Moreover, studies of human METH abusers reveal evidence of neurotoxicity as indicated by long-term decreases in the neuronal marker, n-acetylaspartate (Ernst *et al*, 2000), and in animals, long-term decreases in markers of dopamine (DA) and 5-HT terminals, including decreases in DA and 5HT transporters and content, VMAT2, and tyrosine and tryptophan hydroxylases. Despite these findings, it is unclear if these changes are indicative of actual neuronal damage, although recent evidence indicates that oxidative stress, hyperglutamatergic activity and microglial activation have important roles.

Emerging findings support the contention that METH produces excitotoxicity and oxidative damage. Calcium influx through ionotropic glutamate receptors and the activation of calcium-dependent proteases cause the breakdown of the structural membrane component, spectrin, in an AMPA receptor-dependent manner (Staszewski and Yamamoto, 2006). Although, METH increases free radicals (Giovanni *et al*, 1995), only recently has there been evidence of actual oxidative damage after METH. Eyerman and Yamamoto (2007) showed that decreases in VMAT2 after METH were likely due to the nitrosylation of VMAT2 as early as 1 h after METH. Furthermore, the nitrosylation and the long-term reduction in VMAT2 and DA transporter protein were attenuated by inhibition of neuronal nitric oxide synthase (nNOS). This indicates that METH causes a rapid glutamate and nNOS-dependent oxidation of VMAT2 that precedes the long-term reductions in DA and 5HT content, thereby linking glutamate and oxidative damage to long-term decreases in markers of monoamine terminals.

Recent evidence shows that METH can affect protein degradation through oxidative damage. Impairment of the ubiquitin–proteasome system (UPS) can result in neurodegeneration such as that observed in Parkinson's disease. Most recently, Moszczynska and Yamamoto (2011) showed that METH causes an oxidative modification to parkin, one of the E3 ubiquitin–protein ligases, which add polyubiquitin chains to proteins destined for degradation. Parkin protein was decreased at 1 to 24 h after METH administration through the conjugation of parkin with 4-hydroxy-2-nonenal, a lipid peroxidation product. Moreover, METH also decreased the activity of the 26S proteasome. Both the oxidative conjugation of parkin protein and the decreased activity of the 26S proteasome were attenuated by pretreatment with antioxidant, vitamin E. Other evidence indicates that METH can oxidatively modify pyruvate kinase isoform M2, a mediator of cellular energetics and proliferation of neural progenitor cells (Venkatesan *et al*, 2011), thereby producing decrements in cell metabolism and turnover.

Recently, our preliminary data indicate that α-synuclein levels increased by 200% in the striatum and hippocampus of the rat after METH. α-synuclein is a presynaptic protein that is overexpressed in some neurodegenerative conditions. Its accumulation and the eventual degeneration of the dopaminergic neuron have been associated with parkin, although α-synuclein is not traditionally considered a substrate of parkin and E3 ligase activity. This suggests that there could be a different E3 protein ligase that is oxidatively modified by METH. Further studies are warranted that examine how METH can affect the UPS and its subsequent effects on protein accumulation and degradation.

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DISCLOSURE

The authors declare that except for income received from their primary employer, no financial support of compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

Ernst T, Chang L, Leonido-Yee M, Speck O (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. *Neurology* **54**: 1344–1349.

Eyerman DJ, Yamamoto BK (2007). A rapid oxidation and persistent decrease in the vesicular monoamine transporter 2 after methamphetamine. *J Neurochem* **103**: 1219–1227.

Giovanni A, Liang LP, Hastings TG, Zigmond MJ (1995). Estimating hydroxyl radical content in rat brain using systemic and intraventricular salicylate: impact of methamphetamine. *J Neurochem* **64**: 1819–1825.

Moszczynska A, Yamamoto BK (2011). Methamphetamine oxidatively damages parkin and decreases the activity of 26S proteasome *in vivo*. *J Neurochem* **116**: 1005–1017.

Staszewski RD, Yamamoto BK (2006). Methamphetamine-induced spectrin proteolysis in the rat striatum. *J Neurochem* **96**: 1267–1276.

Venkatesan A, Uzasci L, Chen Z, Rajbhandari L, Anderson C, Lee MH *et al* (2011). Impairment of adult hippocampal neural progenitor proliferation by methamphetamine: role for nitrotyrosination. *Mol Brain* **4**: (in press); e-pub ahead of print at http://www.molecularbrain.com/content/pdf/1756-6606-4-28.pdf.

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Placental Source for 5-HT that Tunes Fetal Brain Development

Deciphering the influences of fetal programming on adult mental disorders causality depends on the identification of specific molecular pathways involved in their etiology. New insights will provide the means for reducing developmentally based disorder risk, and new therapeutic targets for treatments in adulthood. For example, our recent discovery of maternal–placental–fetal interactions that may influence brain development leads to new hypotheses regarding the mechanisms by which fetal programming of adult mental disorders may occur. A tryptophan (the precursor of serotonin—5-HT) metabolic pathway in the placenta (Bonnin *et al*, 2011) reflects the potential importance of extra-embryonically derived 5-HT in modulating developmental processes such as brain circuit wiring, thus affecting long-term brain function. This concept is consistent with classic genetic (5-HT1A knockout) and pharmacological (SSRI exposure) studies showing that disruption of 5-HT

signaling transiently, during a restricted period of pre- or postnatal development, results in long-term behavioral abnormalities, such as increased anxiety in adulthood (Ansorge *et al*, 2008; Oberlander *et al*, 2009). Because many 5-HT receptors are expressed early and in complex temporal and spatial patterns during brain development (Bonnin *et al*, 2006), the full extent of the mechanisms through which disruption of 5-HT signaling leads to adult phenotypes is not yet understood. One possible route through which it could occur is the disruption of the modulatory activity of 5-HT signaling on fetal forebrain wiring. This was demonstrated *in vitro* via the modulation of netrin-1 axon guidance activity by 5-HT, and *in vivo* by simultaneous, targeted disruption of two 5-HT receptors (5-HT1B/1D) (Bonnin *et al*, 2007). Altered 5-HT signaling in the forebrain could preferentially influence wiring in this brain region *in utero* (Bonnin *et al*, 2007; Bonnin *et al*, 2011), ultimately leading to long-term dysfunction of circuits underlying mood and emotion. Control of 5-HT signaling, through the number and/or type of 5-HT receptors activated, may thus be critical for normal brain development.

During pregnancy, altered availability of 5-HT itself also may lead to abnormal signaling in the fetal brain. The newly discovered placenta-derived 5-HT accumulates in the fetal forebrain (but not the hindbrain; (Bonnin *et al*, 2011)). The period during which placental 5-HT reaches the forebrain in the mouse corresponds to the first and early second trimesters in the human, prenatal periods of neuronal migration, and initial circuit formation that are associated with greater risk for mental illnesses due to maternal perturbations. Thus, like other placenta-derived molecules (eg, growth factors), placental 5-HT output could be affected by both genetic (the embryo and placenta are genetically identical) and environmental disturbances that are known to increase risk for mental illnesses. In fact, altered tryptophan metabolism during pregnancy in mice has long-term functional consequences in the offspring, and has been implicated in increasing the risk for schizophrenia, bipolar disorder, and autism in humans (Miller *et al*, 2009). Although long-term follow-up studies are needed, prenatal exposure to SSRI antidepressants induces an array of disturbances in childhood. It is hypothesized that maternally ingested SSRIs cross the placental barrier and directly impact fetal brain development. However, as the serotonin transporter (SERT; *Slc6a4*) is also highly expressed in the placenta, SSRIs may impact placental function and have indirect effects on fetal development. The SSRIs impact on placental physiology at different stages of gestation is currently under investigation, using the newly developed *ex vivo* dual perfusion system for the mouse placenta (Bonnin *et al*, 2011).

These newest discoveries should stimulate further animal model and human research efforts to examine gene–environment influences during pregnancy that will address the developmental etiology of adult-onset mental disorders.

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Ansorge MS, Morelli E, Gingrich JA (2008). Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. *J Neurosci* **28**: 199–207.

Bonnin A, Goeden N, Chen K, Wilson ML, King J, Shih JC *et al* (2011). A transient placental source of serotonin for the fetal forebrain. *Nature* **472**: 347–350.

Bonnin A, Peng W, Hewlett W, Levitt P (2006). Expression mapping of 5-HT1 serotonin receptor subtypes during fetal and early postnatal mouse forebrain development. *Neuroscience* **141**: 781–794.

Bonnin A, Torii M, Wang L, Rakic P, Levitt P (2007). Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. *Nat Neurosci* **10**: 588–597.

Miller CL, Murakami P, Ruczinski I, Ross RG, Sinkus M, Sullivan B *et al* (2009). Two complex genotypes relevant to the kynurenine pathway and melanotropin function show association with schizophrenia and bipolar disorder. *Schizophr Res* **113**: 259–267.

Oberlander TF, Gingrich JA, Ansorge MS (2009). Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. *Clin Pharmacol Ther* **86**: 672–677.

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Mainstreaming Mice

Autism is a neurodevelopmental disorder for which diagnosis is based on three domains of behavioral symptoms: (1) abnormal social interactions, (2) impaired communication, and (3) repetitive behaviors. Currently, the only treatments that effectively improve these core symptoms are behavioral interventions implemented at early ages (Vismara and Rogers, 2010). Although pharmacological treatments are available for associated symptoms, including self-injury, tantrums, aggression, and seizures, considerable research is needed to discover pharmacological targets for the diagnostic domains.

Mouse models of autism spectrum disorders provide translational research tools for understanding the causes of autism spectrum disorders and for developing treatments (Ehninger *et al*, 2008; Silverman *et al*, 2010). We are interested in the mechanisms that underlie improvements in autism-relevant behavioral phenotypes in genetic mouse models. Given the effectiveness of early behavioral therapies for reducing symptoms in autism, we reasoned that behavioral interventions might similarly rescue social and/or repetitive abnormalities in mouse models. To test this hypothesis, we used an inbred strain of mice, BTBR T + tf/J (BTBR), which displays low sociability on multiple social tasks, reduced ultrasonic vocalizations