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Towards Medication-Enhancement of Cognitive Interventions in Schizophrenia

Hsun-Hua Chou, **Elizabeth Twamley**, and **Neal R. Swerdlow**
Department of Psychiatry, School of Medicine, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0804, USA

Neal R. Swerdlow: nswerdlow@ucsd.edu

Abstract

Current antipsychotic medications do little to improve real-life function in most schizophrenia patients. A dispassionate view of the dispersed and variable neuropathology of schizophrenia strongly suggests that it is not currently, and may never be, correctable with drugs. In contrast, several forms of cognitive therapy have been demonstrated to have modest but lasting positive effects on cognition, symptoms, and functional outcomes in schizophrenia patients. To date, attempts to improve clinical outcomes in schizophrenia by adding pro-cognitive drugs to antipsychotic regimens have had limited success, but we propose that a more promising strategy would be to pair drugs that enhance specific neurocognitive functions with cognitive therapies that challenge and reinforce those functions. By using medications that engage spared neural resources in the service of cognitive interventions, it might be possible to significantly enhance the efficacy of cognitive therapies. We review and suggest several laboratory measures that might detect potential pro-neurocognitive effects of drugs in individual patients, using a “test dose” design, aided by specific biomarkers predicting an individual’s drug sensitivity. Lastly, we argue that drug classes viewed as “counter-intuitive” based on existing models for the pathophysiology of schizophrenia—including pro-catecholaminergic and NMDA-antagonistic drugs—might be important candidate “pro-cognitive therapy” drugs.

Keywords

Antipsychotics; Cognitive training; Cognitive therapy; Cognitive remediation; Neurocognition; Schizophrenia

1 Introduction

Schizophrenia (SZ) is a severe brain disorder affecting 1% of the world population. Its cost to society in terms of health care demands and lost productivity is well documented (Rice 2009), as are the personal stories of lifelong anguish and suffering among SZ patients and their families. While both genetic and epigenetic factors are associated with a risk for developing this disorder (Dick et al. 2010), the etiology and pathophysiology of SZ remain incompletely understood. More than 50 years after the introduction of drugs that target its symptoms, the standard medications for SZ are at best modestly effective.

Pharmacotherapy of SZ is dominated by drugs that functionally reduce dopamine (DA) neurotransmission, and primarily target “positive” symptoms of this disorder (hallucinations

Correspondence to: Neal R. Swerdlow, nswerdlow@ucsd.edu.

and delusions). Although antipsychotics can blunt the most severe psychotic symptoms, they do not have a meaningful impact on the course of SZ or on real-life function (Leucht et al. 2009; Lieberman et al. 2005). It is clear that cognitive deficits are major factors in the functional disability of SZ patients (Keefe and Harvey 2012). At a time when treatments based on old paradigms have resulted in only modest gains in the function and wellbeing of SZ patients, we must look for new approaches to make substantial improvements in patients' lives.

In contrast to antipsychotic drugs—which are primarily developed to overcome pathologically elevated levels of dopaminergic neurotransmission in SZ—several forms of cognitive therapies (CTs; broadly including cognitive-behavioral and cognitive remediation or training) may both reduce symptoms and improve function in schizophrenia *by engaging healthy neural systems to learn adaptive cognitive and behavioral strategies* (Demily and Franck 2008; Klingberg et al. 2009; McGurk et al. 2007a; Medalia and Choi 2009; Tai and Turkington 2009). A number of meta-analyses document clear safety, feasibility, acceptance, and efficacy of cognitive interventions in SZ, with sustained benefits in many cases lasting years (Eack et al. 2009; Granholm et al. 2007; McGurk et al. 2009; Sellwood et al. 2007). Response predictors are being identified (Brabban et al. 2009; Kumari et al. 2009; Kurtz et al. 2009); treatments that target specific functional outcomes measures [e.g., vocation (McGurk et al. 2007a)] and specific symptoms [e.g., hallucinations (Penn et al. 2009)] are also being developed. Despite findings from several meta-analyses (e.g., Wykes et al. 2011), some individual studies have failed to detect significant benefits of CTs in SZ patients (e.g., Lynch et al. 2010), suggesting that important determinants of study outcome (e.g., patient characteristics, study design, forms of CT being used) may not yet be fully understood.

Although the neurobiological basis for therapeutic effects of CTs in SZ is not fully known, 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 resulting in an additive effect. Such a use of medications would depart substantially from the traditional approach to pharmacotherapy for SZ. However, This does not discount the importance of controlling psychosis: most psychotherapeutic interventions are complicated by severe psychiatric symptoms, and it is clear that controlling psychosis should benefit ongoing cognitive interventions in SZ. Compared to antipsychotic medications, drugs with pro-cognitive effects might more directly, and perhaps synergistically, enhance the clinical benefits of specific "learning therapies." For example, drugs that enhance specific components of neurocognition, e.g., attention, might be predicted to yield clinical benefits in SZ when paired with interventions that access those components by placing demands on enhanced attention.

2 Distributed Neuropathology of SZ and Failures of the Simple "Medication Model"

Some prevailing models for the pharmacotherapy of SZ have been based on the misconception that this disorder reflects pathology that is restricted in scope, both in terms of the neurotransmitters that are dysregulated (e.g., dopamine, glutamate) and the brain region(s)—and neuronal element(s) within those regions—that are abnormal. It is now clear—as briefly reviewed below—that 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 dispersed aberrant connections in schizophrenia seems unlikely.

Evidence for distributed neural dysfunction in SZ 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 [cf. Brown and Thompson 2010; Dolan et al. 1995; Heckers et al. 1998; Heckers and Konradi 2010; Kumari et al. 2003; Silbersweig et al. 1995; Volz et al. 1999)]. Findings document significant volumetric and/or morphometric abnormalities in over 20 brain regions in SZ patients (cf. Levitt et al. 2010; Swerdlow 2011). 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; Akil et al. 1999; Aparacio-Legarza et al. 1997; Cruz et al. 2009; Dean et al. 2009; Gur et al. 2007; Howes et al. 2009; Kessler et al. 2001, 2009; Laruelle 1998; Lee and Seeman 1980; Lewis et al. 2008; Roberts et al. 2009; Urban and Abi-Dargham 2010; Volk and Lewis 2010; Wong et al. 1986).

For several reasons, we can be confident that the neural disturbances in many SZ patients impact brain circuitry extending well beyond the neural disturbances listed in published reports from large samples of patients. First, studies of the neural circuit disturbances in SZ have been circumscribed in their targets, but findings of cortical abnormalities that extend 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; Kvajo et al. 2010). Such a "cascade" of disturbances will inevitably intersect in time and space with a wide range of neurobiological processes. 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 postmortem 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 SZ, 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 versus controls, any given patient might exhibit some but not all of the regional abnormalities. And with any given cortico-striato-pallido-thalamic locus, reduced volumes in two different patients might reflect disturbances in different cell populations, resulting in different patterns of abnormal efferent projections and innervation.

Perhaps most important, as it relates to therapeutic approaches to this disorder, is the fact that neuropathology in SZ evolves across early life, and likely reflects failures of early cell development and migration. These early developmental failures disrupt the tightly choreographed processes that lead to the proper population of forebrain nuclei, and formation of the synaptic connectivity both within [e.g., prefrontal laminar connectivity (Volk and Lewis 2010)] and between [e.g., hippocampal-frontal synchronization (Heckers and Konradi 2010)] these regions. By the time that SZ symptoms emerge, treatment that merely antagonizes or augments receptors at the molecular level cannot reasonably be expected to normalize function within the proper connections that did not form, nor the improper ones that did, across 20 different brain regions and their substantially larger "fall-out field."

3 Cognitive Therapies for Schizophrenia

While it is not classically viewed as a "biological" intervention, it is now clear that psychotherapy (particularly cognitive and behavioral therapy) changes the brain (Baxter et al. 1992; Saxena et al. 2009; Schwartz et al. 1996). *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; Keller and Just 2009; Korosi and Baram 2009; Porto et al. 2009; Saxena et al. 2009).

While some forms of psychotherapy are considered to be suboptimal, and even potentially harmful for patients with psychotic disorders—e.g., psychoanalytic or other "regressive" forms of psychotherapy—a variety of therapies based on cognitive constructs and behavioral theories have been found to be helpful for SZ patients. Most frequently studied and commonly cited is Cognitive Behavioral Therapy (CBT), a manualized therapy in which maladaptive thoughts and beliefs (cognitions) that affect the patient's function are identified and explored with the patient to examine how they affect the patient's interpretations of their experiences and the resulting behaviors; behavioral techniques are then applied to help modify maladaptive patterns. Other evidence-based psychosocial treatments for SZ patients include social skills training (SST) and supported employment (SE), which target the psychosocial deficits and occupational impairments commonly found in patients in order to help them reach their functional goals. SST teaches skills to help patients communicate with others and understand both verbal and nonverbal cues; these classes provide a setting for patients to discuss challenges they encounter and to practice their newly learned skills. SE interventions take an individualized approach to teaching the skills a client needs to get and keep competitive work in the community. While the types of cognitive processes and "learning" engaged varies widely across these different forms of therapy, they each have both primary and secondary consequences on brain function, i.e., the neurobiological changes produced by the therapy-specific learning, and those resulting from the positive social and functional consequences that are based on the learned adaptive behaviors.

As cognitive deficits in SZ patients have been found to reduce response to psychosocial rehabilitation (McGurk and Mueser 2004; Mueser et al. 1991; Wykes et al. 1990), and to impact functional outcome far more than the more prominent positive symptoms of hallucinations and delusions (Green et al. 2000), the development of strategies and programs to improve cognitive functioning has been a focus in SZ therapies. Cognitive interventions use repeated drills, compensatory strategies, or a blend of both approaches, to help patients with basic neurocognitive processes such as attention, information processing, problem solving, decision-making, and memory. Cognitive training differs from CBT interventions in both focus and methodology. While CBT targets the form and content of thought, such as attributional style and core beliefs, cognitive training targets the neurocognitive processes

that underlie thought. Notably, although many studies have shown effectiveness of CBT in schizophrenia, some studies have shown that, when compared to some other control interventions, CBT was not necessarily better at reducing symptoms or preventing relapse (e.g., Lynch et al. 2010). Given that 70–80% of SZ patients are 1–2 standard deviations below normal populations in relevant neurocognitive measures (Heinrichs and Zakzanis 1998; Reichenberg and Harvey 2007) and that cognitive deficits correlate highly with life functioning and ability to meet functional goals (Green et al. 2004), the premise of cognitive training is that when cognitive function improves, these gains will generalize to functioning in the community. Indeed, substantial evidence indicates that cognitive training reduces symptoms and improves functioning in SZ patients (Klingberg et al. 2009; Kurtz et al. 2001; McGurk et al. 2007b; Medalia and Choi 2009; Wykes et al. 2011) with sustained benefits often lasting years (Eack et al. 2009; Granholm et al. 2007; McGurk et al. 2007a; Sellwood et al. 2007).

Also referred to as cognitive remediation or cognitive rehabilitation, cognitive training derives much of its background from the rehabilitation of brain injury patients (Twamley et al. 2008b). While the approach can be classified into three strategies—compensatory (strategies to work around deficits) versus restorative (correcting the deficits) versus environmental (modifying environment to accommodate deficits)—most cognitive training programs integrate the three approaches into various programs. In fact, which of the three approaches is most beneficial depends on each individual circumstance, and hence, there is significant range in cognitive training approaches. Some programs utilize a primarily restorative approach, which attempts to “repair” impairments by drill and practice exercises. These can be executed using paper–pencil worksheets, computer programs, or therapist-based interactions. Other programs use a compensatory approach that attempts to circumvent deficits by relying on other skills or environmental modifications. These programs tend to use a strategies-teaching approach, conveyed either by individual didactics or group discussions, followed by practice of strategies and planning for implementation in the community (McGurk et al. 2007a; Twamley et al. 2008b).

Even within a specific modality, such as the use of computer programs for restorative training, there is variation in the particular skills developed (e.g., memory vs. attention vs. other cognitive skills), the number of skills targeted simultaneously, the methods of developing the skill, how contextualized the exercises are (e.g., a dot in the center of the screen vs. a dot representing an oncoming train), the degree of engagement, interest and motivation incorporated in the practicing, the level of difficulty, and immediacy of feedback, as well as the type of feedback (Medalia and Choi 2009). Programs can be provided one-on-one or in groups; some regimens are manualized and allow more measured learning, while others utilize personalized and tailored curricula that allow for more flexibility. Some programs are centralized: patients come to the institution for training; others offer separate or integrated psychosocial programs to help transfer and generalize the acquired skills to real-life functioning, and still others use “coaches,” who help organize living and work environments, and help patients apply the newly acquired skills to particular situations. The duration of programs can range from several weeks to 2 years (most last about 3–6 months), with most requiring from 1 to 4 hr sessions per week (Medalia and Choi 2009).

Despite early studies suggesting no clear evidence for the effect of social skills training and cognitive remediation (Pilling et al. 2002), recent studies show the effectiveness of cognitive training for both measures of cognitive test performance and real life functioning. Six meta-analytic studies showed effect sizes (d) ranging from 0.2 to 1.2, with greatest improvement in neuropsychological measures, followed by psychosocial functioning, and lastly symptom reduction (Medalia and Choi 2009). A meta-analysis of 40 randomized, controlled trials of 2,104 patients (Wykes et al. 2011) showed a medium effect size (0.5) for cognitive

performance as measured by standardized cognitive tasks and a medium effect size (0.42) for psychosocial functioning as measured by the ability to obtain and work competitive jobs, quality of and satisfaction with interpersonal relationships, and ability to solve interpersonal problems. Effect sizes for cognition and functioning were maintained at follow-up. Notably, the effects on the more generalized psychosocial functioning were stronger in studies that provided adjunctive psychosocial rehabilitation as part of the program and when compensatory strategy training was provided in the context of psychosocial rehabilitation. For symptoms, a small effect size (0.18) was found, perhaps reflecting, in part, the positive training experiences that improved self-esteem, thereby improving mood. Notably, in all studies, there is variability in effectiveness in various domains, and the difficulty of knowing which therapeutic approach will work for which patient likely reflects the heterogeneity of the disorder.

Given the potential for cognitive training to improve real life functioning, efforts are underway to identify response predictors. While factors such as instructional technique, patient's motivation, and the control of psychiatric symptoms including psychosis and mood changes are key to effective cognitive training, neurocognitive abilities also significantly impact outcome. The type and extent of neurocognitive impairment has been found to consistently affect the therapeutic impact of cognitive training (Fiszdon et al. 2006). Delayed verbal memory impairs training (Medalia and Richardson 2005), while sustained attention, working memory, and verbal learning are also important determinants of outcome, even in the context of crystallized verbal intelligence (Fiszdon et al. 2005; Kurtz et al. 2008, 2009). However, Twamley et al. (2011) found that in a compensatory cognitive training intervention, lower baseline cognitive and functional abilities predicted greater improvement, possibly because lower functioning participants had more room to improve or because those with higher abilities had a narrower scope of dysfunction and the intervention did not match their needs. For example, improvement in attention (forward digit span) at post-treatment was associated with lower baseline attention ($r = -0.73$, $p < 0.001$, $n = 20$), and improvement in functional capacity (UPSA) at follow-up was associated with lower functional capacity scores at baseline ($r = -0.56$, $p = 0.007$, $n = 22$). It is thus rational to consider whether medications that enhance these basic neurocognitive functions in patients with SZ might increase the therapeutic impact of cognitive training or other cognitive therapies. By bolstering a patient's abilities to engage spared neural substrates for memory, attention, learning, etc., these medications would maximize their ability to meet the demands of a variety of cognitive interventions.

4 Pro-Cognitive Agents in the Treatment of SZ: The Bad News and the Good News

The concerted effort by our field to develop and apply pro-cognitive agents in SZ, however, has not been based on their potential ability to enhance the therapeutic impact of cognitive interventions. Thus far, most of these efforts have used a "stand-alone" drug strategy similar to that used to justify standard antipsychotic therapy: if we can make a pill that normalizes a neurochemical abnormality in an adult SZ patient, it should help normalize their neurocognitive function, and this should automatically translate into improved life function. For example, based on emerging models for NMDA receptor hypofunction in SZ, a number of putative pro-cognitive agents have been tested that directly or indirectly enhance forebrain glutamate neurotransmission. To date, however, trials of potential pro-cognitive glutamatergic agents in SZ have largely yielded negative results (Barch 2010; Buchanan et al. 2007; Goff et al. 1996, 1999, 2007, 2008; Green 2007). A large, multicenter study of the glycine-site agonist, D-cycloserine (DCS) showed no benefit on negative symptoms or cognition in SZ (Buchanan et al. 2007). A small study reported in 2007 with the mGluR2/3 agonist, LY2140023, suggested some modest clinical benefit (Patil et al. 2007) that has yet

to be reproduced in larger samples. Studies are in progress with a number of compounds, including glycine transport inhibitors and nicotinic agonists, but preliminary findings reported as Conference Proceedings suggest minimal, if any benefit from these agents (e.g., Marder and Buchanan 2009).

In fact, in their comprehensive review of clinical trials of putative pro-cognitive agents in SZ, Barch (2010) concluded that well-controlled, double-blind studies have, to date, failed to yield any particularly encouraging results; and Keefe noted that the majority of completed trials thus far were underpowered and short in duration, but that ongoing trials have larger samples sizes and longer durations, and may provide insight into the subject characteristics that have greatest potential for cognition enhancing drugs (Keefe et al. 2011a). Clearly, the use of cognition enhancing medications in SZ requires further studies with validated measures to illuminate how these medications can be used to improve function in SZ patients. Interestingly, some single-dose studies with nicotine and amphetamine have demonstrated enhanced performance on specific neurocognitive measures in SZ patients, but it is not known whether these changes are “of a clinically significant magnitude.” It is important to recognize, however, that of the many (>100) trials of potential pro-cognitive agents in SZ—almost all yielding negative or inconclusive results—until very recently, none were conducted within the context of systematic cognitive interventions (Barch 2010; Buchanan et al. 2007; Goff et al. 1996, 1999, 2007, 2008; cf. Green 2007). In fact, given the prevailing state of outpatient care for SZ patients, it is likely that—absent specific experimental designs to do otherwise—*most SZ patients in trials of putative pro-cognitive agents took these medications within an environment relatively void of constructive cognitive challenges.* It is not surprising that little benefit was gleaned from pro-cognitive agents among patients whose daily activities are often dominated by social isolation, and at best passive cognitive engagement by television and sedentary “board and care” surroundings: *drugs designed to enhance specific components of neurocognition might not be beneficial unless paired with interventions that access, utilize, and place demands on those components*. Without a structure for acquiring reparative or compensatory thoughts or behaviors, any gains in neurocognitive capacity would be wasted. Analogous reasoning underlies the use of anabolic steroids to promote exercise-increased muscle mass, and perhaps more importantly (as discussed below), the use of pro-extinction drugs to enhance therapeutic benefits of CBT for anxiety disorders (Ressler et al. 2004). By adding pro-cognitive drugs that engage spared neural resources and enhance specific neurocognitive functions to CT regimens, it might be possible to significantly enhance the efficacy of the CTs.

Had these studies been designed differently, how might pro-cognitive medications have enhanced the therapeutic impact of an ongoing cognitive intervention in SZ? Let’s pick a specific form of cognitive training to provide a concrete example. As reviewed earlier, compensatory cognitive training is a cognitive intervention that encourages patients to develop compensatory strategies—both internal (e.g., acronyms or visual imagery) and external (e.g., writing information down to remember it later)—for learning and remembering information. In so doing, it specifically activates prefrontal regions subserving working memory and attention (Haut et al. 2010). One form of cognitive training includes four modules (Twamley et al. 2008a, b), addressing: (1) prospective memory (i.e., remembering to do things in the future); (2) conversational and task vigilance; (3) learning and memory; and (4) cognitive flexibility and problem-solving (i.e., executive functioning). Drugs that enhance working memory, attention and vigilance, cognitive flexibility, and problem-solving will enhance a SZ patient’s ability to develop and utilize new strategies for learning and remembering; this should then translate to improved function in addressing the demands of daily life.

In truth, most studies of CT effects in SZ patients have been conducted using CT as an "add-on" to "standard" medication therapy; as a result, the beneficial effects of CTs reported in many studies (e.g., Grant et al. 2012) may have reflected, indirectly or directly, the positive impact of antipsychotics on CT. Though the pseudospecificity of the results is difficult to tease out, as in the case of Grant et al. (2012), the antipsychotic class or dose has not been determined to significantly impact the benefits of CT. It seems highly likely that the control of overt psychotic symptoms with antipsychotic medication will, for the foreseeable future, be a prerequisite for any effective cognitive intervention; this issue is orthogonal to the question of whether pro-neurocognitive agents can directly enhance the benefits of CTs.

One recent report did pair a putative pro-cognitive agent with a cognitive intervention—in this case, CBT for delusions—to examine their potential synergistic effects in SZ patients. In this case (Gottlieb et al. 2011), D-cycloserine (DCS) was selected both based on its potential ability to compensate for a proposed NMDA receptor hypofunction in SZ, and because DCS has been reported to facilitate extinction (Davis et al. 2006), and to enhance memory consolidation in SZ patients after a single dose (Goff et al. 2008). DCS also has complexities related to its propensity to produce rapid tolerance (Parnas et al. 2005; Quartermain et al. 1994), though once-weekly dosing for 8 weeks has been reported to reduce negative symptoms in SZ patients (Goff et al. 2008). In their study, Gottlieb et al. examined the effects of DCS (placebo or 50 mg) on the ability of two CBT sessions to reduce the intensity of delusions in 20 SZ patients; in this design, the active drug (DCS 50 mg) was administered prior to only one training session. The findings of this small study were complex—there was no overall effect of DCS on the beneficial effects of CBT for delusions, but a potential order effect with some DCS benefits among subjects receiving DCS before placebo (Gottlieb et al. 2011). Conceivably, a larger study, or one designed differently, might have detected more robust effects of DCS. One might also question whether the choice of DCS based on its neurochemical properties (to compensate for NMDA hypofunction) or primary neurocognitive effects (enhancing fear extinction) makes sense, in the search for a drug to enhance CBT effects in SZ. Conceivably, pro-extinction agents might be useful for reducing the perceived "threat" posed by a specific paranoid object, but it is not clear that such extinction would impact an underlying frontal dysfunction that is manifested more generally in a propensity for developing fixed, irrational beliefs.

5 Medication-Enhancement of Therapeutic Learning and Neurocognition: "Proof of Concept"

Cognitive deficits predict poor outcomes in a number of cognitive and vocationally oriented therapies (Becker et al. 1998; Green 1996; McGurk and Meltzer 2000; McGurk and Mueser 2004), and it thus seems parsimonious to suggest that patients will benefit the most if they are able to meet the cognitive demands of CTs. It would then follow that interventions that enhance a patient's cognitive abilities should enable them to glean the most clinical benefit from CT. While there is ample experience from everyday clinical practice to support the notion that psychotherapeutic agents that reduce cognitively impairing symptoms—e.g., severe depression, anxiety, or psychosis—can enhance the benefits of psychotherapies, there has not yet been a robust "test" of whether drugs that specifically enhance neurocognition can enhance the benefits of CT in SZ patients.

Perhaps the closest "proof of concept" comes again from the use of DCS for its pro-extinction properties, but in this example, it was not used to help "extinguish" psychotic thinking, but rather to facilitate extinction of a specific phobia (Ressler et al. 2004). In this study, acrophobic subjects were treated with two brief virtual reality-based exposure sessions, separated by 1–2 weeks. Prior to each session, subjects took one pill of either placebo ($n = 10$), 50 mg DCS ($n = 8$), or 500 mg DCS ($n = 9$). When tested 1–2 weeks or 3

months later, height-related distress—both experimental and "real-world"—was significantly reduced in both active dose groups compared to the placebo group. Importantly, the ability of DCS to enhance the effects of CT on acrophobia was not thought to reflect a hypoglutamatergic basis of acrophobia, or even an "extinction deficit" in acrophobia. Rather, they were attributed to the ability of DCS to enhance the function of intact, healthy "extinction circuitry" in acrophobics, which is specifically "exercised" by a symptom-directed cognitive intervention. *By combining a drug that enhances a specific cognitive process with a therapy that demands that process, patients were able to benefit more from that therapy.* Certainly, we cannot assume that SZ patients will benefit from a therapeutic algorithm that reduced agoraphobia, or even that the type of "learning" enhanced by DCS in reducing height-related distress is relevant to the type of "learning" engaged during CT in SZ patients. Nonetheless, the findings of Ressler et al. (2004) support the concept that *drugs that enhance a specific neurocognitive process can enhance the benefits of a psychotherapeutic intervention that places demands on that process.*

6 Predicting Medication Effects on Neurocognitive Function in Individual Patients

It is apparent that many different forms of cognitive interventions might be useful in treating individuals with SZ, and that each of these different forms of therapy likely places "demands" on different neurocognitive and psychological processes. Furthermore, we can anticipate that the mechanisms of action will differ substantially across many different putative "pro-CT" agents. Because of the time and resources required to complete a full program of CT, it will be particularly valuable to be able to predict which patients will benefit most from which therapy, and which pro-CT medication. It is thus worth considering how one might make such predictions.

At a neurobiological level, the model for the efficacy of cognitive interventions in SZ comes primarily from its 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 circuit elements (cf. Taub et al. 2002). In fact, schizophrenia patients with the largest "reserve" of cortical function—particularly temporal lobe—are most likely to benefit from CT (Keshavan et al. 2011). An implication of the variability in neuroimaging and neuropathological findings in schizophrenia is that in many patients, portions of the cortico-striato-pallido-thalamic circuitry may remain relatively intact. The model proposed herein suggests that medications that enhance specific cognitive functions (e.g., attention, memory, reasoning, or processing speed) by acting on remaining healthy brain circuits (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 (Fig. 1).

One key step in predicting whether a patient might benefit from a particular "pro-CT" agent would be to identify evidence for medication-responsive, healthy or "spared" brain circuitry within any individual or biomarker-identified subgroup of SZ patients. Towards this end, specific neurophysiological, psychophysiological, or neurocognitive changes in response to a drug challenge may provide indication that "spared" healthy neural circuitry exists and can be a target for medication-enhanced CT. There is both a theoretical and an empirical basis for making such a prediction. Theoretically, if specific laboratory measures are regulated by elements of the cortico-striato-pallido-thalamic circuitry that also regulates neurocognitive functions important for CT, then drug-induced enhancement of laboratory-based performance would be expected to translate into a real-world enhancement of CT. In fact, independent of their specific neural substrates, if laboratory measures index basic

psychological functions of value to CT—e.g., attention, vigilance, sensorimotor gating, etc.—one might expect that drug-enhanced laboratory performance might predict pro-CT effects of these drugs. 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 many factors, including the propensity for tolerance, a potential negative impact on other cognitive processes (e.g., impulsivity), symptoms, or other forms of toxicity.

There is also empirical support that greater performance on specific laboratory-based measures should predict enhanced CT effects. For example, higher levels of mismatch negativity (MMN; discussed below) are associated with a positive therapeutic response to 12 weeks of social skills/cognitive rehabilitative therapy in SZ (Kawakubo et al. 2007). In many [but not all (e.g., Hasenkamp et al. 2011)] studies, higher levels of prepulse inhibition of startle (PPI; discussed below) are associated with higher performance on measures of executive functioning (Bitsios et al. 2006; Giakoumaki et al. 2006; Greenwood et al. 2012; Light et al. 2007a; van der Linden et al. 2006), which in turn predict greater benefit from some forms of CTs (Becker et al. 1998; Green 1996; McGurk and Meltzer 2000; McGurk and Mueser 2004). In fact, a recent study determined that pre-therapy levels of PPI were strongly correlated with symptomatic improvement after CBT in schizophrenia patients (Kumari et al. 2012). Thus, empirical evidence suggests an association between performance on specific laboratory measures, basic psychological processes of relevance to CTs, and clinical improvement resulting from CT in schizophrenia. There remains a conceptual gap, though we submit one well worth exploring: whether medications that increase an individual's performance on these laboratory measures or in the basic neurocognitive processes of relevance to CTs, will improve that individual's ability to benefit clinically from CTs. Certainly, given the complex neural regulation of even simple laboratory measures, neurocognition, CTs and SZ, one would anticipate that studies not specifically designed to test these relationships would identify both false positive and negative outcomes. For example, PPI appears to be enhanced in SZ patients by atypical APs (e.g., Swerdlow et al. 2006a), which may—or may not—directly enhance the therapeutic effects of CTs (discussed above).

7 Biomarkers?

As with any therapeutic intervention in complex disorders, it will be very important to identify biomarkers that predict an increased sensitivity to the ability of a drug to enhance CT. This biomarker profile might inform both the choice of drug and the predictive measure. For example, high levels of dopamine D_3 receptor expression are associated with working memory-enhancing effects of the D_3 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 carrying one or more of these predictive biomarkers could 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 a drug effect is "spared," and could be drug-activated in the service of CT. The patient might then be entered in a structured CT program with daily drug augmentation. While one might imagine reasons for continuing such "pro-CT" drugs beyond the course of the cognitive intervention, it is also conceivable that their therapeutic value would be maximized by administration concurrent with CT, and *thus the value of limited* versus *long-term dosing of such medications would need to be assessed empirically* (Fig. 2).

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; prospective trials would identify the strongest biomarker- and laboratory measure-predictors of positive drug effects on specific forms of CT.

An overview of several "candidate" laboratory measures for identifying potential "pro-CT" drugs is provided below. This overview is not meant to be comprehensive, and it is clear that many other measures might have predictive value for such drugs.

7.1 PPI

Prepulse inhibition of startle (PPI) might be a good neurophysiological "biomarker" for predicting positive drug effects on neurophysiological processes and the therapeutic impact of CT. PPI is regulated by the cortico-striato-pallido-thalamic circuitry (cf. Swerdlow et al. 2008), reduced in schizophrenia patients (Braff et al. 1978; Swerdlow et al. 2006a), correlated with CT-relevant executive functions including working memory, attention, strategy formation, execution times, and degree of mental fatigue (Bitsios et al. 2006; Giakoumaki et al. 2006; Light et al. 2007a; van der Linden et al. 2006) and sensitive to acute drug effects in a manner that might be useful for predicting individualized drug sensitivities in patients (e.g., Swerdlow et al. 2006b, 2009a, b; Talledo et al. 2009; Vollenweider et al. 2006). Also, as noted above, PPI levels prior to CBT correlate significantly with symptomatic improvement in SZ patients (Kumari et al. 2012); this finding suggests that it is rational to speculate that drugs that increase basal PPI levels might enhance CBT outcome in SZ.

In PPI, a weak lead stimulus (prepulse) inhibits the magnitude of a startle response to an intense, abrupt stimulus occurring 30–120 ms later. On average, the amount of reflex inhibition generated by the prepulse is diminished in SZ patients, as reported by more than a dozen independent research groups on 4 continents (cf. Braff et al. 1978; Grillon et al. 1992; Kumari et al. 1999; Kunugi et al. 2007; Quednow et al. 2010; Swerdlow et al. 2006a; Weike et al. 2000). This PPI deficit appears to be particularly marked among patients carrying the Val158Met polymorphism (homozygous Val/Val) conferring high activity of the enzyme, catechol-*O*-methyl transferase (COMT) (Quednow et al. 2010), suggesting that a Val/Val COMT genotype might be a useful biomarker predicting pro-CT effects for PPI-enhancing agents.

With only 10–120 ms separating the prepulse and startling stimulus in the "uninstructed" PPI paradigm, PPI is generally viewed as a measure of automatic, preattentional inhibition (Swerdlow 1996). Surprisingly, in several [but not all (e.g., Hasenkamp et al. 2011)] studies, the amount of this "automatic" inhibition correlates significantly with higher cognitive measures, including measures of working memory (Fig. 1) and strategy formation, as well as measures of cognitive efficiency (Bitsios et al. 2006; Giakoumaki et al. 2006; Light et al. 2007a; van der Linden et al. 2006). The PPI-enhancing effects of tolcapone among Val/Val healthy control subjects are accompanied by significant increases in n-back and letter–number sequencing performance (Giakoumaki et al. 2008). Perhaps most surprising is the finding that higher levels of PPI among SZ outpatients significantly predict higher global functioning (Swerdlow et al. 2006a), though we view this relationship as correlative and not causal (i.e., greater neural dysfunction is associated both with more global functional impairment, and with reduced PPI) (Fig. 3).

PPI is regulated in both laboratory animals and humans by neural circuits connecting portions of the prefrontal cortex and mesial temporal lobes, with subcortical systems

extending from the basal ganglia to the primary startle circuit in the pons (cf. Swerdlow et al. 2001). Drugs acting at prominent nodes in this circuitry, particularly via changes in DA, 5-HT, and NMDA neurotransmission, have very potent effects on PPI that have been studied extensively in rodents, and more recently in humans (cf. Swerdlow et al. 2008).

In healthy individuals under specific conditions, some drugs increase PPI; of these, clozapine (Vollenweider et al. 2006) and quetiapine (Swerdlow et al. 2006b) are atypical antipsychotics, which also increase PPI in SZ patients (Swerdlow et al. 2006a). Other PPI-increasing drugs come from drug classes not intuitively associated with SZ 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 SZ. For example, amantadine has both DA agonist and NMDA antagonist properties, and has been safely used in SZ patients for over four decades (Kelly and Abuzzahab 1971), despite prevailing hypotheses linking SZ to excessive DA activity and deficient NMDA activity. The inverse is also true: as noted above, atypical antipsychotics increase PPI in healthy subjects and SZ patients, yet it is not known whether these drugs contribute to the benefits of CTs, and if so, whether they do so via a specific effect on neurocognition versus a secondary result of reduced psychosis.

7.2 Electro-Encephalographic Measures

Two electro-encephalographic (EEG)-based neurophysiological phenotypes—mismatch negativity (MMN) and gamma band synchronization (GBS)—may also serve as "biomarkers" to predict sensitivity to pro-cognitive and therapeutic drug effects, and/or therapeutic response to CT in SZ patients.

MMN is an auditory ERP component elicited 50–150 ms after a sequence of repetitive standard sounds is interrupted infrequently by deviant, "oddball" stimuli. MMN is the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based comparison process (cf. Turetsky et al. 2007). It is rapidly assessed, impaired in SZ and highly stable; MMN deficits in SZ patients are of large effect size ($d > 1.0$), and after 1 year, MMN reliability coefficients (ICC's) in patients are ~0.90 (Light and Braff 2005a). While MMN is predominantly automatic and "preattentional," MMN is strongly associated with neurocognition and psychosocial functioning in healthy subjects (Light et al. 2007b) and SZ patients (Kawakubo et al. 2007; Kawakubo and Kasai 2006; Light and Braff 2005a, b; Wynn et al. 2010). MMN is regulated by forebrain circuitry, and may be particularly sensitive to NMDA activity: MMN is disrupted in nonhuman primates by phencyclidine, and in healthy subjects by ketamine, but existing evidence suggests that *MEM is associated with increased MMN* in healthy subjects (Korostenskaja et al. 2007). In turn, increased MMN is associated with a positive therapeutic response to 12 weeks of social skills/cognitive rehabilitative therapy in SZ (Kawakubo et al. 2007).

Synchronous neural oscillations (GBS) in the 30–80 Hz range (centered near 40 Hz) appear to reflect a fundamental brain resonance frequency that is critical for cortico-cortical communication and the large-scale integration of distributed neural functions (Uhlhaas and Singer 2006). EEG evidence demonstrates that the automatic entrainment ("synchronization") of gamma band oscillations to 40 Hz auditory stimuli is deficient and correlates with working memory in SZ patients (Light et al. 2006). Relatively little is known regarding the neural regulation of GBS; gamma frequency oscillations appear to be enhanced by ketamine in both mice (Lazarewicz et al. 2010) and healthy humans (Hong et al. 2010).

MMN and GBS are EEG-based measures of processes underlying automatic, preattentive information processing that are impaired in SZ, and associated with neurocognition in HCS (MMN) and SZ patients (MMN and GBS). There is evidence that NMDA regulates both MMN and GBS, that memantine increases MMN, and that greater MMN predicts a positive therapeutic response to cognitive rehabilitation in SZ.

7.3 MATRICS Consensus Cognitive Battery (MCCB)

With the recognition of cognitive deficits as a core feature of SZ and its major impact on function, an NIMH initiative brought together a group of experts from the Neurocognition Subcommittee for the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to identify the most important domains of cognitive deficits in SZ. Their consensus opinion was that working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition comprised the primary domains of cognitive deficits in SZ (Green et al. 2000).

The MATRICS Consensus Cognitive Battery was developed to evaluate these key cognitive domains relevant to SZ (Kern et al. 2008; Nuechterlein et al. 2008). It was designed as an outcome measure for clinical trials of cognition-enhancing drugs for SZ, an outcome measure for studies of cognitive remediation, a measure of cognitive change in repeated testing applications, and a cognitive reference point for nonintervention studies of SZ and related disorders, and is accepted by the FDA as a primary endpoint measure for clinical trials targeting cognition in schizophrenia.

The MCCB includes ten tests that assess seven cognitive domains: speed of processing, attention/vigilance, working memory (verbal and nonverbal), verbal learning, visual learning, reasoning and problem solving, and social cognition. In a variety of multi-site clinical trials, it has demonstrated sensitivity to cognitive deficits in all domains, excellent test–retest reliability and inter-site reliability, and is highly correlated with measures of functional capacity (Buchanan et al. 2011; Keefe et al. 2011b). The use of the MCCB as a validated measure for studies evaluating cognition-enhancing drugs is well underway and the use of this standardized measure will be critical for the comparison of results between studies evaluating the ability of a drug to enhance the therapeutic effects of CT.

8 Examples of Candidate “Pro-CT” Drugs

A variety of candidate pro-cognitive agents might warrant assessment for their ability to enhance the functional impact of cognitive interventions in SZ. Two classes of drugs will be discussed here as examples. Importantly, many other classes of compounds might certainly warrant investigation, but as reviewed by Barch (2010), compelling support for one drug class over another at this point is lacking.

8.1 Direct and Indirect Catecholaminergic Agents

Several direct and indirect catecholaminergic agonists enhance neurocognitive performance in clinically normal subjects. For example, methylphenidate (Clark et al. 1986; Elliott et al. 1997; Mehta et al. 2000), amphetamine (Mattay et al. 2000, 2003), bromocriptine (Kimberg et al. 1997; Luciana et al. 1992, 1998; Luciana and Collins 1997), and pergolide (Kimberg and D’Esposito 2003; Müller et al. 1998) enhance working memory in healthy subjects. Perhaps the most-studied of the catecholaminergic drugs is the indirect DA agonist, amphetamine; it has been reported to enhance performance on several neurocognitive measures both in medicated SZ patients (e.g., Barch and Carter 2005) and in unmedicated individuals with schizotypal personality disorder (Kirrane et al. 2000; Siegel et al. 1996; Wonodi et al. 2006). Amphetamine and other DA agonists may be particularly effective in

enhancing neurocognitive performance in individuals with low basal performance levels (Kimberg et al. 1997; Kimberg and D'Esposito 2003; Mattay et al. 2000, 2003; Mehta et al. 2001; Swerdlow et al. 2011) and in individuals carrying certain genetic biomarkers or related phenotypes (Ersche et al. 2011; Fleming et al. 1995; Giakoumaki et al. 2008; Mattay et al. 2003; Roussos et al. 2009).

Among other laboratory measures, PPI is sensitive to the positive effects of pro-catecholamine agents, in a manner that might predict CT-enhancing effects of these drugs. Catecholaminergic drugs that increase PPI in healthy subjects include amphetamine (Talledo et al. 2009); the COMT inhibitor, tolcapone (Giakoumaki et al. 2008; Roussos et al. 2009) and the D_3 agonist, pramipexole (Swerdlow et al. 2009a). Similar to what is observed with several neurocognitive measures, the PPI-enhancing effects of catecholaminergic drugs can be 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)—or most marked among individuals with low basal performance levels (Fig. 4). Theoretically, this might suggest that amphetamine would be most effective in increasing PPI (and its associated neurocognitive functions) in SZ patients, who as a group exhibit low basal PPI, particularly among those patients carrying a Val allele in the COMT polymorphism (Quednow et al. 2010).

Certainly, there are rational arguments against the indiscriminate use of pro-catecholaminergic drugs in SZ, 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), and—as suggested by Barch (2010) and others—their use in concert with antipsychotics might prevent potentially deleterious effects of subcortical D_2 activation, while permitting potentially beneficial activation of cortical D_1 receptors. 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.

8.2 Low-Potency NMDA Antagonists

NMDA antagonists increase PPI in humans. While the potent competitive NMDA antagonist phencyclidine (PCP) disrupts PPI in both rodents and nonhuman primates (Linn and Javitt 2001; Mansbach and Geyer 1989), low-potency NMDA antagonists that increase PPI in healthy human subjects include amantadine (Swerdlow et al. 2002) and memantine (Swerdlow et al. 2009b) (Fig. 5). Amantadine's PPI-enhancing effects were detected only under conditions where subjects were instructed to rate the intensity of the startling stimulus (Swerdlow et al. 2002), suggesting that the mechanisms engaged by amantadine were attentionally dependent. Consistent with this, when studied in a sample of 19 healthy men, memantine enhanced PPI only at relatively long prepulse intervals (120 ms), which are known to be attentionally sensitive, compared with intervals below 60 ms (Swerdlow et al. 2009b).

Interestingly, 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 (Giakoumaki et al. 2008; Golimbet et al. 2007; Roussos et al. 2009), suggesting a potential biomarker for identifying an enriched treatment cohort. In addition to PPI, memantine challenge in healthy subjects enhances other markers of cortico-striato-pallido-thalamic and functional deficits in schizophrenia, including MMN (Korostenskaja et al. 2007; Light and Braff 2005a, b), and in preliminary studies appears to increase working memory performance in some individuals (Swerdlow et al. 2010). Consistent with the model presented herein, the ability of a memantine "challenge" to enhance PPI or other specific

neurophysiological measures in a patient could provide evidence for residual, healthy circuitry that could be recruited to enhance the effectiveness of CT.

As with other putative "pro-cognitive" agents, memantine does not appear to have dramatic positive effects on symptoms or function in SZ patients, without the concomitant use of cognitive interventions. A recent double-blind study did report large reductions in positive and negative symptoms (d = 1.38–3.33) and improved Mini-Mental State Exam scores after 12 weeks of memantine (20 mg/d; n = 10) versus placebo (PBO; n = 11) added to clozapine (de Lucena et al. 2009). However, an earlier 8-week double-blind, study of memantine (20 mg/d; n = 70) vs. PBO (n = 68) added to atypical antipsychotics detected no change in positive or negative symptoms or Brief Assessment of Cognition in Schizophrenia scores (Lieberman et al. 2009), but found that memantine was associated with more adverse events (adverse events memantine vs. PBO = 8.7% vs. 6.0%) and treatment discontinuation due to AEs (11.6% vs. 3.0%). A smaller, 6-week, open label study of memantine (5–20 mg/d) in symptomatic SZ inpatients reported a significant improvement in positive and negative symptoms but not cognitive performance, with no adverse events (Krivoy et al. 2008). Three case reports (cf. Zdanys and Tampi 2008) described beneficial effects of memantine (5–10 mg/d) in SZ patients, with reductions in negative symptoms and functional impairment and no adverse events; in two reports, symptoms returned on memantine discontinuation and resolved again after restarting memantine.

As with catecholaminergic agents, the utility of an NMDA *antagonist* in SZ patients would seem counterintuitive, based on prevailing models for NMDA hypofunction in SZ. In truth, we can only speculate about the neural mechanisms that might underlie such utility. Memantine enhances cortical metabolic efficiency (Willenborg et al. 2011) and protects cerebral function under conditions of hypoglycemic challenge in healthy adults, and increased frontal and parietal cortical glucose utilization after memantine correlates with increased Mini-Mental State performance among individuals with traumatic brain injury (Kim et al. 2010). Conceivably, such properties might represent a basis for bolstering frontal cortical function—and thereby the neurocognitive resources necessary to successfully engage in CTs—particularly among patients whose frontal cortical efficiency is already taxed by risk factors related to COMT status or schizophrenia-related pathological changes. While it is always wise to consider whether drugs with NMDA antagonist properties might have deleterious consequences in SZ patients, there is evidence that, in fact, memantine is neuroprotective (Kornhuber et al. 1994; Lipton 2006; Rogawski and Wenk 2003), well-tolerated by SZ patients (de Lucena et al. 2009; Krivoy et al. 2008; Lieberman et al. 2009; Zdanys and Tampi 2008) and has been safely used in many millions of patients, including elderly, frail clinical populations (cf. Jones 2010). Conceivably, in addition to memantine, "next generation" low-affinity NMDA antagonists would warrant investigation in studies of neurophysiological and neurocognitive measures of relevance to cortico-striato-pallido-thalamic function and SZ, to assess their potential as pro-CT candidates.

9 Summary

Current pharmacotherapy for SZ primarily targets positive symptoms but does not significantly impact either the substantial neurocognitive or life functional impairments associated with this disorder. It is not surprising that current medications yield limited symptomatic relief, in a disorder caused by disturbances in early brain development producing pervasive, widely distributed and variable patterns of neuropathology. In contrast, controlled studies of a variety of cognitive interventions in SZ patients have demonstrated modest yet significant neurocognitive and functional gains. In the absence of such CTs, drugs with putative "pro-cognitive" properties have failed to benefit patients with SZ. We propose here that a rational strategy for future therapeutic development in SZ is to identify

drugs that can enhance the therapeutic impact of CTs in SZ; such “pro-CT effects” would result from the ability of these drugs to engage spared, healthy brain circuits in SZ patients, in the service of basic neurocognitive demands of particular forms of CT. We propose an experimental approach for identifying such drugs via the use of single drug challenges in concert with laboratory-based neurophysiological and neurocognitive measures, in patients with particular biomarkers predicting drug sensitivity. Among the candidate “pro-CT” drugs are ones with properties—e.g., pro-catecholaminergic or NMDA-antagonistic—that, on the surface, would seem counter-productive in the treatment of SZ. A rationale is discussed—supported by convergent empirical findings—that suggests that evolving strategies for new SZ therapeutics should not be based on imprecise models for the widespread and variable brain dysfunction that occurs because of this disorder, but should be based instead on models that identify and engage spared, healthy brain functions that persists despite it.

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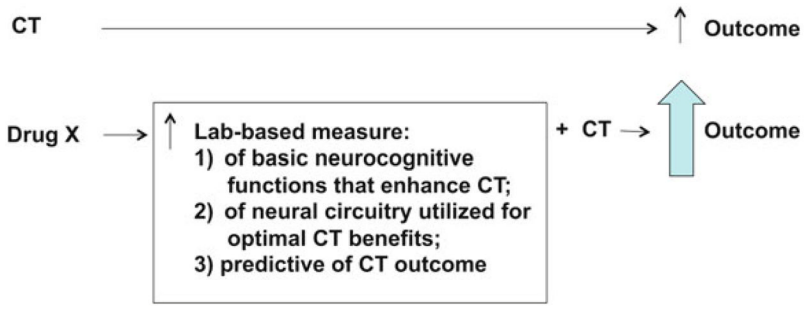

Fig. 1.
Schematic of theoretical and empirical rationale for predictive value of laboratory measures in identifying potential "pro-CT" drugs

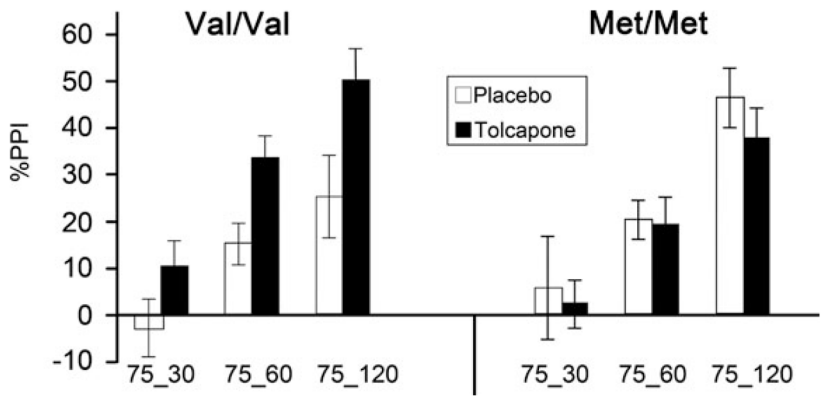

Fig. 2.

Biomarker predicting drug-enhanced PPI in normal subjects (figure modified from Roussos et al. 2009). %PPI is shown on *Y*-Axis; trial type (intensity in dB and prepulse interval in ms) is shown on *X*-axis. As in SZ patients, clinically healthy subjects carrying the Val allele of the Val158Met COMT polymorphism exhibit lower basal levels of PPI; in this important report, the authors demonstrated that the COMT inhibitor, tolcapone, increases PPI selectively among Val/Val individuals

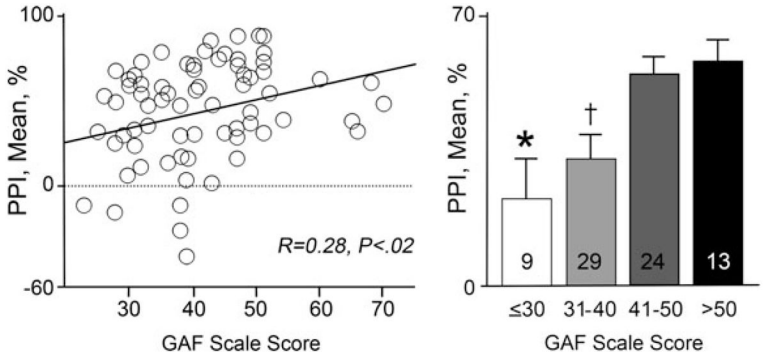

Fig. 3.

Relationship between levels of sensorimotor gating, as measured by %PPI, and global functioning, as measured by GAF in male schizophrenia outpatients (from Swerdlow et al. 2006a). "*N*" indicated by numbers inside bars; *P<.004 vs "41–50" and vs ">50." †P<.01 vs "41–50" and vs ">50" by Fisher protected least-significant difference. Clearly, the causal pathway from higher PPI to higher GAF is indirect, but these findings suggest that the ability of a drug to enhance PPI in schizophrenia patients might be one rational "signal" for selecting compounds with the potential for enhancing the functional impact of cognitive interventions

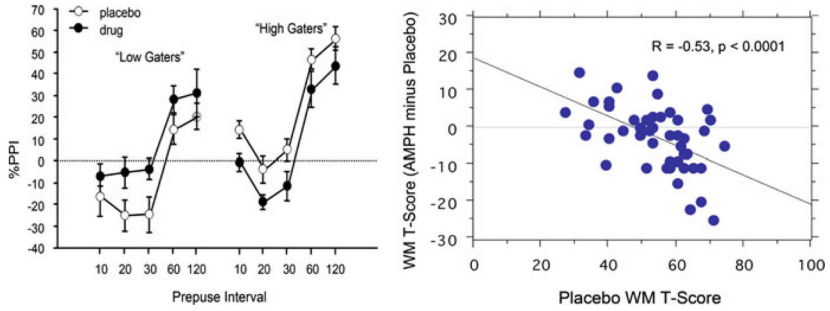

Fig. 4.

"Rate-dependent" effects of AMPH (20 mg po) on measures of %PPI (*left*; Talledo et al. 2009) and working memory (MCCB domain T-scores; Swerdlow et al. 2011) in clinically normal adults. AMPH-enhanced PPI was detected in specific subgroups of healthy women with PPI- or personality-based phenotypes associated with the COMT Val/Val allele. Working memory-enhancing effects of AMPH were detected among a subgroup of 50 healthy men and women characterized by low-basal working memory performance. Schizophrenia patients as a group have reduced PPI and impaired working memory; thus, based solely on the rate-dependent effects detected in normal adults, schizophrenia patients would be predicted to show PPI- and working memory-enhancing effects of acute AMPH treatment. The latter finding was already reported by Barch and Carter (2005)

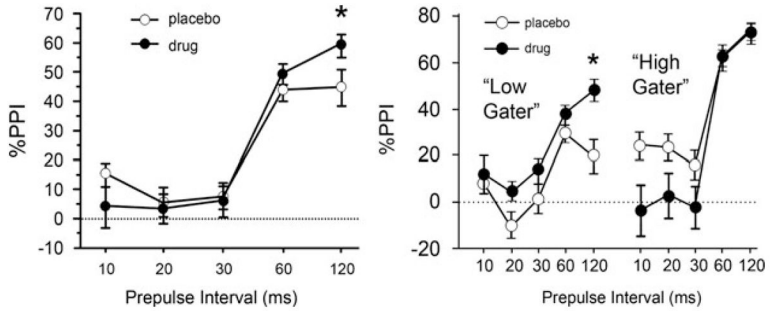

Fig. 5.

In healthy men, PPI was significantly increased by 20 mg memantine at 120 ms prepulse intervals (*left*). When subjects were divided into those in the upper or lower 50% of baseline PPI values (right, “high” and “low”, respectively), ANOVA revealed PPI-enhancing effects of memantine only among the “low gaters” (Swerdlow et al. 2009b)