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Are we studying and treating schizophrenia correctly?

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Abstract

New findings are rapidly revealing an increasingly detailed image of neural - and molecular-level dysfunction in schizophrenia, distributed throughout interconnected cortico-striato-pallido-thalamic circuitry. Some disturbances appear to reflect failures of early brain maturation, that become codified into dysfunctional circuit properties, resulting in a substantial loss of, or failure to develop, both cells and/or appropriate connectivity across widely dispersed brain regions. These circuit disturbances are variable across individuals with schizophrenia, perhaps reflecting the interaction of multiple different risk genes and epigenetic events. Given these complex and variable hard-wired circuit disturbances, it is worth considering how new and emerging findings can be integrated into actionable treatment models. This paper suggests that future efforts towards developing more effective therapeutic approaches for the schizophrenias should diverge from prevailing models in genetics and molecular neuroscience, and focus instead on a more practical three-part treatment strategy: 1) systematic rehabilitative psychotherapies designed to engage healthy neural systems to compensate for and replace dysfunctional higher circuit elements, used in concert with 2) medications that specifically target cognitive mechanisms engaged by these rehabilitative psychotherapies, and 3) antipsychotic medications that target nodal or convergent circuit points within the limbic-motor interface, to constrain the scope and severity of psychotic exacerbations and thereby facilitate engagement in cognitive rehabilitation. The use of targeted cognitive rehabilitative psychotherapy plus synergistic medication has both common sense and time-tested efficacy with numerous other neuropsychiatric disorders.

Keywords

antipsychotic; cognitive therapy; dopamine; hippocampus; prefrontal cortex; schizophrenia

Introduction

With increasing pace, findings are revealing the structural and functional properties of limbic cortical and subcortical circuits that are conveyed through programmed cell migration, pre- and post-natal synaptic reorganization and apoptosis across normal development (cf. Tau & Peterson 2010). Current models for the etiology of the schizophrenias (e.g. Bigos et al. 2010; Kleinman et al. 2011) suggest that this intricate weaving is turned to chaos by predisposing genes and epigenetic events; the resultant or compensatory changes are then hard-wired by tightly choreographed, inter-dependent developmental processes. The molecular and micro-structural rearrangements within a long

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list of neural elements created by any one of dozens of schizophrenia "risk genes" are being elaborated one-by-one (e.g. Papaleo & Weinberger, 2011); this list will grow, when we consider interactions with many possible epigenetic "second hits." Making sense of this chaos, and ways to reverse or prevent it, has become a daunting task.

Indeed, as we dig deeper into the smaller spaces of the neuro-molecular world of schizophrenia, we have no good roadmap. Schizophrenia is not like diabetes, where one hormone can replace one lost, or hypertension, where therapeutics target not the myriad causes but instead their final common pathways. It is not like Parkinson's Disease (PD), where motoric symptoms largely reflect the loss of one neuron, whose role is to supply one chemical to cells in a way that can be mimicked by administering one precursor for that chemical; this is possible in PD *because the organization of the post-synaptic circuitry develops normally, and for much of adulthood, retains the detailed interconnections in the "intended" design.*

In schizophrenia, the root cause appears to be a developmental interruption and tangling of neural connections (Weinberger 1987; Murray et al. 1991; Lewis & Levitt 2002) that are orders of magnitude too complex to restore or replace, and which in their complexity regulate not motor functions but rather the psychological identity of the individual (cf. Nelson et al. 2009). This complexity can be appreciated by considering even just one of the many brain regions implicated in this disorder. The prefrontal cortex (PFC) is not a homogeneous group of cells, but rather a hub for neural interactions, within which pathology triggers pre- and post-synaptic compensatory changes among many functionally distinct subregions and cell types, and convergent influences of neurotransmitters, peptides and other neuromodulators, all within adjacent lamina. Calculate the permutations of synaptic interactions in the simplest cartoon schematic, the number of different risk genes and epigenetic events, and multiply by orders of magnitude, and you appreciate the level of chaos into which we introduce medications. Without some fundamental paradigmatic change, it is implausible that pharmacology will, in the foreseeable future, *be able to reach backwards two decades through a variable web of absent and misguided neural connections, replace missing and improper ones with healthy ones, and thereby disentangle schizophrenia from the self.* Despite our growing understanding of its genetic control and molecular pathology, I will argue that prefrontal and limbic cortico-striato-pallido-thalamic (CSPT) dysfunction in schizophrenia is too widely distributed, complex and variable to be predictably engaged with medications, and that our field should therefore consider alternative strategies for understanding and treating the schizophrenias.

Distributed neural dysfunction

Evidence for distributed neural dysfunction in schizophrenia is compelling, even when considering only the areas where structural abnormalities are reported (and not, for example, areas activated abnormally under experimental or symptomatic conditions (Dolan et al. 1995; Silbersweig et al. 1995; Heckers et al. 1998; Volz et al. 1999; Kumari et al. 2003; cf. Brown & Thompson 2010, Heckers & Konradi 2010)). A preponderance of findings in different schizophrenia cohorts support significant volumetric and/or morphometric abnormalities in *over 20 brain regions* (Table 1; cf. Levitt et al. 2010). These abnormalities reflect perturbations in the number, size or shape of cells, fibers or extra-parenchymal elements: *Medline* lists numerous papers reporting laminar- and subregion-specific reductions and other abnormalities in the number of neurons, length of their dendrites, density of their dendritic spines and varicosities, and levels of cellular proteins and mRNA in prefrontal, mesial temporal and auditory cortex, striatum and thalamus, and even the cerebellum and midbrain DA nuclei, among other regions. Studies also document abnormalities in the number or distribution of neurotransmitter receptors in these and other

brain regions, which may reflect a primary loss of cells that support them, a secondary response to abnormalities of the fibers that innervate them or the chemicals they deliver, or combinations thereof (cf. Abi-Dargham et al. 1998; Aparacio-Legarza et al. 1997; Cruz et al. 2009; Dean et al. 2009; Howes et al. 2009; Kessler et al. 2009; Kestler et al. 2001; Roberts et al. 2009; Laruelle 1998; Lee & Seeman 1980; Lewis et al. 2008; Gur et al. 2007; Urban & Abi-Dargham 2010; Volk & Lewis 2010; Wong et al. 1986).

The list of neural disturbances reported in large samples of patients is only the "tip of the iceberg". First, studies of neural circuitry in schizophrenia have been circumscribed in their targets, but findings of cortical abnormalities well beyond the prefrontal and mesial temporal regions (Sweet et al. 2007, 2009) suggest more generalized neurodevelopmental disturbances. Second, disturbances in neuronal number, size, shape and connectivity perturb neurotransmission, cellular metabolism, signal transduction molecules, gene expression and other levels of the machinery required for normal neural function (cf. Benes 2010; Kvaajo et al., 2010). Third, identifiable disturbances in one neuronal element translate into widely distributed dysfunction within "intact" brain circuits efferent from, or projecting to, the "damaged" element. For example, pathology that impairs normal " γ -band" synchronization of discharges from large populations of cortical neurons can disrupt information processing among those "normal" cells and the circuits that they form (cf. Uhlhaas and Singer 2006). Thus, disturbances in one cell type can have multiplier effects downstream, even among circuits that – in post-mortem analyses or resting state imaging - *have normal structural and morphological properties*. Fourth, *variance* across and within studies for each abnormality is substantial. In two individuals with schizophrenia, the same brain region may be relatively normal in one and grossly abnormal in another. Furthermore, among the list of regions that are statistically different in cohorts of patients vs. comparison subjects, any given patient might exhibit some but not all of these regional abnormalities. And with any given CSPT locus, reduced volumes in two different patients might reflect disturbances in different cell populations, resulting in different patterns of abnormal efferent projections and innervation. We don't know which of these many different abnormalities are inter-related vs. independent because most studies focus on a small number of measures or neural elements.

What are we studying, and why?

For those studying the pathogenesis and treatments of schizophrenia, its long list of distributed neural deficits raises many questions, of which only 3 are mentioned herein:

Primary vs. Secondary?

Most schizophrenia patients likely have multiple disturbances within limbic CSPT circuitry that do not arise independently. It thus seems reasonable to ask which disturbances are "primary," i.e. a direct result of the root cause of schizophrenia, vs. "secondary," i.e. a consequence of aberrant neural function elsewhere in the brain. But there is no reason to believe that the symptoms of schizophrenia reflect disturbances that are primary rather than secondary. Perhaps, identifying and studying biological processes closer to the genesis of schizophrenia will help narrow the list of etiologies, deduce ways to detect individuals at risk for developing it, and design interventions that limit the progression of disturbances to secondary and tertiary loci. But the *treatment* of schizophrenia *at age 20* will not differ if the symptom-causing neural disturbance is "primary" (e.g. the loss of neuron "A" *in utero* due to an immune response to viral exposure) vs. "secondary" (e.g. the misguided migration of neuron "B" in early development resulting from a loss of trophic factors normally supplied or stimulated by neuron "A"). This argument changes somewhat when considering preventative interventions - e.g. in a 10 year old with biomarkers predicting an increased risk for later developing schizophrenia – but I suggest below that *the conclusion does not*. Prenatal interventions – analogous to using folic acid to prevent neural tube defects (cf.

Wolff et al. 2009) – might conceivably prevent the development of schizophrenia, should a primary “missing ingredient” be identified, but it is hard to imagine that such a finding would emerge from current research strategies.

Risk markers?

Hippocampus, amygdala, anterior cingulate cortex and other structures are reduced in volume and/or functionally impaired in asymptomatic first-degree relatives of schizophrenia probands, and in “ultra-high risk” individuals (Table 1; cf. Pantelis et al. 2009; Ho & Magnotta 2010; Boos et al. 2007). Some disturbances in unaffected individuals are associated with genetic polymorphisms that also appear to convey a risk for schizophrenia (Kempf et al. 2008; Esslinger et al. 2009; Hall et al. 2008; Gruber et al. 2008). One implication of these findings is that while these circuit disturbances are associated with a heritable vulnerability for schizophrenia, they are insufficient to produce the disorder. This could reflect a need for multiple “hits” (e.g. the inherited neural dysfunction plus epigenetic events) or it could reflect resilience conveyed by “protective” factors in unaffected relatives. Even if these familial phenotypes are not sufficient to produce the illness, one could argue that they are risk markers that inform us about etiologies and preventative interventions. However, it requires more complicated reasoning to suggest that these markers should be *targets for “corrective” interventions*: after all, most people with these abnormalities *do not have schizophrenia*, so why would “correcting” this circuitry be of benefit to someone who does?

Vulnerability markers can certainly inform corrective strategies. In colorectal cancer, vulnerability is linked predominantly to one phenotype – adenomatous colon polyps (Grodin et al. 1991). The biology of colon cancer therefore reflects a common foundation (“polyp biology”), acted upon by different “second hits” (diet, smoking, other risk genes, etc.). Schizophrenia is quite different: neural circuit “vulnerability markers” in unaffected relatives appear at multiple different loci, which may be associated with different genetic polymorphisms and perhaps rare gene variants. There is no *a priori* reason to assume that two different individuals carrying different predispositions to schizophrenia based on reduced hippocampal vs. thalamic volumes, respectively, would be vulnerable to the same epigenetic events. Thus, unlike colon cancer, heterogeneity in schizophrenia may *not* reflect the additive impact of “second hits” on a common foundation of a single “vulnerable” phenotype but rather the *mathematical product* of the different vulnerability phenotypes and the different epigenetic events. This suggests a more complex model, at the levels of genetics, neurobiology, and ultimately, therapeutics.

But let’s suppose that a list of neural phenotypes, epigenetic events and genetic markers could be identified in clinically normal 10 year-olds, which conveyed a fractionally increased risk for the development of schizophrenia. *What would we, as clinicians, do with this information?* Would we widely administer prophylactic drugs to asymptomatic children, to prevent the development of schizophrenia in a small percentage of them? It’s difficult to get parents to vaccinate children for measles (Yarwood et al. 2005; Omer et al. 2009); do we think that there would be acceptance of preventative drugs for schizophrenia, or that such drugs – as neuroactive agents - would be innocuous in children? Would we stratify children or fetuses based on genetic testing? Not likely: genetic markers could at best suggest a statistical increase in the risk for developing schizophrenia. Many genes are associated with an increased risk for schizophrenia, and/or neurocognitive deficits in this disorder (cf. SchizophreniaGene: www.schizophreniaforum.org/res/sczgene/default.asp Eisenberg & Berman 2010), and this list may underestimate the number of rare highly penetrant gene mutations contributing to different forms of schizophrenia (Walsh et al. 2008). Even highly predictive genetic testing – absent effective preventative interventions - may not be widely utilized in an asymptomatic population (Riedijk et al. 2009).

Which target?

Given the “target-rich” environment of distributed neural disturbances in schizophrenia, which are the best targets for medications? Perhaps we should select specific targets based on the convergence of known functional localization and known functional deficits in schizophrenia. Thus, to remediate working memory (WM) deficits in schizophrenia, perhaps we should target cellular disturbances within regions known to regulate WM, e.g. the PFC. But this logic is “circuitous”: the ability of the PFC to function normally depends on the normal microcircuit patterns of MD and hippocampal efferents onto specific laminar and sublaminar PFC targets (cf. Pakkenberg et al. 2009). We cannot reasonably expect medications to replace in any physiological manner (e.g. synchronized with moment-to-moment load demands) the specificity and complexity of this convergent PFC input, and thereby restore normal neurocognitive function. And because some of the MD and hippocampal cells that normally form these PFC afferents appear to be missing or dysfunctional both prior to and after the onset of the illness (Table 1), does it make sense to study or intervene within either of these regions, as a means to normalize PFC activity and thus neurocognition?

Historically, the primary therapeutic targets in schizophrenia have been DA receptors. Despite evidence (Lieberman et al. 2005) that current DA antagonists have modest therapeutic impact, it remains the hope that targeting DA receptors at a “nodal” juncture within an aberrant reverberating circuit might offer “feed-forward” therapeutic benefits – with each pass through the CSPT loop – sensing or blunting the intrusion of aberrant cortical activity into consciousness. The goal of this treatment is essentially “spin control” – constraining re-entrant misinformation – and its impact is quantitative more than qualitative: i.e. it primarily reduces the “volume” (frequency and intensity) of disruptive and disorganized cortical information, more so than directly impacting cognitive structure (the latter being a function of intrinsic cortical circuits). Developing better drugs to act at limbic-motor “nodal points” (Stevens 1973) to limit psychotic exacerbations remains an important goal, but because these drugs cannot untangle higher cortical disturbances in neural function, *they will not likely produce sustainable clinical gains in the absence of a second level of intervention in many patients.*

Where does this lead us?

What we have learned about the neural circuit and genetic complexities of this heterogeneous condition raises the conundrum that existing interventional models – pharmacologic, immunologic, surgical or genetic – *may not be appropriate for schizophrenia*. This is not a failure of translational neuroscience: *while we have not “solved” schizophrenia and its treatment, we have learned enough to make key refinements to the expectations of our interventional models.* From a neural circuit perspective, this paper has superficially addressed three options for interventions within dysfunctional CSPT circuitry: Option 1) at the “highest” cortical levels, where (I suggest) drugs offer little hope of predictably recreating in any physiological manner the complexity of healthy synaptic dynamics; Option 2) elsewhere within higher cortico-thalamic or cortico-cortical connections, that also appear to be intrinsically perturbed beyond reach of even the “smartest” drugs; or Option 3) at targets “downstream” from aberrant cortical activity, blunting the impact of disorganized cortical information but not restoring order to cognition. *A fourth option is to intervene within healthy circuitry, using the intact complexity of intrinsic healthy circuits to compensate for, and potentially subsume the function of damaged circuit elements, or even protect this circuitry from future damage.*

Among the most important findings in modern psychiatry is that psychotherapy (particularly cognitive and behavioral therapy) changes the brain (Baxter et al. 1992; Schwartz et al.

1996; Saxena et al. 2009). *How* psychotherapy changes the brain, and the extent to which these changes reflect processes from gene expression up to the organization of circuits and systems, are questions of ongoing investigation (de Lange et al. 2008; Fox 2009; Kellar and Just 2009; Korosi and Baram 2009; Porto et al. 2009; Saxena et al. 2009). To what extent can we expect psychotherapeutic interventions to prevent or compensate for neural dysfunction in schizophrenia, where the structure of cognition (a primary tool in these interventions) is fundamentally impaired?

Substantial evidence indicates that different forms of cognitive therapies reduce symptoms and improve function in schizophrenia patients (Klingberg et al. 2009; Medalia and Choi 2009; McGurk et al. 2007), with sustained benefits often lasting years (e.g. Granholm et al. 2007; McGurk et al. 2009; Sellwood et al. 2007; Eack et al. 2009). Response predictors are being identified (Kurtz et al. 2009; Brabban et al. 2009; Kumari et al. 2009; Premkumar et al. 2009), as are specific clinical targets and response metrics (McGurk et al. 2009; Penn et al. 2009; Klingberg et al. 2009), and these therapies are being manualized and computerized (e.g. Cavallaro et al. 2009; Davis et al. 2005; Klingberg et al. 2009; Roberts and Penn 2009). In contrast, relatively little is known about the *specific pharmacological augmentation of cognitive interventions*. While reducing active psychosis with antipsychotics benefits any cognitive intervention, it is possible that drugs with pro-cognitive effects might more specifically, and perhaps synergistically, *enhance the clinical benefits of cognitive therapies*. Trials of potential pro-cognitive agents in schizophrenia yielding negative results *were not conducted within the context of systematic cognitive interventions* (cf. Green 2007; Barch 2010; Buchanan et al. 2007; Goff et al. 1996, 1999, 2007, 2008). Thus, drugs designed to enhance specific components of neurocognition, e.g. WM, might not be beneficial unless paired with interventions that access those components, i.e. utilize/place demands on enhanced WM. An analogy comes from anabolic steroids, which increase muscle mass only if used in concert with muscle-engaging activities. Furthermore, schizophrenia is a heterogeneous disorder, and pro-cognitive trials in schizophrenia suffer from the absence of biomarkers that identify "sensitive" clinical subgroups of patients (cf. Hagan & Jones 2005; Javitt et al. 2008).

One model for the efficacy of cognitive interventions in schizophrenia comes from their use in treating stroke syndromes: these interventions engage the normal physiological and anatomical properties of healthy brain circuits (e.g. in neighboring regions or parallel circuits) to restore or subsume the function of damaged ones (cf. Taub et al. 2002). An implication of the variability in neuroimaging and neuropathological findings in schizophrenia is that in many patients, portions of CSPT circuitry may remain relatively intact. The model proposed herein suggests that medications that enhance specific cognitive functions (e.g. WM) by acting on remaining *healthy brain circuits* (i.e. not on areas of neural dysfunction per se) might reasonably be expected to amplify the clinical benefits of cognitive interventions, *even if these medications are clinically ineffective when administered without the demands of cognitive interventions*. How might pro-cognitive medications enhance the therapeutic impact of cognitive interventions in schizophrenia? Cognitive therapies (CTs) place demands on patients to develop compensatory strategies for learning and remembering information. In so doing, they specifically activate prefrontal regions subserving WM and attention (Haut et al. 2010). Cognitive deficits predict poor outcomes in a number of cognitive and vocationally-oriented therapies (Green 1996; Becker et al. 1998; McGurk & Meltzer 2000; McGurk & Mueser 2004), and parsimony suggests that patients will benefit most if they are able to meet the cognitive demands of CTs.

Evidence for the presence of requisite "spared" healthy neural circuitry in any given patient, and hence an accessible target for pro-CT drug action, might be provided by specific neurophysiological changes in response to a single drug challenge, as discussed below

(Figure 1) (Swerdlow et al. 2010; Tomasi et al. 2011). This approach parallels the use of a "test dose" to predict clinical benefit from interventions ranging from hormones (Biller 2007) to anti-Parkinsonian therapies (Hughes et al. 1990) to bronchodilators (Fruchter & Yigla 2009), and suggests a research focus on identifying and characterizing *healthy brain tissue in schizophrenia*, rather than the clear focus to date, which has been on *unhealthy* circuitry. Laboratory measures of particular interest would be ones that are regulated by elements of CSPT circuitry, deficient in schizophrenia, associated with neurocognitive functions important for CT and experimentally appropriate for a within-subject repeated testing design. As with any predictive model, this strategy would have limits of sensitivity and specificity, and drugs yielding "positive" findings might be clinically irrelevant based on their toxicity or tolerability. While specific drugs and measures are described below, this is done not to suggest a "recipe", but rather to illustrate a proposed strategy: *a drug-induced increase in a CSPT-regulated measure serves as evidence that the requisite substrate for these drug effects remains functional, and could potentially be activated in the service of CT.*

One direct approach to screening drugs for pro-CT potential combines a double-blind, placebo- and active-dose challenge with a repeatable neurocognitive battery, to assess drug effects on WM or related functions. This approach is being used to identify "pro-cognitive" agents, without specific consideration of their potential impact on CTs (cf. Marder 2006). In some cases (e.g. pramipexole, see below (Ersche et al. 2011)), these approaches have identified genetic predictors of drug sensitivity. A disadvantage to this approach, however, is the dearth of existing isomorphic translational models for studying mechanisms of positive drug effects on neurocognition.

Another candidate predictive measure, prepulse inhibition of startle (PPI), is sensitive to acute drug effects in a manner that might predict pro-CT candidates. PPI is regulated by CSPT circuitry (cf. Swerdlow et al. 2008), reduced in schizophrenia patients (Braff et al. 1978; Swerdlow et al. 2006a) and correlated with CT-relevant executive functions including WM (Bitsios et al. 2006; Giakoumaki et al. 2006; Light et al. 2007; van der Linden et al. 2006). In healthy individuals under specific conditions, some drugs increase PPI (Table 2); of these, clozapine (Vollenweider et al. 2006) and quetiapine (Swerdlow et al. 2006b) are atypical antipsychotics, which also increase PPI in schizophrenia patients (Swerdlow et al. 2006a). Other PPI-increasing drugs come from drug classes not intuitively associated with schizophrenia therapeutics: NMDA antagonists and catecholamine agonists. In this regard, it is important to not categorically reject candidate drug classes based on hypotheses for the pathogenesis of schizophrenia. For example, amantadine has both DA agonist and NMDA antagonist properties, and *has been safely used in schizophrenia patients for over 4 decades* (Kelly et al. 1971), despite prevailing hypotheses linking schizophrenia to excessive DA activity and deficient NMDA activity.

Low affinity NMDA antagonists that increase PPI in healthy subjects include amantadine (Swerdlow et al. 2002) and memantine (Swerdlow et al. 2009b). Memantine's PPI-enhancing effects appear to be most potent among individuals with phenotypes linked to the Val/Val alleles of the Val158Met COMT polymorphism (Golimbet et al. 2007; Roussos et al. 2008; Giakoumaki et al. 2008), suggesting a potential biomarker for identifying an enriched treatment cohort. In addition to PPI, memantine challenge in healthy subjects enhances other markers of CSPT and functional deficits in schizophrenia, including mismatch negativity (Korostenkaja et al. 2007; Light & Braff 2005), and in preliminary studies appears to increase WM performance in some individuals (Swerdlow et al. 2010). *Conceivably, the ability of a memantine (or other drug) "challenge" to enhance PPI or other neurophysiological measures in a patient could provide evidence for residual, healthy circuitry that could be recruited to enhance the effectiveness of CT.*

Memantine is neuroprotective (Kornhuber et al. 1994; Rogawski and Wenk 2003; Lipton 2006), enhances cortical metabolic efficiency (Willenborg et al. 2011), is well-tolerated by schizophrenia patients (Lieberman et al. 2009; de Lucena et al. 2009; Krivoy et al. 2008; Zdanys and Tampi 2008) and has been safely used in many millions of patients, including elderly, frail clinical populations (cf. Jones 2010). It has shown modest or no benefit in schizophrenia trials to date (Lieberman et al. 2009; de Lucena et al. 2009; Krivoy et al. 2008), but importantly, *no studies have tested its ability to enhance the therapeutic impact of CT, or utilized biomarkers to test this drug effects among “enriched” subgroups.* “Next generation” low affinity NMDA antagonists, currently in development, would warrant investigation in studies of PPI and neurophysiological and neurocognitive measures of relevance to CSPT function and schizophrenia; such drugs might also be pro-CT candidates.

Several pro-catecholamine drugs also increase PPI in some healthy subjects, including the COMT inhibitor, tolcapone (Giakoumaki et al. 2008; Roussos et al. 2009), the indirect DA agonist, amphetamine (Talledo et al. 2009) and the D3 agonist, pramipexole (Swerdlow et al. 2009a). PPI-enhancing effects of these drugs are generally either subgroup - or biomarker-sensitive (e.g. in individuals carrying the Val/Val alleles of the Val158Met COMT polymorphism (Giakoumaki et al. 2008; Roussos et al. 2009) or its associated phenotypes (Talledo et al. 2009)). These drugs also enhance neurocognitive performance among individuals carrying certain genetic biomarkers or related phenotypes (Flemming et al. 1995; Giakoumaki et al. 2008; Roussos et al. 2009; Ersche et al. 2009). Certainly, there are rational arguments against the indiscriminate use of pro-catecholaminergic drugs in schizophrenia, and some drugs (e.g. tolcapone (cf. Haasio 2010)) carry other medical contraindications. However, DA agonists have been used safely in schizophrenia for many years (e.g. Benkert et al. 1995; Kasper et al. 1997); whether there is a role for some of these agents in biomarker-identified subpopulations, in time-limited combinations with CT and antipsychotic agents, remains an empirical question.

Can cognitive, behavioral and psychosocial interventions prevent schizophrenia (e.g. Morrison et al. 2004)? A society that would balk at the widespread use of drugs or vaccines in children to prevent a small percentage from developing schizophrenia, might embrace the notion of providing evidence-based educational and social enrichment to children with special needs. Paradigms might be identified that activate components of developing CSPT circuitry in a manner that protects these developing circuits. Presumably, activity within developing synaptic arrays - stimulated or sustained endogenously by self-initiated, contextually appropriate effects of cognitive, behavioral or social interventions - would better approximate normal physiological properties, compared to those stimulated by the passive administration of medications. Tasks with high prefrontal demands, for example, might be part of a special educational regimen for high-risk children who have a particular neurocognitive or genetic profile. Therapies that engender appropriate trust, and nurture areas of identified cognitive or emotional strengths (and their underlying limbic and frontal substrates), might be protective against pathological processes that would otherwise later lead to paranoia and social isolation. The development and implementation of such tasks might parallel successful programs used in early childhood development (Anderson et al. 2003) and pediatric brain injury (Ylvisaker et al. 2005; Kirton et al. 2007; Johnston et al. 2009), and draw from substantial preclinical and clinical data supporting the benefits of environmental enrichment on neural development, cognitive function (Hack et al. 1995; Diamond et al. 1976; Briones et al. 2009; Sweatt 2009) and the creation of a protective “cognitive reserve” (Mandolesi et al. 2008; Dhanushkodi and Shetty 2008).

Implications, beyond treatment

There are broader implications to the awareness that the schizophrenias result from widely distributed and complex neural disturbances that arise early in life and reflect multiple and variable neurodevelopmental and genetic events. While we cannot predict how future findings might cause a “paradigm shift” in the treatment of schizophrenia, in my opinion *we can neither afford nor justify a single-minded pursuit of the molecular bases of a disorder for which such information will not (in the foreseeable future) lead to practical clinical interventions.* Certainly, the molecular genetics of complex psychiatric disorders has evolved rapidly over the past 10 years: each year it seems that we are learning that what we knew last year was wrong. An optimist views this as progress, but resources for studying schizophrenia are finite and non-renewable, both in terms of research funding and its impact on the critical mass of focused intellect required to solve complicated problems. Clearly, research in pursuit of the basic brain mechanisms underlying schizophrenia must proceed, but perhaps it is time to reassess the balance struck between basic vs. applied research in our field. In the narrow pursuit of scientific knowledge about processes that common sense suggests will not soon provide therapeutic targets, we are risking - on a societal scale - the surgeon’s lament: “the operation was a success; the patient died.” In my opinion, we will best serve our patients and their families by using the substantial knowledge gained about schizophrenia as an impetus to refocus our field away from interventional models that no longer make sense, and towards the use of evidence-based psychotherapies and medications in ways that are both biologically informed and clinically rational.

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Clinical (and Research) Strategy for Drug-Enhanced CT in Schizophrenia

Figure 1.

Schematic overview of one proposed clinical strategy for identifying drug candidates for enhancing the effectiveness of CT in schizophrenia (parallel research activities are shown in parentheses). As discussed in the text, biomarkers are identified in a patient that predict an increased sensitivity to the ability of a drug to augment a CSPT-regulated laboratory measure that is: 1) deficient in schizophrenia, and 2) associated with neurocognitive processes that might enhance CT. This biomarker profile would inform the choice of drug and predictive measure; for example, high levels of DRD3 expression are associated with WM-enhancing effects of the D3 agonist, pramipexole (Ersche et al. 2011), while individuals carrying the Val/Val alleles of the Val158Met COMT polymorphism exhibit greater sensitivity to the ability of tolcapone (Roussos et al. 2009) to enhance sensorimotor gating, and individuals with low basal levels of PPI are most sensitive to the PPI-enhancing effects of memantine (Swerdlow et al. 2009b). A patient would then be tested in a within-subject “challenge dose” design (placebo vs. active dose), and findings of drug-enhanced performance in one or more predictive measure would suggest that the requisite neural circuitry for such an effect is “spared” and could be drug-activated in the service of CT. The patient might then be entered in a structured CT program (e.g. for 12 weeks), with daily drug augmentation. Conceivably, some forms of CT might benefit most from enhanced performance in specific neurocognitive or neurophysiological processes, and might be matched according to such drug effects identified in any given patient. Parallel translational research activities might identify the neural mechanisms for drug effects on specific neurophysiological processes; large, prospective trials would identify strongest biomarker- and laboratory measure-predictors of positive drug effects on specific forms of CT.

Table 1

Brain regions with reported neuropathological- or neuroimaging-based abnormalities in schizophrenia patients and **their asymptomatic relatives (in bold)** and representative citations (including meta-analyses)

Region ¹	Examples (not complete list) of Citations
Prefrontal cortex	Akil et al. 1999, Beasley et al. 1997, Beasley & Reynolds 1997, Benes et al. 1991, Cruz et al. 2009, Glantz & Lewis 2000, Jung et al. 2009 , Rosso et al. 2010, Zhou et al. 2005
Anterior cingulate cortex	Benes et al. 1991, Calabrese et al. 2008 , Koo et al. 2008, Ellison-Wright et al. 2008, Jung et al. 2009
Hippocampus	Benes et al. 1999, Bogerts et al. 1990, Boos et al. 2007 , Conrad et al. 1991, Gruber et al. 2008 , Hall et al. 2008, Heckers et al. 1998, Ho & Magnotta 2010 , van Erp et al. 2004, Velakoulis et al. 2001, Wang et al. 2008, Weiss et al. 2005
Entorhinal cortex	Joyal et al. 2002, Jakob & Beckmann 1986
Parahippocampal gyrus	Jakob & Beckmann 1986, Jung et al. 2009 , Prasad et al. 2004, Seidman et al. 2003
Superior temporal gyrus	Jung et al. 2009 , Matsumoto et al. 2001
Insula	Jakob & Beckmann 1986, Ellison-Wright et al. 2008,
Amygdala	Bhojraj et al. 2011 , Joyal et al. 2003, Ellison-Wright et al. 2008, Suzuki et al. 2005
Superior frontal gyrus	
Inferior frontal gyrus	Bhojraj et al. 2011 , Yamasue et al. 2004
Orbitofrontal gyrus	Bhojraj et al. 2011 , Nakamura et al. 2008,
Angular and supramarginal gyrus	Bhojraj et al. 2011
Inferior parietal cortex	Jung et al. 2009
Planum temporale	Kasai et al. 2003b
Superior temporal gyrus	Anderson et al. 2002
Transverse temporal gyrus	Takahashi et al. 2006a
Middle temporal gyrus	Kuroki et al. 2006b
Inferior temporal gyrus	Onitsuka et al. 2004
Occipitotemporal gyrus	Takahashi et al. 2006b
Auditory cortex/auditory association area	Bhojraj et al. 2010 , Sweet et al. 2007, Sweet et al. 2009
Caudate nucleus	Mamah et al. 2008 , Qui et al. 2009, Wang et al. 2008
Putamen	Mamah et al. 2008 , Menon et al. 2001, Qiu et al. 2009
Nucleus accumbens	Aparacio-Legarza et al. 1997, Pakkenberg 1990, Qiu et al. 2009 , Wang et al. 2008
Globus pallidus (incl. internal pallidum)	Bogerts et al. 1985, Early et al. 1987, Mamah et al. 2008 , Menon et al. 2001,
Thalamus	cf. Cronenwett et al. 2010; Davidsson et al. 1999, Ellison-Wright et al. 2008, Harms et al. 2007 , Menon et al. 2001, Pakkenberg 1990, Wang et al. 2008
Cerebellum	Borgwardt et al. 2010, Katsatos et al. 1997, Liu et al. 2009

Region as identified in the corresponding citation(s)

Table 2

Examples of drugs that enhance prepulse inhibition of startle and effects on other CT-relevant measures in healthy individuals

Drug (dose p.o.)	PPI paradigm/parameters	Reported effects on other relevant measures	Potential predictors
<i>Atypical antipsychotics:</i>			
clozapine (30 mg) ¹	60–120 ms INT	impaired CANTAB pattern recognition and attentional tasks	Low basal PPI *
quetiapine (12.5 mg) ²	20–30 ms INT	increased "drowsiness"	Low basal PPI * High novelty seeking (NS) men
<i>Low potency NMDA antagonists:</i>			
memantine (20 mg) ³	120 ms INT	enhanced mismatch negativity& MATRICS WM performance	Low basal PPI * High NS, SSS, DIS men
amantadine (200 mg) ⁴	20 ms INT; 120 ms INT if attentional component is used	enhanced measures of executive function in traumatic brain injury patients	
<i>Pro-catecholamine agents:</i>			
tolcapone (200 mg) ⁵	30–120 ms INT	enhanced WM performance in "Val/Val" subjects	Low basal PPI * Val/Val alleles of COMT Val158Met polymorphism
amphetamine (20 mg) ⁶	10–120 ms INT	enhanced verbal memory in "low NS" subjects	Low basal PPI * Low NS *, SSS women
pramipexole (0.125–0.1875 mg) ⁷	120 ms INT	enhanced CANTAB spatial WM in subjects with high blood DRD3 mRNA expression	

Abbreviations: CANTAB: Cambridge Neuropsychological Test Automated Battery; DIS: Disinhibition subscale of the Sensation Seeking Scale (SSS); INT: prepulse interval; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

References:

- ¹ Vollenweider et al. 2006;
- ² Swerdlow et al. 2006b;
- ³ PPI: Swerdlow et al. 2009; MMN: Korostenkaja et al. 2007; WM: Swerdlow et al. 2010;
- ⁴ PPI: Swerdlow et al. 2002;
- ⁵ Giakoumaki et al. 2008; Roussos et al. 2009;
- ⁶ PPI: Talledo et al. 2009; verbal memory: Flemming et al. 1995;
- ⁷ PPI: Swerdlow et al. 2009; WM: Ersche et al. 2011;

* Association of Val158Met COMT polymorphism with low basal PPI (Roussos et al. 2008; Giakoumaki et al. 2008; Quednow et al. 2010) and NS (Golimbet et al. 2007)