multiple important biological roles, including in receptor binding, neurotransmission, signal transduction, and eicosanoid synthesis. A growing body of studies suggests significant reductions in PUFA levels in people with schizophrenia (Berger *et al*, 2006). Concordant with these findings, fatty acids, particularly the omega-3 PUFA, may have a beneficial role in the treatment of first-episode schizophrenia, and in the prevention of schizophrenia, while results in chronic schizophrenia have been mixed (Peet, 2008). We have recently tested whether supplementation with omega-3 PUFA could reduce the rate of transition to first-episode psychosis in an ultra-high risk (UHR) cohort. In our study, we randomized 81 individuals aged 13–25 years to 12 weeks of either 1.2 g/day of omega-3 PUFA or placebo, followed by a 40-week monitoring period. In all, 2 of 41 (4.9%) of those receiving the active agent transitioned to psychosis, compared with 11 of 40 (27.5%) in the placebo group, a statistically significant difference (Amminger *et al*, 2010). While PUFAs have been investigated in schizophrenia, their role in the onset of psychotic symptoms is unclear. Therefore, we examined the relationship between omega-3 PUFA (ie, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA)) levels in erythrocyte membrane phosphatidylethanolamine and measures of psychopathology in our UHR cohort at baseline. Erythrocyte membrane phospholipid composition closely reflects that of neuronal membranes, and provides an easily accessible indicator of brain phospholipids. While ALA, EPA, and DHA did not correlate significantly with any symptom measure, low levels of DPA and the summary score of all assessed omega-3 fatty acids (ie, ALA, EPA, DPA, and DHA) correlated with more severe negative symptoms. These correlations remained significant after adjustment for potential confounders (ie, age, sex, and nicotine use). Reduced DPA has been previously reported in neuroleptic-naïve first-episode schizophrenia patients (Reddy *et al*, 2004). Given our intervention study provided support for the 'dose–response' criterion (McNamara, 2011), as an increase in erythrocyte omega-3 PUFA levels reduced the rate of transition to psychosis and correlated with functional improvement, we tested if the subjects with the lowest erythrocyte omega-3 levels at baseline were at higher risk for transitioning to psychosis. To eliminate treatment effects, we only investigated those participants who had received placebo. Cox regression analyses with adjustment for age, sex, and nicotine use indicated that no single omega-3 PUFA or their summary score predicted conversion to psychosis. Following studies reporting lower levels of arachidonic acid (AA) and nervonic acid (NA), as well as DHA, in people with schizophrenia (Assies *et al*, 2001), we also examined if these fatty acids predicted transition to psychosis. While AA was not found to be predictive, low NA levels at baseline significantly predicted transition to psychosis (Amminger *et al*, submitted). As NA is a major constituent of the myelin sheath, low levels of NA could reflect suboptimal myelination in those UHR individuals who develop a psychotic disorder. The finding is consistent with the well-established finding of white matter abnormalities in schizophrenia (Ellison-Wright and Bullmore, 2009). Notably, the observation that supplementation with omega-3 PUFAs may prevent transition to psychosis suggests that omega-3 fatty acids may offset the risk conferred by decreased levels of NA. A randomized controlled multicenter phase III clinical trial of omega-3 PUFA is now underway to replicate the findings (Australian New Zealand Clinical Trials Registry - ACTRN12608000475347).

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DISCLOSURE

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Beyond Antipsychotics: Pharmacologically-Augmented Cognitive Therapies (PACTs) for Schizophrenia

The neuropathology of schizophrenia is substantial in scope and complexity. In patients, structural abnormalities in about 20 brain regions span wide swaths of cortical and subcortical tissue, reflecting processes presumably well advanced at birth. Roughly half as many regions are abnormal in unaffected relatives (cf. Swerdlow, 2011). Within any region, laminar synaptic and cellular arrangements

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