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Neurophysiological Biomarkers Informing the Clinical Neuroscience of Schizophrenia: Mismatch Negativity and Prepulse Inhibition of Startle

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Abstract With the growing recognition of the heterogeneity of major brain disorders, and particularly the schizophrenias (SZ), biomarkers are being sought that parse patient groups in ways that can be used to predict treatment response, prognosis, and pathophysiology. A primary focus to date has been to identify biomarkers that predict damage or dysfunction within brain systems in SZ patients, that could then serve as targets for interventions designed to "undo" the causative pathology. After almost 50 years as the predominant strategy for developing SZ therapeutics, evidence supporting the value of this "find what's broke and fix it" approach is lacking. Here, we suggest an alternative strategy of using biomarkers to identify evidence of spared neural and cognitive function in SZ patients, and matching these residual neural assets with therapies toward which they can be applied. We describe ways to extract and interpret evidence of "spared function," using neurocognitive, and neurophysiological measures, and, suggest that further evidence of available neuroplasticity might be gleaned from studies in which the response to drug challenges and "practice effects" are measured. Finally, we discuss examples in which "better" (more normal) performance in specific neurophysiological measures predict a positive response to a neurocognitive task or therapeutic intervention. We believe that our field stands to gain tremendous therapeutic leverage by focusing less on what is "wrong" with our patients, and instead, focusing more on what is "right".

Keywords Biomarker · Cognitive remediation · Mismatch negativity · Neurocognition · Prepulse inhibition · Schizophrenia

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1 Overview: Biomarkers of Health

Our field's ability to understand and effectively treat mental illness has advanced in developmental "stages," each new stage building on the ideas and technologies that preceded it. The current stage of neuroscientific inquiry into brain disorders is most notable for the increasing acceptance by the scientific community of the notion—long held within clinical spheres—that many major psychiatric "disorders" are biologically heterogeneous syndromal endpoints of different etiological pathways. In embracing the heterogenous underpinnings of conditions like the schizophrenias (SZ), our field has both de-prioritized pursuits that seek to uncover unitary pathogenic processes (i.e., single causative gene), and has prioritized those designed to clarify the more complex biologies and treatments of these syndromes. One clear priority in this new "stage" is the development and application of biomarkers for mental illness.

Biomarkers are objective measures that can be informative about a variety of different clinical characteristics, such as an individual's normal biology, their pathology including the trajectory of illness, or their response to a therapeutic intervention. While it is clear that symptom-based diagnostic schema can distinguish patients in a manner that to some degree predicts their trajectory and therapeutic sensitivity (e.g., in the parsing of a primary anxiety disorder vs. a primary psychotic disorder), it is equally clear that these schema have reached their limits of resolution in terms of pathophysiology and the development of novel and individualized therapeutics. Biomarkers offer the hope that despite great heterogeneity and multivariate interactions in the pathogenesis of brain disorders, meaningful clusters of individuals can be associated with an objective measure, and then reliably stratified in terms of the cause, course and/or treatment sensitivity of a given disorder. Of course, this is not a new hope—the search for biomarkers for mental illness can be traced back decades, and perhaps centuries—nor is it a hope fulfilled, as we presently have no biomarkers that add in a meaningful way to our treatment of any major psychiatric syndrome.

One assumption driving the search for psychiatric biomarkers is that the biology of these biomarkers will be simpler, more easily understood and less heterogeneous than the biology of clinical psychiatric syndrome. But if the pathogenic pathways leading to the syndrome are highly heterogeneous, we might expect that the

biomarkers for these pathways might also be highly heterogeneous. In essence, if we identify a biomarker of "Bill's schizophrenia," this information might be very important to Bill, but not generalizable to larger populations. For this reason, we have endorsed an approach in which biomarkers in psychiatric disorders are used to identify not pathological processes, but rather intact, healthy processes (e.g., brain circuitry). This approach has several advantages over the search for pathology biomarkers. For example, it is in many ways easier to interpret a biomarker of health than one of pathology. In a simple analogy, if you enter a room, flip on the light switch and no light goes on, there can be numerous explanations for this deficit. However, if you flip on the light switch and the light DOES go on, there can be only one parsimonious explanation: electrons are getting to where they need to be.

It is not simply that biomarkers of health are easier to understand than biomarkers of pathology, but rather, that they may be more "actionable," i.e., their presence may lead more directly to a predicted therapeutic intervention. To underscore this point, let's examine some putative biomarkers of pathology for schizophrenia. Hippocampus, amygdala, anterior cingulate cortex, and other structures are reduced in volume and/or functionally impaired in SZ patients *as well as their asymptomatic first-degree relatives* (cf. Swerdlow 2011a) One implication of these neuroanatomical "" of pathology is that while these circuit disturbances may be associated with a heritable vulnerability for SZ, they are insufficient to produce the disorder. Thus, while these biomarkers of impairment may inform us about various different etiologies and perhaps even preventative interventions, they do not by themselves provide "actionable" targets for corrective interventions: after all, most people with these abnormalities *do not have SZ*, so why would "correcting" this circuitry be of benefit to someone who does?

By contrast, biomarkers of healthy brain function in "system X" might provide more direct "actionable" evidence that a patient with SZ is likely to benefit therapeutically from "intervention Y." Several clinical models support this approach. For example, many interventions in stroke rehabilitation are designed not to re-grow brain circuitry that is lost or damaged, but rather to 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). In many forms of psychotherapy, the therapist's task is to identify an individual's psychological strengths (ego, intellectual, social, or otherwise) and then to engage them to overcome damaging thoughts or behaviors that are otherwise sustained by areas of psychological weakness. At a neural level, both stroke rehabilitation and psychotherapy engage viable and healthy systems to compensate for, or re-establish, functions lost to illness. Similarly, biomarkers of "health" can reveal a patient's neural "assets," which can then be leveraged in the service of therapy. There are several hurdles to clear in this process, e.g., (1) it requires biomarkers that identify these assets with sufficient sensitivity, specificity, and other limits of resolution discussed below, and (2) it requires therapies that can engage these assets to improve function. There is growing evidence that both of these hurdles can be cleared.

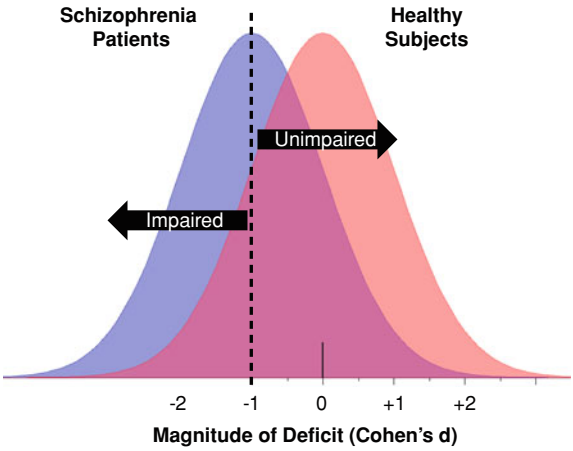

Fig. 1 Example of overlapping distributions in a robust ($d = 1$) effect size biomarker deficit in schizophrenia patients. In neuropsychological assessments, $d = 1$ standard deviations below the mean is commonly used for impairment classification. In this case, 50 % of patients exhibit unimpaired/normal range biomarker values

For example, as discussed below, reliable, repeatable, and robust measures can quantify working memory (WM) in SZ patients. Certain cognitive therapies place demands on SZ patients to engage WM to develop compensatory strategies for learning and applying information (Twamley et al. 2003). In doing so, these therapies specifically activate prefrontal regions subserving WM and attention (Haut et al. 2010). It is both parsimonious and testable that patients with the available "neural asset" of relatively intact WM—demonstrated by sensitive, specific and reliable laboratory measures—and hence frontal circuits that subserve WM, will benefit most from WM-targeted cognitive therapies.

What is the likelihood of identifying "healthy" biomarkers in patients who are suffering from obvious brain dysfunction associated with profound functional impairment? We view this likelihood to be substantial: even in the most "robust" biomarkers suggesting "pathology" in the most severe cohorts of chronic SZ patients, many and sometimes most patients "score" in the normal range. This is true in markers using volumetric or functional neuroimaging, or neurophysiology, or neurocognition. Biomarkers that identify differences in SZ patient versus healthy comparison subjects with a Cohen's standardized effect size of $d = 1.0$ are generally considered "robust"; *in fact, most of the highly replicable SZ biomarkers fail to reach this level of group separation*. Notably, falling 1 standard deviation below normative samples (i.e., effect size $d = 1.0$) is commonly used as a cutoff for impairment classification in neuropsychological assessments. This means that even in the case of a $d = 1.0$ biomarker impairment, 50 % of patients will *by definition* fall in the "normal" range (Fig. 1)—an often overlooked fact. Moreover, in this "best case" example of a pathology biomarker, "only" 54.5 % of the patients versus healthy group distributions are nonoverlapping. Whether the metric is hippocampal volume (Simm et al. 2006) or prepulse inhibition of startle (PPI) (Swerdlow et al. 2014) or WM (Horan et al. 2008) or mismatch negativity (MMN; (Umbricht and Krljes 2005; Rissling et al. 2012; Light and Braff 2005a, b; Kiang et al. 2009), some or even most SZ patients exhibit evidence of intact function: the

"light switch works," and thus the neural assets can conceivably be applied toward a therapeutic response.

Does the search for biomarkers of health imply that we simply forego therapeutic options for patients whose biomarkers suggest a lack of health? Of course not. Given the heterogeneity of performance across measures, it is often the case that patients exhibiting deficits in one biomarker or neural domain will perform normally in others. Indeed, many of the common neurophysiological biomarkers and endophenotypes of SZ are uncorrelated with one another even when measuring similar operational constructs (e.g., sensory/sensorimotor gating: Schwarzkopf et al. 1993; Light and Braff 2001; Braff et al. 2007; sensory discrimination: Rissling et al. 2012; Horvath et al. 2008). The key to using this strategy in a heterogeneous population is to be able identify areas of neural strengths using a battery of well-validated and dissociable battery of laboratory-based biomarkers. And while cognitive therapies are generally benign and not prone to adverse events as traditionally measured in medicine, they are time-consuming, resource-intensive, and taxing; they require many hours of time, in addition to the logistical complexities involved in accessing treatment for a severely impaired individual, and the psychological implications of treatment failure if unsuccessful. Thus, a haphazard pairing of an individual with severe impairments in a biomarker of, say, WM, with a time- and resource-intensive cognitive intervention that places heavy demands on WM, is likely to be unsuccessful. *Unfortunately, such incidental couplings of individual patient characteristics with therapies represent the current state of the art.* Treatment "failures" are far too common and have the potential to cost the patient, family, therapist, and larger social system dearly. In contrast, biomarkers of health can guide patients toward viable therapies, and their absence can steer patients away from therapies that are not likely to be successful and whose failure carries significant real-life consequences.

There may be ways to "uncover" biomarkers of potential function in SZ, even among neural systems that appear by some biomarker evidence to be defective. The general principle behind this strategy is that a neural system at baseline may perform poorly, but may still respond to a "push" of a pharmacologic challenge. In this case, evidence for the requisite "spared" neural circuitry, and hence a target for therapeutic intervention, might be provided by specific neurophysiological or neurocognitive changes in response to a "push" produced by a drug challenge. This approach parallels the use of a "test dose" to predict clinical benefits from treatments ranging from hormones (Biller 2007) to anti-Parkinsonian drugs (Hughes et al. 1990) to bronchodilators (Fruchter and Yigla 2009). If a patient generates a specific neurobehavioral signal in response to a drug challenge—e.g., increased neurocognitive or neurophysiological performance, or enhanced performance of a computerized cognitive training task (discussed below)—this suggests that neural circuits spared by their SZ remain viable targets under the right conditions. Creating such conditions is the goal of "Pharmacologically Augmented Cognitive Therapy," as described previously (Swerdlow 2011a, b),

and departs significantly from what has been a 50-year-old largely failed strategy of trying to use drugs to "undo" the neuropathology of SZ (Lieberman et al. 2005).

In the process of using a "drug challenge" to probe a biomarker of spared neural function, it is often the case that neurocognitive and/or neurophysiological measures are repeated under drug-free, placebo, and active drug conditions. One complexity of this experimental design is that brain mechanisms at many levels, and particularly at levels of higher order functions, exhibit "learning," as detected in practice /order effects. These changes in performance with repeated task experience are typically viewed as experimental confounds, as they can arithmetically complicate the interpretation of a drug effect (Chou et al. 2013b). However, it is possible that the brain's ability to "learn," particularly in specific neurocognitive domains, may—in and of itself—be a valuable biomarker of spared neural function. We have no data yet to support this notion, but it makes intuitive sense that the ability to increase one's performance with experience provides evidence of neuroplasticity that might be harnessed in the service of an appropriate therapy. Our data (Chou et al. 2013a) is consistent with previous reports (Nuechterlein et al. 2008) that different neurocognitive domains are differentially sensitive to such "learning" processes, and that the amount of learning exhibited by SZ patients varies substantially within any given domain. These data are typically collected as part of any "procognitive" drug trial involving more than one drug condition; that such personalized profiles of cognitive "neuroplasticity" are predictive of sensitivity to specific cognitive or medication therapies is a testable hypothesis.

Regardless of whether the intended use of a biomarker is to identify health or pathology in SZ, its utility will depend on its ability to meet a number of important criteria. The background for the development and application of such criteria for biomarkers relevant to SZ is discussed in the next section of this chapter.

2 SZ Biomarkers

What are the optimal characteristics of biomarkers for informing the clinical neuroscience and future treatments of SZ? Over the past decade, several expert consensus panels were convened to attempt to overcome some of the obstacles of developing treatments to improve cognition and psychosocial functioning in schizophrenia. The first initiative, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), brought together academia, the pharmaceutical industry, and the Food and Drug Administration to identify cognitive targets in schizophrenia and develop a brief, repeatable, and standardized battery of tasks for use in clinical outcome studies (Green et al. 2004). In this context, a RAND panel carefully evaluated the desired measurement characteristics of individual tests for inclusion in the final FDA-approved battery and concluded that measures should exhibit: (1) high test–retest reliability; (2) utility as a repeated measure; (3) a relationship to functional outcome; (4) potential response to

pharmacologic agents; and (5) practicality/tolerability. Clearly, both the *process* for evaluating measures and the *specific criteria* is also highly relevant for evaluating promising neurophysiologic biomarkers that can inform the development of next-generation personalized treatments.

The benefits of neurophysiologic biomarkers were also recognized in the MATRICS initiative since such measures can probe the earliest stages of sensory-perceptual information processing and the subsequent transitions to higher order cognitive operations with millisecond resolution. In many cases, responses can be automatically elicited in the absence of directed attention and do not require substantial effort or motivation on the part of the participant (Braff and Light 2004). Neuroscience-derived biomarkers are also well-suited for linking cognitive deficits to specific neural systems using source-imaging, pharmacology, and animal models. Thus, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia initiative (CNTRICS) was launched after MATRICS to identify the most promising brain-based tools for measuring cognition and testing new treatments in schizophrenia (Carter et al. 2008). This panel extended the five MATRICS criteria of cognitive tests described above by adding requirements that measures exhibit construct validity, clear links to neural circuits and cognitive mechanisms, and have an available an animal model (Barch et al. 2009). Out of this extensive process of evaluating the many promising measures in the existing literature, several tests were selected for further study and development. Critically, two neurophysiological measures were deemed already "mature," fulfilling all of the MATRICS/CNTRICS criteria and suitable for immediate incorporation into multi-site clinical studies: MMN and Prepulse Inhibition (Butler et al. 2012; Green et al. 2009)—the focus of this chapter. Below, we also provide examples of rational and deliberate matching of patients with intact biomarker functioning with appropriately targeted cognitive therapies that depend upon the engagement of the neural substrates of these measures.

3 Mismatch Negativity

Mismatch negativity is a preattentive event-related potential (ERP) component with tremendous promise as a biomarker for predicting and tracking response to novel therapeutic interventions (Light and Näätänen 2013; Nagai et al. 2013; Light et al. 2012; Perez et al. 2014a, b; Kawakubo et al. 2007). MMN is a negative-going deflection in the ERP that is evoked when a sequence of repetitive "standard" stimuli is occasionally interrupted by infrequent oddball or "deviant" stimuli that differ in some physical characteristic such as duration or pitch. The onset of MMN typically occurs within 50 ms of stimulus deviance, and peaks after an additional 100–150 ms. Since MMN requires no overt behavioral response and can be elicited even in the absence of directed attention (Näätänen 1992; Rinne et al. 2001; Sussman et al. 2003; Rissling et al. 2013), it is presumed to reflect a predominantly

automatic, preconscious process of detecting a "mismatch" between the deviant stimulus and a sensory-memory trace (Näätänen et al. 1989).

MMN amplitude reduction in schizophrenia was first reported over 20 years ago (Shelley et al. 1991) with subsequent studies consistently identifying deficits in chronic ($d \cong 1.00$ Javitt et al. 1994; Shelley et al. 1991; Catts et al. 1995; Javitt et al. 2000; Michie 2001; Umbricht et al. 2003; Umbricht and Krljes 2005; Salisbury et al. 2002; Oknina et al. 2005; Oades et al. 2006; Light and Braff 2005a, b; Rissling et al. 2012, 2013), recent onset (Salisbury et al. 2002, 2007; Brockhaus-Dumke et al. 2005; Umbricht et al. 2006; Oknina et al. 2005; Oades et al. 2006; Hermens et al. 2010; Bodatsch et al. 2011; Jahshan et al. 2012; Atkinson et al. 2012; Perez et al. 2013), and even unmedicated schizophrenia patients (Rissling et al. 2012; Bodatsch et al. 2011; Brockhaus-Dumke et al. 2005; Kirino and Inoue 1999; Catts et al. 1995). MMN is supported by a distributed network of fronto-temporal sources with deficits in schizophrenia prominent in medial frontal brain regions (e.g., Takahashi et al. 2012) and a sensitive index of *N*-methyl D-aspartate (NMDA) receptor functioning (Javitt et al. 1996; Umbricht et al. 2000, 2002; Gil-da-Costa et al. 2013; Lavoie et al. 2007; Ehrlichman et al. 2008; Nakamura et al. 2011). The temporal window indexed by MMN may serve as a gateway to some higher order cognitive operations necessary for psychosocial functioning (e.g., Rissling et al. 2013). MMN accounts for substantial portions of variance in cognition (Baldeweg et al. 2004; Näätänen et al. 2011; Light et al. 2007b; Kawakubo et al. 2006), psychosocial functioning (Light and Braff 2005a, b; Kawakubo et al. 2007; Wynn et al. 2010; Rasser et al. 2011), and level of independence in community living (Light and Braff 2005a). MMN amplitude also exhibits utility as a repeated measure with high test–retest stability over short and long (e.g., 12-month) retest intervals in both healthy subjects and schizophrenia patients (Light et al. 2012). Indeed, MMN reliability coefficients are comparable to or even exceed those obtained from neuropsychological tests over 1 year (ICCs $\cong$ 0.90; Light et al. 2012; Light and Braff 2005b). This collection of attributes has contributed to the view of MMN as a "breakthrough biomarker" (Light and Näätänen 2013) that is "translatable" (Nagai et al. 2013) and potentially "the one we have been waiting for" (Belger et al. 2012) in neuropsychiatry.

There is certainly ample evidence that MMN is an informative biomarker index and correlate of "what's wrong" in schizophrenia. In fact, we have previously argued for pharmacologic and nonpharmacologic treatments that target early auditory perceptual processing with the hope that an amelioration of MMN deficits might accompany or even precede improvements in highly associated cognitive and psychosocial functioning (Braff and Light 2004; Perez et al. 2014a, b). We now consider a "figure-ground" reversal: rather than focus on the 50 % of patients with deficient MMN, perhaps the remaining 50 % with normal range MMN will be most likely to benefit from therapies that are designed to target low-level auditory perceptual processes.

MMN may be particularly sensitive to one particular form of "bottom-up" CT—termed Targeted Cognitive Training (TCT; Fisher et al. 2009). TCT uses "neuroplasticity-based" computerized exercises designed to improve the accuracy

and fidelity of auditory sensory information processing and auditory/verbal WM. TCT relies on intensive, attentionally engaging, adaptive, and reinforcing tasks to facilitate procedural learning (Adcock et al. 2009)—a mechanism that is largely intact in SZ (Perry et al. 2000). Conceptually, the goal of TCT is to capitalize on plastic changes within the neural substrates of low-level auditory information processing, which then feed forward to improve higher order cognitive operations such as attention, WM, and the encoding and retrieval of verbal information. Fisher and colleagues have shown (Vinogradov et al. 2012) that SZ patients exhibit large effect size ($d = 0.86$–0.89; Fisher et al. 2009) gains in auditory-dependent cognitive domains (verbal learning and memory), global cognition, and quality of life after 50 h of training. Importantly, these gains persist for at least 6 months after the cessation of training (Fisher et al. 2010). Although TCT is efficacious at the group level, individual patient responses to this resource and time-intensive intervention vary considerably; some patients exhibit little or no benefit after even an extended 100 h course of training (Fisher et al. 2014). Could MMN or other neurophysiological biomarkers of auditory sensory processing be used to predict whether an individual patient is likely to respond to this time- and resource-intensive intervention?

In addition to the emerging applications in neuropsychiatry, MMN is supported by a substantial cognitive neuroscience literature. Indeed, MMN is already regarded a dynamic index of central auditory system neuroplasticity that predicts cognitive enhancement in response to specific TCT-like auditory training interventions (Menning et al. 2000; Näätänen 2008). For example, Menning and colleagues (2000) demonstrated that 3 weeks of intensive ($\sim$1 h/day) auditory frequency discrimination training produced significant increases in MMN amplitude that persisted for several weeks after the cessation of training in healthy volunteers. Other studies have shown that MMN *both predicts and corresponds* to changes in language acquisition, musical training, and other auditory-dependent cognitive tasks in nonpsychiatric individuals (for review, Näätänen 2008). Likewise, MMN exhibits malleability after even a single 3 h session of auditory training in dyslexic children, which was associated with a significant amelioration of cognitive impairment in phonological processing, reading, and writing (Lovio et al. 2012). Thus, changes in MMN are detectable in the early stages of cognitive training, predict generalized improvements in nontrained higher order cognitive domains, and correspond to measurable changes of cortical plasticity in intact and impaired neuropsychiatric populations. In all instances, larger MMN (i.e., associated with healthy function) was associated with greater training gains.

Little is known about the neural mechanisms that underlie enhanced global cognition and inter-individual variation in TCT response in schizophrenia. Better characterization of biomarkers of TCT response will lead to more selective targeting of patients and neurobiological systems for preventive interventions. We have conducted a proof of concept validation study to begin to understand the potential relationship between MMN and immediate TCT effects (Perez et al. 2014b). MMN was assessed immediately before and after a 1 h TCT session (PositScience, Frequency Sweeps) in 31 chronic, medicated SZ patients. MMN

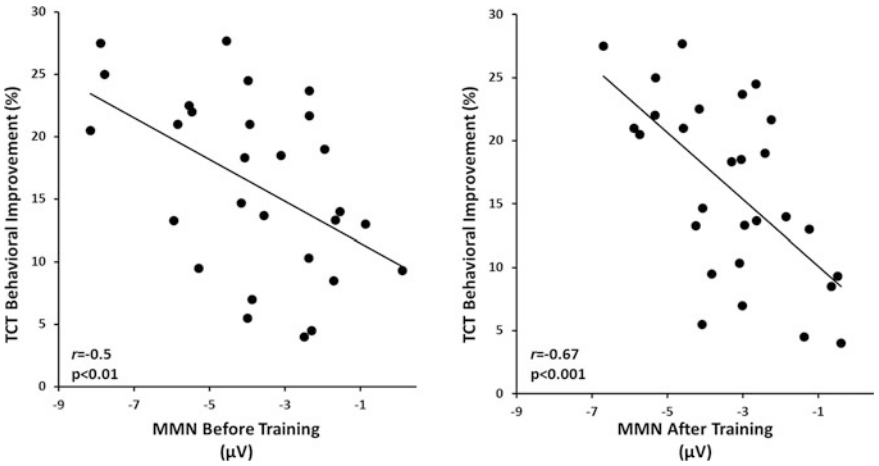

Fig. 2 MMN recorded before and after 1 h of training is associated with initial behavioral performance gains during TCT in schizophrenias patients. Larger pre-training MMN significantly predicted greater TCT improvements; post-training MMN was also significantly associated with performance gains (Perez et al. 2013)

amplitude exhibited significant change at frontocentral electrodes ($p < 0.02$) confirming our prediction that MMN is sensitive to early "target engagement" after just 1 h of training. In addition, patients with larger pretraining MMN amplitude exhibited greatest improvements across the single TCT session ($r = -0.5$, $p < 0.01$), confirming our hypothesis that baseline MMN predicted initial TCT performance gains (Fig. 2). In addition, post-training MMN accounted for 45 % of the variance in TCT performance gains. Thus, patients with larger (i.e., more normal) levels of MMN (i.e., "what's right") exhibited a larger initial response to training. While these results are encouraging, it is important to emphasize that behavioral response to a single TCT session is not known to predict longer term neurocognitive or functional gains in schizophrenia patients undergoing a full course of training. In support of this model of larger biomarker values predicting treatment response, Kawakubo and colleagues (2007) showed that larger baseline MMN predicted greater response to an intensive, 3 month social skills training program (Fig. 3). This approach may therefore serve as a useful platform for identifying patients who are likely to be "responders" to TCT (Light and Näätänen 2013; Perez et al. 2014b), social skills training (Kawakubo et al. 2007), or perhaps other forms of cognitive remediation. Such predictive biomarkers may also facilitate screening drugs to augment cognitive training.

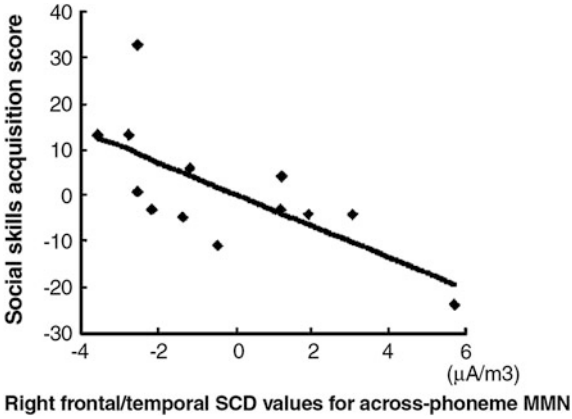

Fig. 3 Larger pre-training MMN amplitude predicts greater acquisition of social skills following an intensive 3-month training program (reprinted from Kawakubo et al. 2007)

4 Prepulse Inhibition of Startle

When a neuro- or psychophysiological biomarker can be studied across species, there is the potential that the measure can be used to elucidate neural and cellular substrates underlying its predictive properties. This concept has motivated studies of PPI as one potential neurophysiological biomarker predicting pro-cognitive drug effects. PPI is a laboratory-based operational measure of sensorimotor gating, in which a weak prepulse inhibits the magnitude of a startle response to an intense, abrupt "pulse" occurring 30–120 ms later. PPI is easily studied in animal models, including mice, rats, guinea pigs, pigs, and infrahuman primates, using stimulus parameters and equipment for stimulus delivery and response acquisition that are similar or identical to what are used in humans (cf. Swerdlow et al. 2008). While there appear to be differences in the neurochemical regulation of PPI across species, the basic parametric properties of PPI exhibit striking similarities from rodents to humans (e.g., Swerdlow et al. 1994). PPI is under significant genetic control in both rodents (Francis et al. 2003) and humans (Greenwood et al. 2011). While it has been advertised as a "simple" behavior, in reality PPI is a complex, heritable phenotype regulated by numerous different genes, as described in many reports (e.g., Greenwood et al. 2011, 2012, 2013). Reduced PPI is not specific to patients with SZ: in addition to SZ (Braff et al. 1978), PPI has been reported to be deficient in patients with Huntington's Disease (Swerdlow et al. 1995; Valls-Sole et al. 2004), Obsessive Compulsive Disorder (Swerdlow et al. 1993a, Hoenig et al. 2005; Ahmari et al. 2012), nocturnal enuresis (Ornitz et al. 1992), Asperger's Syndrome (McAlonan et al. 2002), 22q11 Syndrome (Sobin et al. 2005), Klinefelter Syndrome (Van Rijn et al. 2011), Fragile-X Syndrome (Frankland et al. 2004) and blepharospasm (Gomez-Wong et al. 1998) and Tourette Syndrome (Castellanos et al. 1996; Swerdlow et al. 2001b). However, PPI deficits in SZ patients have been perhaps the best studied: over 40 PubMed reports describe PPI deficits in SZ or "prodromal" patients (cf. Swerdlow et al. 2014).

There are a number of measures that show strong structural similarity to PPI, in that they all assess the amount of behavioral and/or neural inhibition generated by a lead stimulus, as determined by the amount to which the response to a second stimulus is suppressed. In measures of "recovery cycle" (also called "blink excitability," Smith and Lees 1989), "paired pulse inhibition" (Swerdlow et al. 2002), or "intracortical inhibition" (Ziemann et al. 1997), the dependent measure is the motor response to a target stimulus ("pulse" or "S2"), presented either alone or shortly after the presentation of a lead stimulus ("prepulse" or "S1"). A "healthy" response is generally indicated by a diminished motor response to S2 in the presence of S1, compared with the response to S2 alone. Thus, in its simplest view, PPI is a measure of the degree to which a motor response is inhibited by a sensory event, i.e., sensorimotor inhibition. With only 10–120 ms separating prepulses and startling pulses in the "uninstructed" PPI paradigm, PPI is generally viewed as a measure of largely automatic, preattentional inhibitory processes (Graham 1975; Filion et al. 1993). Nonetheless, the amount of PPI at relatively longer (60–120 ms) prepulse intervals correlates significantly with higher cognitive processes, including WM (Letter-Number Span (Greenwood et al. 2013; Light et al. 2007a, b)), strategy formation, measures of cognitive efficiency (Bitsios et al. 2006; Giakoumaki et al. 2006; Light et al. 2007a, b; van der Linden et al. 2006) and even global functioning (Swerdlow et al. 2006a).

PPI deficits in SZ patients might potentially reflect abnormalities at any one or more levels of PPI-regulatory circuitry that stretches from the prefrontal cortex to the pons. Thus, reduced PPI might be found under conditions of excessive dopamine (DA) neurotransmission in subcortical structures, deficient DA, or glutamate transmission in cortical structures, excessive serotonin, or deficient GABA transmission in pallidum (cf. Swerdlow et al. 2008), etc. In fact, PPI *deficits* in a particular patient might reflect an almost infinite number of deficits in isolation or combination. But for a SZ patient to exhibit *robust levels* of PPI requires functionality within some or all of PPI-regulatory circuitry, and perhaps more importantly the integrity of the process of sensorimotor gating. So, compared to PPI deficits, a biomarker of "normal" PPI might be more interpretable.

PPI levels in SZ are highly stable, with 1-year ICC's approaching 0.80 (Light et al. 2012). While some groups have reported medium-to-large effect size deficits in PPI in SZ versus healthy cohorts, our most recent large single-site reports have detected deficits with 60 ms prepulse intervals with effect sizes that ranged from 0.24 (Swerdlow et al. 2006a, b) to 0.58 (Light et al. 2012). Factors that may contribute to "artificially" small PPI differences between SZ and healthy cohorts include: (1) SZ-linked PPI deficits generally appear to be most robust under specific sets of stimulus parameters, i.e., the type of prepulse used [auditory vs. tactile; tone vs. noise; prepulse intensity over background and prepulse interval, etc. (Braff et al. 2001; Swerdlow et al. 2006a, b)]; (2) women have lower PPI than do men (Swerdlow et al. 1993a, b), and in most studies, healthy subjects are predominantly women, while SZ patients are predominantly men; (3) PPI is generally increased by nicotine (Hong et al. 2008; Kumari et al. 2001), and smoking is both more common and heavier among SZ patients versus healthy

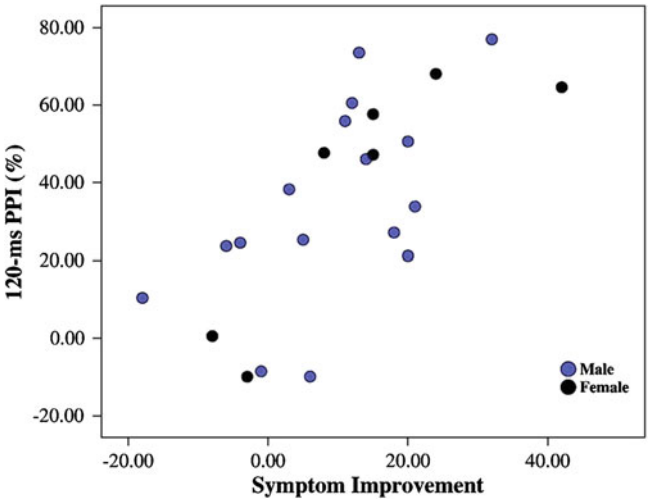

Fig. 4 Higher levels of baseline PPI predict positive response to cognitive-behavioral therapy in schizophrenia patients (reprinted from Kumari et al. 2012)

subjects; (4) PPI is higher in medicated versus unmedicated SZ patients, and especially in patients medicated with second-generation antipsychotics (SGAPs) (Csomor et al. 2009; Kumari et al. 1999; Swerdlow et al. 2006a, b; Weike et al. 2000); SGAPs are used by more than 80 % of SZ patients in most recent studies.

One implication of the relative modest effect sizes of PPI deficits in SZ cohorts is that many SZ patients exhibit PPI levels at, or above, HS "mean" values. Presumably, these "normal" PPI levels in SZ patients can serve as a biomarker of normal function in PPI neural circuitry; this does not mean that the entire PPI-regulatory apparatus is intact in these individuals, but simply that the overall circuit properties—with or without the influence of nicotine, SGAPs, and other moderating factors—remain adequately intact to perform its "function" of sensorimotor gating. Thus, "higher" neurocognitive processes that rely on intact sensorimotor gating would be not be expected to impaired in these individuals based solely on this reliance; certainly, these processes might nonetheless be impaired, based on deficits in other basic information processing mechanisms.

In keeping with our model of using biomarkers to identify residual "intact" neural mechanisms and function, it is reasonable to consider whether "high PPI" could be used as a biomarker of SZ patients who might be capable of marshaling adequate cognitive resources to meet the demands of, and reap the benefits of a particular therapeutic intervention. Consistent with such a model, Kumari et al. (2012) were able to demonstrate that baseline PPI levels positively predicted the therapeutic response to cognitive-behavioral therapy (CBT; Fig. 4). Schizophrenia patients who exhibited the highest pretherapy PPI levels were the ones who benefitted most from CBT, in terms of reductions in symptom severity. This finding supports the notion that evidence of intact, functioning neural mechanisms,

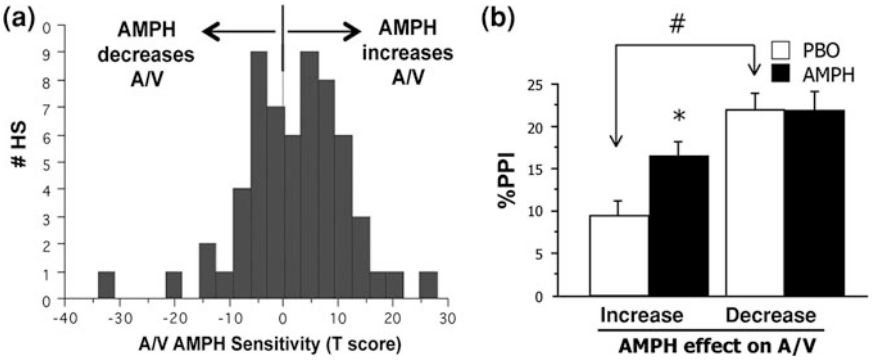

Fig. 5 Using a drug challenge to identify residual plasticity in sensorimotor gating and attentional capacity: a "proof of concept" in healthy subjects. **a** Distribution of the change in MCCB A/V T-scores after amphetamine (AMPH; 20 mg p.o.) versus placebo, corrected for order effects, in 60 healthy subjects (Swerdlow et al. 2013). **b** Baseline PPI was significantly lower (#) and more sensitive to AMPH-enhancement (*), among subjects in whom AMPH increased versus decreased A/V in "A"

provided by a psychophysiological biomarker, can positively predict the therapeutic response to a higher cognitive intervention.

The neural circuitry regulating PPI includes neurotransmitters and receptors that are targets of many of the major classes of psychotropic medications. Drugs acting at prominent nodes in this circuitry have potent effects on PPI, which have been studied extensively in rodents, and more recently in humans (cf. Swerdlow et al. 2008). Among our proposed applications of biomarkers for SZ therapeutics, we suggested a model in which a neural system at baseline may perform poorly, but still respond to a "push" of a pharmacologic challenge; in this case, evidence for the requisite "spared" neural circuitry, and hence a target for therapeutic intervention, is provided by changes in response to a drug challenge. In essence, the acute drug challenge is used to determine whether the impaired system retains sufficient plasticity to respond to therapeutic input.

To date, our "proof of concept" studies for the potential to detect residual plasticity in neurocognitive substrates via drug challenges in "low performers" have exclusively involved healthy subjects. We reported that in specific subgroups of HS—groups characterized by low basal PPI, low novelty-, or sensation-seeking traits—a single dose of the psychostimulant, amphetamine (AMPH, 20 mg p.o.) potently enhances PPI (Talledo et al. 2009). This suggests that among some individuals—even (though not exclusively) in the presence of low basal PPI—the neural circuitry regulating PPI retains significant plasticity, in that it can respond positively to a drug challenge. We also reported that this same dose of AMPH enhances MCCB performance, particularly in the domain of attention /vigilance (A/V), among 60 healthy individuals with low baseline A/V performance (Chou et al. 2013b; Fig. 5). When we stratified these 60 subjects according to baseline PPI, those with low baseline PPI were the ones most sensitive to both the PPI- and

A/V-enhancing effects of AMPH. Presumably, the neural circuit plasticity evident in low PPI healthy subjects predicts the likelihood of exhibiting a pro-attentional response to AMPH. We are currently testing these relationships in SZ patients. Ultimately, among patients exhibiting deficits in biomarkers, we might use a "challenge" paradigm to reveal those whose residual plasticity would predict benefits from the addition of a specific drug to a cognitive intervention. Clearly, we are several steps from fully testing this "drug challenge" biomarker model, but the path to such a test is clear.

5 Discussion

One of the challenges facing the use of biomarkers in SZ populations is that, for the most part, biomarkers are being applied "after the fact." In other words, if we acknowledge that SZ is a neurodevelopmental disorder (or set of disorders), likely reflecting perturbations of in utero neural development, then the events (genetic, environmental or otherwise) that lead to the late-adolescent/early adult manifestations of the disorder have come and gone, decades before biomarker data are measured. And the number of variations in the expression of these early events—e.g., variable neuronal migratory routes, the adjustments of the surrounding developing brain to them, the consequent alterations in premorbid behavior and the reflected impact of environmental responses onto brain development—from in utero causative event to adult manifestation are substantial if not limitless. And unlike disorders of adult onset in which an anatomically or neurochemically constrained "lesion" is superimposed on a normally developed brain, in SZ, the absent connections lost to cells that did not arrive, and the aberrant connections formed in their place, are infused throughout the matrix of a very complex forebrain circuitry. Making sense of "right" and "wrong" in this circuit context, as a basis for understanding the biology of SZ, its courses or treatments, may not be feasible, or even productive, in the foreseeable future.

We have proposed an alternative use of biomarkers in predicting treatment response in SZ patients, that is consistent both with the therapeutic goals of personalized medicine and the scientific strategies of experimental medicine (Insel 2014). Individuals are characterized via measures of brain activity that are associated with neurocognition and function, and areas of "healthy" or "normal range" performance are identified. In this process, drugs or other experimental manipulations and designs can be used as clinical probes to identify targets of residual neuroplasticity. Treatments are then identified that leverage the intact neural circuit or neurocognitive resources so that the individual patient can utilize their capacities to reap the gains of the therapeutic intervention. In truth, the basic principles of the "biomarkers of health" approach are simple ones, long espoused by disciplines ranging from childhood education to career counseling: a successful outcome is best achieved by matching residual strengths—areas of "resiliency"—with task demands. In the frenzied search for the genetic and molecular markers

and mechanisms of what's wrong with individuals with SZ, our field and its treatments may not have fully appreciated and leveraged all that is "right".

One key to the successful use of biomarkers in this model is the ability to link a "healthy" biomarker with a positive response to a specific therapy. For example, as we allude to in our Introduction, some forms of cognitive training put demands on processes requiring "healthy" WM and attention (Haut et al. 2010), and thus would be best pursued in patients with biomarker evidence of relatively intact WM and attentional capacity. Alternatively, evidence that WM and attentional performance could be enhanced in that patient by a psychostimulant challenge (e.g. Barch and Carter 2005) might predict benefits of psychostimulant augmentation of cognitive training. Different biomarkers of neurocognitive and neural circuit strengths might predict optimal responses of SZ patients to CBT, (e.g. Kumari et al. 2009) computerized cognitive training, social skills training, or even medications like the pro-extinction drug, D-cycloserine (Gottlieb et al. 2011), or the "pro-social" drug, oxytocin (Davis et al. 2014). While there is substantial evidence that baseline cognitive deficits generally predict poor outcomes in cognitive interventions (Becker et al. 1998; Green 1996; McGurk and Meltzer 2000; McGurlk and Mueser 2004; Spaulding et al. 1999), we are not yet at a point where we can apply specific algorithms other than "clinical intuition" to match biomarkers of intact neural function in a SZ patient, with treatment response to different types of therapies. Developing such algorithms will be advanced by incorporating informative biomarkers, like MMN and PPI, and detailed neurocognitive assessments, into the designs of trials of cognitive interventions for SZ. Importantly, the fidelity and optimal methods for many potential biomarkers have already been established in multi-site studies, where deficits in these measures have been used as endophenotypes to identify risk genes for SZ (Turetsky et al. 2007). In the figure-ground reversal proposed here, these biomarkers are used not to predict a risk of illness, but rather, they are used to predict a likelihood of recovery.

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