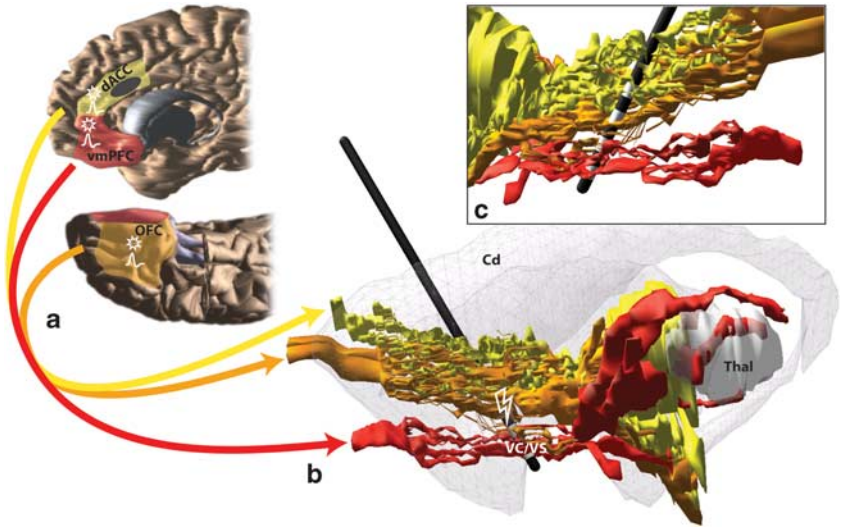

Figure 1. Schematic illustrating key cortical areas involved in obsessive-compulsive disorder (OCD) and their pathways through the internal capsule. (a) Red, orange, and yellow fibers originate in ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and dorsal anterior cingulate (dACC), respectively. The approximate cingulotomy site is depicted as a dark gray oval. (b) Medial view of a sagittal section with vmPFC, OFC, and dACC fibers passing through the internal capsule. The striatum is indicated in gray. A model of the electrode with its four contacts is placed at ventral internal capsule (VC)/ventral striatum (VS) deep brain stimulation (DBS) site. (c) Lateral view of a sagittal section shows the four electrode contact points in the VC/VS. VmPFC and OFC fibers pass through the ventral contacts, and OFC and dACC fibers pass through the dorsal contact points (Lehman *et al*, 2011). Action potential symbols indicate possible regions with changes in firing rates and/or local field potentials following HFS in the VS (McCracken and Grace, 2009); stars indicate regions with possible changes in plasticity following HFS to VS (Rodriguez-Romaguera *et al*, 2012).

in the circuits associated with fear conditioning and OCD dysfunction suggests that these patients may be less flexible in adjusting adverse responses based on new information. Indeed, using a rat model of DBS, with the HFS targeting the VS, a recent study showed that stimulation strengthened fear extinction and retention (Rodriguez-Romaguera *et al*, 2012), while enhancing plasticity in the infralimbic, orbitofrontal, and prelimbic cortices (probable homologs of the vmPFC, OFC, and, perhaps, dACC). Taken together, dysfunction of the vmPFC/OFC/dACC network may lead to an increase in incentive-based fear learning and habit formation.

However, PFC regions associated with OCD pathology are not only involved in aversive behaviors and avoidance; they also mediate reward processing. Indeed, OCD patients are also impaired on tasks using rewarding outcomes (Gillan *et al*, 2011). They underperform when required to flexibly adjust responses based on new or changing reward feedback. These tendencies suggest impairment in goal-directed behaviors and may lead patients to rely too heavily on habit-based responding, even in the positive-incentive domain (Gillan *et al*, 2011). Therefore, rather than being specific to aversive *vs* reward processing, the vmPFC, OFC, and dACC cortices are involved in value representation, stimulus-outcome associations, and action-outcome associations, regardless of valence. Thus, a heuristic approach could posit that OCD symptoms may not be specific to fear learning and habits, but are related to interference in the normal balance between negative and positive-incentive learning based on values attributed to particular stimuli or actions. Probing potential abnormalities in incentive learning strategies and linking them with functional neurocircuitry can be used both as a research tool and to help design innovative therapeutic approaches.

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Brain Serotonin Function in MDMA (Ecstasy) Users: Evidence for Persisting Neurotoxicity

3,4-methylenedioxymethamphetamine (MDMA; ecstasy) is a popular recreational drug, and clinical trials are investigating MDMA as a treatment for anxiety. Animal models suggest that MDMA causes chronic serotonin neurotoxicity, especially in neocortex. Given the role of serotonin in a broad range of brain functions, it is critical to determine whether MDMA is associated with serotonin neurotoxicity in humans. Studies examining the

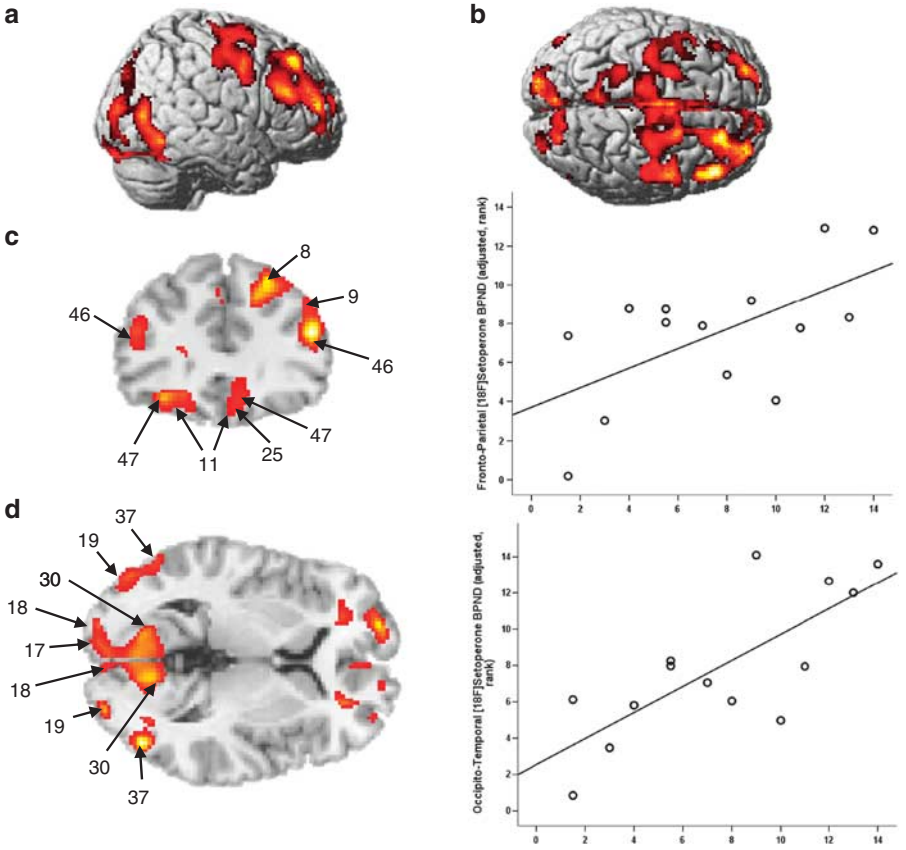

Figure 1. (a and b) Right-hemisphere and bilateral superior regions are depicted, respectively, in which lifetime ecstasy use correlates positively with serotonin-2A-binding potential in the ecstasy (MDMA) user group after adjusting for birth control, estrogen, and age. (c–f) Representative clusters from a and b with Brodmann area labels on brain sections (left) and scatterplots (right) showing correlation of lifetime MDMA use (as mg ecstasy) with serotonin-2A-binding potential. Color scale indicates *t*-score for significant voxels in the regression analysis (voxel level $p = 0.05$, cluster volume 910 voxels, and family wise error corrected $p = 0.05$). Scatterplots are rank data to account for nonparametric distribution of lifetime ecstasy use (maximum/minimum use in mg: 250–112 500) and adjusted predicted rank data for with serotonin-2A-binding potential (adjusted for age, birth control, and estrogen). Rank of lifetime use was calculated as the product of the average use per episode and the number of use episodes. Ranks were determined within SPSS using the 'rank' function. Reproduced and modified from Di Iorio *et al*, 2012. Permission obtained.

presynaptic serotonin reuptake transporter (SERT) as a marker of serotonin axon integrity in MDMA users have generally found reductions in SERT binding (McCann *et al*, 2008; Urban *et al*, 2012; Kish *et al*, 2010). Although there is some evidence for SERT recovery in subcortical regions with prolonged abstinence (Buchert *et al*, 2006), there is little evidence suggesting SERT recovery in neocortex.

In contrast to the SERT, the postsynaptic serotonin-2A receptor can serve as an indicator of presynaptic serotonin release if it upregulates in the face of reduced agonist signaling. We recently examined the status of neocortical serotonin-2A receptors in female MDMA users who had a median abstinence from MDMA of nearly 2 years. We predicted that MDMA-induced reductions in serotonin would lead to increased serotonin-2A receptors in MDMA users, and that lifetime MDMA use would be positively correlated with receptor level. Consistent with MDMA-induced chronic reductions in serotonin signaling, long-abstinent MDMA users had increased levels of serotonin-2A receptors in multiple cortical areas, and higher lifetime MDMA use predicted higher receptor levels (Figure 1) with no evidence for receptor normalization with long-term abstinence (Di Iorio *et al*, 2012). Urban *et al* 2012 also found increased serotonin-2A levels in MDMA users and they also measured SERT in the same cohort. SERT binding was lower in brain regions where the serotonin-2A receptors were elevated, a finding consistent with reduced serotonin and consequent upregulation of the serotonin-2A receptor.

If MDMA users actually have reduced serotonin signaling, there should be predictable effects of MDMA-induced reductions in serotonin on cortical neurophysiology. Serotonin is largely inhibitory in neocortex, therefore reductions in serotonin signaling should produce increased cortical excitability, reflected as increased activation with fMRI. In support of this hypothesis, we found that greater MDMA use was associated with greater occipital activation during visual stimulation in MDMA users, a finding consistent with increased cortical excitability and in line with the consequences of reduced serotonin signaling (Bauernfeind *et al*, 2011).

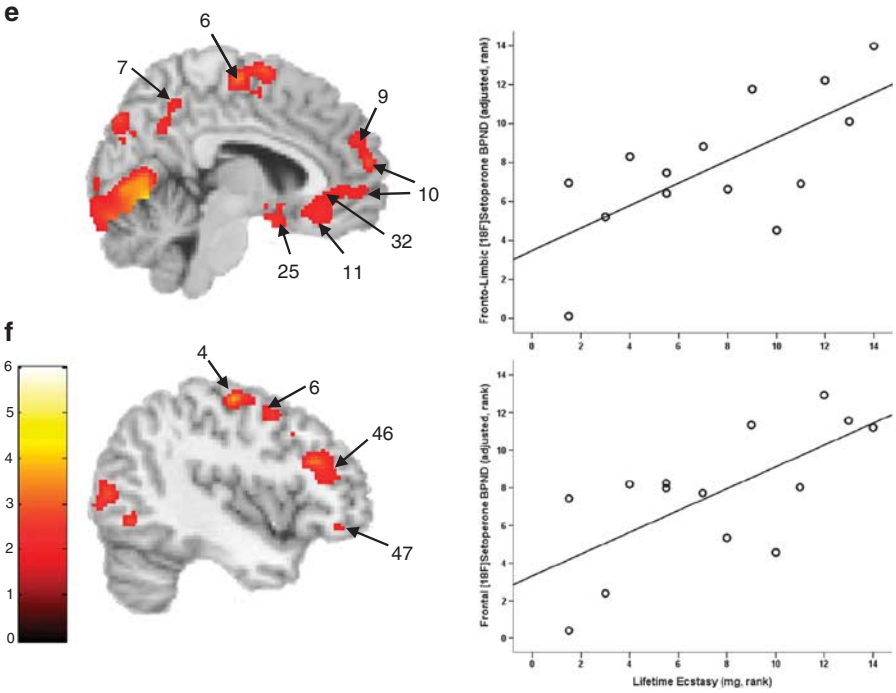

Figure 1. Continued.

Conclusion

Recreational MDMA use in humans is associated with reduced SERT, increased serotonin-2A receptors, and increased excitability in neocortex. It remains possible that preexisting differences, polydrug exposure, or other unknown factors may account for the observed findings. Despite the limitations of suggesting causation from cross-sectional studies, in the absence of evidence suggesting that humans are resistant to the neurotoxic effects of MDMA seen in animals, and given the very strong biological plausibility of the observed findings, we believe that the current evidence strongly suggests that human recreational MDMA use leads to chronic reductions in neocortical serotonin signaling. Further work is needed to understand the clinical consequences of reduced serotonin and whether the inferred reduction in serotonin signaling is secondary to axon loss or a long-lasting functional change.

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