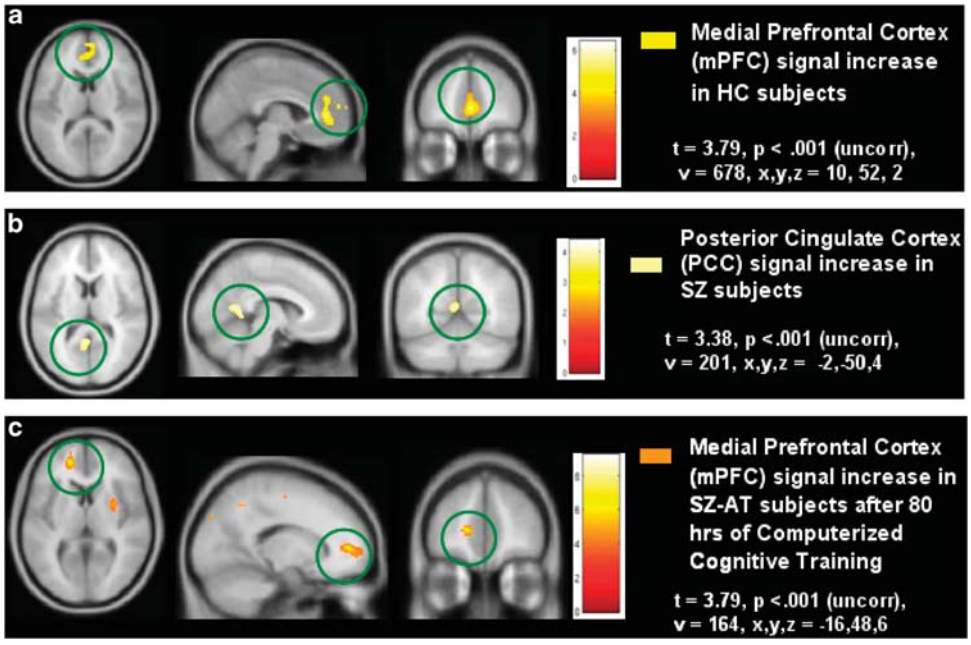

Figure 1. Whole-brain fMRI analysis of reality-monitoring activity reveals signal increase within: (a) the medial prefrontal cortex (mPFC) in 15 healthy comparison (HC) subjects, (b) the posterior cingulate cortex, rather than the mPFC, in patients with schizophrenia (SZ) prior to computerized cognitive 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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DISCLOSURE

One of the authors, Dr Sophia Vinogradov, has financial disclosures to declare, as Dr Vinogradov is a paid consultant in Brain Plasticity, a company with a commercial interest in cognitive training software. Dr Vinogradov is also a consultant to Genentech, Amgen, and Hoffman-LaRoche. Dr Subramaniam declares no conflict of interest.

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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

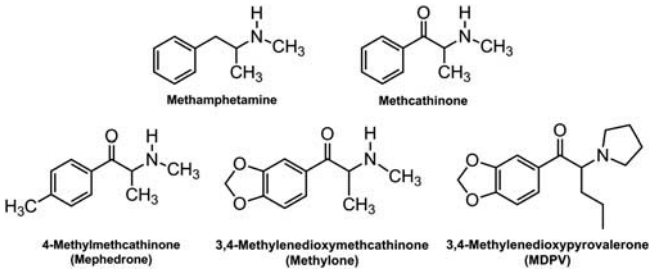

Figure 1. Chemical structures of bath salts cathinones and related compounds.

salts' products sold on the internet and in retail shops. These products have no legitimate use as bath additives, rather they are purchased as legal alternatives to illicit drugs like cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) (Prosser and Nelson, 2012; Spiller *et al*, 2011). Bath salts powders are self-administered by insufflation (ie, snorted), taken orally or injected intravenously (i.v.). Recreational doses of bath salts enhance mood and increase alertness, whereas higher doses can lead to dangerous neurological and cardiovascular complications. The psychoactive constituents in bath salts have been identified as synthetic derivatives of cathinone, an amphetamine-type stimulant (Shanks *et al*, 2012; Spiller *et al*, 2011). Figure 1 illustrates the chemical structures of three popular bath salts compounds: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV). Owing to the public health risks posed by bath salts, the US government placed mephedrone, methylone and MDPV into Schedule I control in November 2011 (DEA, 2011). Unfortunately, a new wave of cathinone derivatives has appeared in the marketplace to replace those drugs now subject to regulatory control (Shanks *et al*, 2012).

Despite the widespread use of bath salts, there is a paucity of information about their pharmacology. Using assay methods in rat brain synaptosomes, it has been shown that mephedrone and methylone act as substrates at plasma membrane transporters for norepinephrine, dopamine, and serotonin, thereby stimulating non-exocytotic release of these neurotransmitters (Baumann *et al*, 2012). Mephedrone is about two-times more potent than methylone as a transporter substrate. *In vivo* microdialysis studies in rats confirm that mephedrone and methylone (0.3 or 1.0 mg/kg, i.v.) increase extracellular levels of dopamine and serotonin in the brain, similar to the effects of MDMA. Little is known about the pharmacology of MDPV, but our unpublished findings show the drug is a potent blocker of dopamine and norepinephrine uptake. The fact that synthetic cathinones enhance dopamine transmission predicts high abuse liability. Hadlock *et al* (2011) reported that i.v. mephedrone (0.24 mg/infusion) is readily self-administered by rats, but reinforcing effects of other synthetic cathinones are largely unexplored. Few preclinical studies have examined the pharmacokinetics and metabolism of synthetic cathinones or the consequences of chronic drug dosing, and these types of investigations are needed.

Serotonin transporter substrates like MDMA are known to produce sustained deficits in brain serotonin neurons of laboratory animals, so mephedrone and methylone could have similar actions. Repeated subcutaneous (s.c.) administration of either drug to single-housed rats (3 or 10 mg/kg, three doses) has no long-lasting effects on brain tissue monoamines (Baumann *et al*, 2012), but administration of higher doses of mephedrone to group-housed rats (10 or 25 mg/kg, s.c., four doses) causes selective depletion of brain serotonin (Hadlock *et al*, 2011). It is noteworthy that MDPV is the chief substance detected in blood and urine from patients hospitalized for bath salts overdose in the US (Spiller *et al*, 2011). Such patients display agitation, combative behavior, hallucinations, delusions, hyperthermia, tachycardia and hypertension (Prosser and Nelson, 2012; Spiller *et al*, 2011). Health care workers should be aware that patients presenting with this constellation of symptoms may have taken bath salts, and appropriate supportive care should be provided. Owing to the increasing availability of 'replacement' cathinones with unknown pharmacology (Shanks *et al*, 2012), it seems likely that emergency departments will continue to encounter patients suffering from adverse effects of synthetic cathinone abuse.

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