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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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

and behavioral responses to olfactory social cues, and high-repetitive self-grooming. BTBR were given opportunities to interact with C57BL/6J (B6), an inbred strain with high-sociability and low-repetitive behaviors.

First, we attempted to model behavioral interventions given by caretakers to young autistic children. Newborn BTBR were cross-fostered with B6 mothers. Cross-fostering produced no significant effects on social or repetitive behaviors in B6 and BTBR mice, either at juvenile or adult ages. B6 and BTBR raised by dams of the opposite strain showed behaviors similar to those raised by foster dams of the same strain and those raised by their biological mothers (Yang *et al*, 2007). This finding is consistent with the rejection of the early 'refrigerator mother' explanation of autism.

Second, we modeled peer interventions in older children and adolescents with autism (Reichow and Volkmar, 2010). Juvenile BTBR were reared with juvenile B6, beginning at weaning. BTBR who lived with B6 cagemates during juvenile ages developed high sociability as adults, whereas control BTBR who lived with BTBR cagemates continued to show social deficits (Yang *et al*, 2011).

Third, we are now engaged in understanding the specific behaviors occurring between BTBR and B6 juveniles in their shared home cages, which might lead to improved sociability in BTBR adults. Video recordings of home cages during the dark phase, when mice are awake and interactive, are being scored on measures including social investigation, proximity states, aggressive interactions, and activity levels. Preliminary observations suggest that BTBR housed with B6 cagemates receive more social investigation than BTBR housed with BTBR cagemates. It is possible that increased exposure to social solicitation behaviors as juveniles may be facilitating the adult sociability seen in BTBR reared with B6 cagemates.

Animal models of autism will need to meet the standard criteria of face validity (analogous symptoms, such as social deficits), construct validity (analogous causes, such as genetic mutations), and predictive validity (analogous responses to treatments). Evidence that an early behavioral intervention rescued adult sociability in BTBR mice gives credence to the predictive value of this mouse model.

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Phospholipase D as a Therapeutic Target in Brain Disorders

Phospholipid-mediated signaling pathways control a myriad of physiological processes including various aspects of brain function. Among the phospholipid enzyme families, phospholipase D (PLD) is emerging as a key player in regulating phospholipid metabolism, and a newly appreciated therapeutic target for Alzheimer's disease (AD), stroke, and other brain disorders (Oliveira and Di Paolo, 2010). PLD catalyzes the conversion of phosphatidylcholine to the lipid second messenger phosphatidic acid and choline. Two mammalian isoforms of conventional PLDs have been identified, PLD1 and PLD2, which share 53% sequence identity and are subject to different regulatory mechanisms. Previous research relied on the overexpression of either catalytically active or inactive forms of either PLD1 or PLD2 in cells, or employed siRNA for the individual isoforms in an effort to discern discrete roles for PLD1 and PLD2 in brain disorders (Oliveira and Di Paolo, 2010). In 2010, PLD1$^{-/-}$ and PLD2$^{-/-}$ mice developed via gene targeting were reported, clearly defining, nonoverlapping roles, and therapeutic potential for both PLD1 and PLD2 in the pathogenesis of AD. From overexpression and biochemical studies, it has been shown that PLD1 (but not PLD2) regulates the trafficking of APP and the assembly of the γ-secretase complex via a direct interaction with PS1 (Cai *et al*, 2006). In 2010, PLD2$^{-/-}$ mice provided the first *in vivo* evidence implicating PLD in AD. Here, PLD2 was shown to be required for the synaptotoxic action of Aβ, and that PLD2 ablation rescues memory deficits and engenders synaptic protection in SwAPP mice, despite a high Aβ load (Oliveira *et al*, 2010). Also in 2010, PLD1$^{-/-}$ mice were shown to display impaired $\alpha_{IIb}\beta_3$ intergrin activation and defective glycoprotein 1b-dependent aggregate formation, leading to protection from thrombosis and ischemic brain injury without increasing bleeding time (Elvers *et al*, 2010). Historically, few small molecule tools existed to study PLD function, and none of the inhibitors displayed PLD isoform-selective inhibition. The classical biochemical approach relies on