Renthal W, Wood MA, Yasui DH *et al* (2008). Epigenetics in the nervous system. *J Neurosci* **28**: 11753–11759.

Lopez JP, Mamdani F, Labonte B, Beaulieu MM, Yang JP, Berlim MT *et al* (2012). Epigenetic regulation of BDNF expression according to antidepressant response. *Mol psychiatry;* doi:10.1038/mp.2012.38.

Miklem G, Hillier L (2012). UCSC CpG islands track (unpublished) based on Gardiner-Garden M. and Frommer M. CpG islands in vertebrate genomes. *J Mol Biol* **196**: 261–282.

Murphy BC, O'Reilly RL, Singh SM (2008). DNA methylation and mRNA expression of SYN III, a candidate gene for schizophrenia. *BMC Med Genet* **9**: 115.

Pieribone VA, Porton B, Rendon B, Feng J, Greengard P, Kao HT (2002). Expression of synapsin III in nerve terminals and neurogenic regions of the adult brain. *J Comp Neurol* **454**: 105–114.

Neuropsychopharmacology Reviews (2013) **38,** 239–241; doi:10.1038/npp.2012.186

Neuroinflammation and Autism: Toward Mechanisms and Treatments

Autism spectrum disorders (ASDs) were originally described by Kanner (1943). The relatively consistent clinical phenotype will likely be shown to comprise numerous etiologic subtypes. Approximately 10% of ASD cases are linked to disorders of genetic etiology, such as Fragile X syndrome, tuberous sclerosis, and Rett disorder. The majority of cases, however, remain idiopathic.

A role for immunological involvement in ASDs has long been hypothesized. Kanner did not comment on this in his initial descriptions, but a detailed review of the original 11 cases reveals important observations. One patient was 'kept in bed often because of colds, bronchitis, chickenpox, streptococcus infection, impetigo and rheumatic fever'. Another was 'given anterior pituitary and thyroid preparations and her father, aged 36 years, was one of those chronically thin persons, nervous energy readily expended', suggesting hyperthyroidism.

In our clinical work and review of the literature, we have been impressed by the possible role of autoimmune disorders as influencing the pathophysiology of a distinct, objectively defined etiologic subtype of ASDs. Money *et al* (1971) published what is widely accepted as the first connection between autism and autoimmune disorders. They described a family in which the youngest child had multiple

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.

ACKNOWLEDGEMENTS

The authors acknowledge support from NIH grants MH077600 and MH083739 (CJM) and MH063266 (to WAC), as well as the Nancy Lurie Marks Family Foundation.

Christopher J McDougle[1,2] and William A Carlezon Jr[2,3]

[1]Departments of Psychiatry and Pediatrics, Massachusetts General Hospital and MassGeneral Hospital for Children, Boston, MA, USA; [2]Harvard Medical School, Boston, MA, USA; [3]Department of Psychiatry, McLean Hospital, Belmont, MA, USA
E-mail: cmcdougle@partners.org or bcarlezon@mclean.harvard.edu

DISCLOSURE

Dr McDougle declares no conflict of interest. Dr Carlezon is an editor of *Neuropsychopharmacology* and receives compensation for this role from the American College of Neuropsychopharmacology.

Kanner L (1943). Autistic disturbances of affective contact. *Nervous Child* **2**: 217–250.

Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, Amaral DG (2008). Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. *Brain Behav Immun* **22**: 806–816.

Money J, Bobrow NA, Clarke FC (1971). Autism and autoimmune disease: a family study. *J Autism Dev Disord* **16**: 146–160.

Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J *et al* (2010). Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol Psychiatry* **68**: 368–376.

Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ (2003). Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics* **112**: e420–e424.

Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M *et al* (1998). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* **351**: 637–641.

Neuropsychopharmacology Reviews (2013) **38,** 241–242; doi:10.1038/npp.2012.174

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