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Room to move: Plasticity in early auditory information processing and auditory learning in schizophrenia revealed by acute pharmacological challenge

Neal R. Swerdlow *, Savita G. Bhakta, Gregory A. Light

Department of Psychiatry, UCSD School of Medicine, 9500 Gilman Dr., La Jolla, CA 92093-0804, United States

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ABSTRACT

Many patients with chronic psychotic disorders including schizophrenia (SZ) maintain meaningful levels of plasticity (i.e., capacity for change) within neurocognition-relevant brain mechanisms, as evidenced by gains in neurocognition and function after interventions such as targeted cognitive training. However, like many clinical features of these disorders, therapeutic responses in SZ are heterogeneous, and prospectively identifying treatment-sensitive individuals and individualized treatment modalities remains an unmet challenge. We propose that available plasticity in neurocognition-relevant brain mechanisms in individual SZ patients can be detected by gains in laboratory measures of early auditory information processing (EAIP) and auditory learning after a single challenge-dose of a pharmacologic agent; here, we present supportive data for this strategy with the non-competitive NMDA antagonist, memantine, and the psychostimulant, amphetamine. We describe a novel therapeutic model where this "challenge dose" strategy is used to prospectively identify a sensitive cohort of patients, and in these patients, a therapeutic response is elicited by pairing drug-enhanced EAIP and auditory learning with auditory-based targeted cognitive training.

1. Introduction

Schizophrenia (SZ) is a severe brain disorder affecting 1% of the world population. Its cost to society is well documented (Rice, 2009), as are stories of lifelong suffering among SZ patients and their families. Almost 60 years after the introduction of drugs designed to target its symptoms, antipsychotics (APs) are at best modestly effective, and the neurobiological targets of these medications are not firmly anchored in a mechanistic understanding of the biology of this disorder.

While APs blunt severe acute psychotic symptoms, they may not have a meaningful impact on real-life function (Keefe et al., 2007, 2016; Leucht et al., 2009; Lieberman et al., 2005). Evidence that daily function in SZ is closely linked to neurocognition (Green, 1996) has stimulated efforts to develop procognitive agents as adjuncts to APs; these efforts have largely yielded negative results (cf. Barch, 2010, 2011; Buchanan et al., 2007; Goff et al., 1996, 1999, 2007, 2008; Green, 2007). Importantly, procognitive trials generally suffer from *two important weaknesses.* First, they are *not conducted in the context of cognitive interventions* (cf. Barch, 2010). Simply adding a putative procognitive drug to a daily AP regimen may not provide a sensitive test of its activity: drugs that enhance specific domains of neurocognition, e.g. working memory, might not yield clinical benefits unless paired with interventions that access those domains, i.e. utilize/place demands on working memory. This is precisely the rationale for the use of pro-extinction drugs to enhance clinical benefits of cognitive and behavioral interventions for anxiety disorders (Choi et al., 2010; Norberg et al., 2008; Ressler et al., 2004). Second, SZ is heterogeneous, and pro-cognitive trials in SZ suffer from the *absence of biomarkers that identify "sensitive" clinical subgroups.*

A key consideration in the development of pro-cognitive agents for SZ is the degree to which neural function underlying neurocognition retains its plasticity (i.e. capacity for change) in this disorder, and may therefore be a rational target for therapeutics. If plasticity of cognition-relevant circuitry is limited due, for example, to inherent flaws in circuit connectivity resulting from significant errors in neuronal migration or synaptic connectivity, this might argue against a viable therapeutic target. No drug will likely unscramble circuit design flaws imparted two decades earlier, which form the foundation of neurocognitive impairments. If, on the other hand, intact plasticity can be identified prospectively, this might indicate sensitivity for positive change, given an appropriate intervention. Because SZ is heterogeneous in presentation and presumably in its underlying pathophysiology, it is very likely that the amount of retained meaningful plasticity will differ greatly across patients, and across brain circuitries that are impacted by their illnesses. Thus, a means to prospectively identify retained plasticity ("room to

* Corresponding author.
E-mail address: nswerdlow@ucsd.edu. (N.R. Swerdlow).

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move") among individual SZ patients, within cognition-relevant brain mechanisms, could serve as a critically important biomarker for stratifying patients into groups that are more vs. less likely to show neurocognitive gains in response to a therapeutic intervention. Implicit in this model is that the therapeutic target would be *healthy brain mechanisms that have retained a degree of plasticity*; by contrast, attempts to "correct" brain function that is disrupted based on presumed neurodevelopmental pathology in schizophrenia have met with little success, despite efforts spanning almost 60 years.

1.1. Using drugs to identify plasticity in cognition-relevant brain substrates in schizophrenia

One way to identify intact plasticity within cognition-relevant brain mechanisms is to "challenge" those mechanisms pharmacologically, while monitoring informative laboratory measures of cognition-relevant brain events. The use of a drug challenge to identify enriched, sensitive subgroups of patients parallels the common 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 and Yigla, 2009); it is an established way to acutely probe the brain for healthy biological mechanisms that might be leveraged in the service of therapeutics.

Which laboratory measures might be most informative for identifying plasticity within cognition-relevant brain mechanisms? One suggestion came from our studies of neurophysiological endophenotypes, conducted by the Consortium on the Genetics of Schizophrenia (COGS). Using structural equation modeling (SEM) in 1415 SZ patients, the COGS group (Thomas et al., 2017) reported that measures of early auditory information processing (EAIP) had a direct (mediating) effect on cognition ($p < 0.001$), that cognition had a direct effect on negative symptoms ($p < 0.001$), and that both cognition ($p < 0.001$) and negative symptoms ($p < 0.001$) had direct effects on functional outcome. Overall, EAIP had a fully mediated effect on functional outcome, engaging general rather than modality (auditory)-specific cognition. One measure of EAIP in this study was mismatch negativity (MMN), a phenomenon described elsewhere in this Special Issue as the negative event-related potential (ERP) that is automatically elicited in response to a deviant sound within the context of repetitive, identical sounds. Explicitly, this model predicts that a 1 μV change in the MMN EAIP response complex will result in improvements of $d = 0.78$ for cognition and $d = 0.28$ for psychosocial functioning. While the time-course for such cognitive and functional changes in relation to increased EAIP is not known (see below, Fig. 4), these findings nonetheless suggest that interventions that reliably enhance measures of EAIP in SZ patients would be rational targets for therapeutic development.

To determine whether measures of EAIP retained plasticity in SZ patients, we also examined changes in EAIP after an acute drug challenge. Memantine (MEM) is an uncompetitive NMDA receptor antagonist with low-affinity but rapid blocking and unblocking ability. It has little impact on basal NMDA transmission; this distinguishes it mechanistically from other NMDA antagonists (Lipton, 2006). It has positive effects on cognitive measures in both healthy animals and a range of human and animal models for dementia, depression, ischemia and neuroinflammation (Kim et al., 2010; Ma et al., 2015). MEM enhances hippocampal long-term potentiation (LTP), and reverses an experimentally-induced loss of LTP (Ma et al., 2015); it also alters excitation/inhibition (E/I) dynamics in frontal circuitry implicated in models of SZ neuropathology (Smith et al., 2011) and associated with MMN and cognitive deficits in SZ (Rowland et al., 2016). Of most relevance to the present topic, acute MEM increased MMN in healthy humans (Korostenskaja et al., 2007); in this particular study, MMN amplitude to frequency deviants increased 0.91 μV – enough to produce large effect-size increases in cognition in these healthy subjects. Such drug effects in intact/healthy brains support the therapeutic model proposed here, in which drugs target healthy rather than pathological brain circuitry.

2. Memantine and early auditory information processing

We studied the acute effects of MEM on measures of EAIP in chronic, antipsychotic (AP)-medicated SZ patients. In addition to MMN, we measured prepulse inhibition of acoustic startle (PPI) and the auditory steady state response (ASSR). These three measures were chosen because they: 1) are neurophysiological measures of EAIP, i.e. of the brain's automatic response to a simple sensory event proximal to, or independent of, a point at which it engages conscious or volitional processing; 2) are reliable, objective and quantitative; 3) consistently detect EAIP deficits in SZ patients; 4) reflect "automatic" vs. volitional processes and are relatively insensitive to motivational or effort-based artifact; 5) are suited to repeated testing in a cross-over design without significant order or "carry-over" effects, and 6) are each regulated by NMDA mechanisms, with at least some evidence for enhanced performance associated with NMDA blockade (Korostenskaja et al., 2007; Swerdlow et al., 2009; Hiyoshi et al., 2014). The study (Light et al., 2017; Swerdlow et al., 2016) used a double-blind, placebo-controlled cross-over comparison of placebo vs. MEM (10 and 20 mg po) in both SZ patients and healthy subjects (HS). Test days were separate by about 1 week. Details of the methods can be found in the original data reports (Light et al., 2017; Swerdlow et al., 2016).

In brief, MEM significantly enhanced performance in each of these 3 measures of EAIP (Fig. 2). For PPI (Fig. 2A), the effects were more robust among patients than HS; for MMN (Fig. 2B), they were somewhat more robust among HS than patients, and for ASSR (Figs. 2C, D), the effects were roughly comparable across groups. Compared to published findings of a 0.91 μV increase in MMN after 30 mg of MEM in HS (Korostenskaja et al., 2007), we detected a maximum increase of about 1.1 μV MMN after 20 mg of MEM in HS, but only a maximum increase of about 0.4 μV among SZ patients. Nonetheless, for each of the 3 EAIP measures, MEM "improved" performance levels, i.e. moved them in a direction associated with less pathology. Importantly, while in this group of patients there were significant deficits in MMN and ASSR, their PPI was quantitatively intact (consistent with the fact that all were AP-medicated, and almost all were taking 2nd-generation AP's, which are known to normalize PPI (cf. Swerdlow et al., 2008)). Thus, MEM's effects were not dependent on deficits in EAIP measures, and were not impacted by AP medication, also consistent with the possibility that MEM was acting on intact mechanisms that were performing at "normal levels".

The only robust predictor of MEM "sensitivity" in these EAIP measures was patient age, which significantly predicted *more* sensitivity to the PPI-enhancing effects of MEM ($p = 0.005$), but also significantly predicted *less* sensitivity to the MMN- ($p < 0.025$) and ASSR-enhancing (coherence: $p < 0.005$; power: $p < 0.0015$) effects of MEM. While illness chronicity is often difficult to disentangle from subject age, each of the 4 relationships noted above were weakened when illness duration was substituted for age, such that only the negative relationships with MEM sensitivity on ASSR measures ($p < 0.045$ and $p < 0.02$) remained statistically significant.

Most importantly, this study revealed that, among EAIP measures thought to mediate cognition and function in SZ patients, significant plasticity (i.e. capacity for change) could be identified via an acute "challenge" with MEM. Clearly, not every patient exhibited this evidence of plasticity (Fig. 3), consistent with the heterogeneous neurobiology of this disorder. When identifying "sensitive" subgroups (Fig. 1), such heterogeneity is expected, and criteria can be tested and empirically validated to identify the magnitude of MEM-stimulated plasticity that predicts a sensitive treatment subgroup (Fig. 3).

The expectation based on these findings is that, over time, in a sensitive subgroup identified based on the magnitude of increased EAIP after acute MEM challenge, MEM (or a mechanistically similar compound) should facilitate gains in neurocognition and function in AP-medicated schizophrenia patients. However, simply based on these findings, we absolutely *would not* expect severely ill schizophrenia

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