may be perturbed, replacing 'intended' spatial and chemical connections with dysfunctional alternatives. The likelihood that medications will functionally untangle these chaotic and dispersed connections in schizophrenia seems increasingly farfetched.

Cognitive therapies, broadly including cognitive-behavioral and neurorehabilitative therapies and cognitive training, may reduce symptoms and restore function in schizophrenia (McGurk *et al*, 2007; and Wykes *et al*, 2008) by engaging healthy neural systems to learn adaptive cognitive and behavioral strategies. The biology underlying learning-based neuroplasticity has been elaborated at levels extending from molecules to systems, and studies are now identifying neural changes accompanying clinical benefits of these specialized 'learning therapies.' *Conceivably*, *these neural changes and their corresponding therapeutic impact might be augmented via medications*.

Although controlling psychosis benefits ongoing cognitive interventions, drugs with pro-cognitive effects (rather than antipsychotics *per se*) might more specifically, and perhaps synergistically, enhance the clinical benefits of CTs. Drugs that enhance specific components of neurocognition, eg, working memory (WM), might be predicted to yield clinical benefits in schizophrenia only if paired with interventions that access those components, ie, utilize/place demands on enhanced WM. Similar reasoning underlies the use of anabolic steroids to promote exercise-increased muscle mass, or perhaps more importantly, the use of pro-extinction drugs to enhance therapeutic benefits of cognitive therapies for anxiety disorders (Ressler *et al*, 2004). Conversely, specific pro-cognitive drugs might be effective in augmenting the clinical benefits of cognitive therapies in schizophrenia even if (as existing data may suggest) they are ineffective when administered without the demands of cognitive therapies.

Initial attempts to develop pharmacologically-augmented cognitive therapies (PACTs) are in progress, using drugs designed to *overcome neuropathological changes* in schizophrenia (eg, *d*-cycloserine (Gottlieb *et al*, 2011)); I have suggested that an alternative strategy might be to utilize medications that *enhance spared neural functions* in these patients (Swerdlow, 2011). Evidence for the requisite 'spared' healthy neural circuitry in any given patient, and hence a target for PACTs, might be provided by specific neurophysiological changes in response to a single drug challenge. The use of a 'test dose' to predict clinical benefit has been successful with interventions ranging from hormones to anti-Parkinsonian therapies to bronchodilators. The goal of enhancing 'spared' function departs from the prevailing failed strategy of trying to use drugs to 'undo' a lifetime of schizophrenia-related neuropathology.

Based on the genetic and neurobiological heterogeneity of schizophrenia, biomarkers might identify subgroups of patients most sensitive to specific PACTs; in some cases, these biomarkers might include neurophysiological measures that identify spared neural circuits in these patients (Javitt *et al*, 2008). Importantly, the use of PACTs shifts our scientific focus from characterizing the widespread (and I submit, uncorrectable) neuropathology and its molecular antecedents in schizophrenia, to identifying areas of neurobiological resilience and function. In this strategy, our patients' spared neural resources become the next generation of therapeutic targets for drug development.

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# From Father to Offspring: Paternal Transmission of Depressive-Like Behaviors

Major depressive disorder is a common and disabling disorder with an overall lifetime risk estimated to be ~15% in the general US population. Depression is thought to be caused by a combination of genetic and environmental factors. Indeed, a rich literature has demonstrated that depression is highly heritable, with roughly 40% of the risk being genetic (Sullivan *et al*, 2000). More recently, there has been interest in the possibility that epigenetic mechanisms might also contribute to the transgenerational transmission of stress-induced vulnerability.

In adult male mice, exposure to chronic social defeat stress induces

a syndrome of behavioral deficits that closely model subtypes of human depression (Krishnan *et al*, 2007). We hypothesized that these behavioral adaptations might be transmitted to subsequent generations, ultimately leading to enhanced susceptibility to depressive-like behaviors in the offspring of mice sired from defeated fathers. Using social avoidance as a measure of depressive-like behavior, our initial findings confirmed that male mice bred from defeated fathers, but not from control fathers, showed pronounced social avoidance when subjected to submaximal defeat stress (Dietz *et al*, 2011).

To further study the role of paternal influences in heritability of depressive-like behaviors, we performed a 'pre–post experiment,' which allowed us to directly compare both male and female offspring sired from the same males before and after having been subjected to social defeat. We performed a battery of behavioral tests (forced swim test, elevated plus maze, sucrose preference, and social defeat) that together examine depressive- and anxiety-like behaviors. Compared with pre-defeat offspring (which were indistinguishable from controls), both male and female offspring from the defeated fathers demonstrated robust depressive- and anxiety-like phenotypes. The offspring of defeated fathers also displayed increased basal levels of plasma corticosterone and decreased levels of vascular endothelial growth factor, both of which have been implicated in depression and antidepressant action (de Kloet *et al*, 2005; Warner-Schmidt and Duman, 2008).

In the final set of experiments, to directly assess the role of epigenetic mechanisms, we used *in vitro* fertilization (IVF) to investigate whether the behavioral phenotypes observed in the above experiments were directly transmissible through the sperm of socially defeated mice. Sperm from defeated and control mice were used to impregnate female mice, and the offspring were tested for depressive- and anxiety-like behaviors. Unlike our previous findings, animals derived using IVF from defeated fathers did not show a robust increase in susceptibility for a depressive- or anxiety-like phenotype, with only very modest differences seen.

Together, our studies demonstrate the clear transmissibility of depressive- and anxiety-like phenotypes to the F1 generation offspring of socially defeated mice. Our IVF experiments indicate that most of this transgenerationally transmitted behavioral phenotype likely occurs through behavioral mechanisms. Nevertheless, our data suggest that a small contribution of epigenetic modifications is possible, which now requires further examination. These and related (Franklin *et al*, 2010) findings in mice raise the possibility that part of an individual's risk for clinical depression or other stress-related disorders may be determined by his or her father's life exposure to stress, a provocative suggestion that now requires direct study in humans.

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