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Can neuroimaging-based biomarkers predict response to cognitive remediation in patients with psychosis? A state-of-the-art review

Bruno Biagianti,[1,2] Davide Bigoni, [1] Eleonora Maggioni,[1] Paolo Brambilla [1,3].

[1] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy;
[2] Department of R&D, Posit Science Corporation, San Francisco, CA, USA;
[3] Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

INTRODUCTION

Major psychotic disorders (MPD) are part of a heterogenous nosographic category of non-affective and affective psychoses that can be classified by duration, by symptom profile and by the relationship between psychotic symptoms and episodes of disturbed mood (occurrence of the psychotic symptoms during mood disturbance, or beyond) (Jeffrey, A., Lieberman, M.D., Michael, B., and First, 2018).
MPD are characterized by a range of neurocognitive impairments (Heinrichs et al., 2013) – with up to 75% of patients showing performances on standardized neuropsychological tests that range from about 1.0 to 1.7 SD below that of the healthy adult normative sample (McCleery and Nuechterlein, 2019). Cognitive impairments better correlate with future functional outcome than positive and negative symptoms (Galderisi et al., 2016), and are directly responsible for poor long-term psychosocial outcomes, including difficulties in bonding, keeping an occupation, and attaining independent living (Dziwota et al., 2018; Lam et al., 2018). Therefore, for people with MPD, intervening early to address cognitive impairments becomes of critical importance (Bellani et al., 2019).
While antipsychotic medications are known to reduce positive and negative symptoms, they show no effect on cognitive impairments (Goldberg et al., 2007; Keefe et al., 2007). Cognitive remediation (CR) is an intervention based on behavioral training that has been developed with the objective of improving cognitive processes in a generalized and long-lasting manner (Cognitive Remediation Experts Workshop – CREW). Most of the research on CR has been conducted on MPD patients and has mainly focused on the improvement of cognitive functions that are most commonly impaired: attention, working memory, executive functions, metacognition and social cognition (Vinogradov et al., 2012).
CR is designed to halt or reverse the pathological neural systems that characterize MPD, and its main objective is to assure cognitive remediation, as well as amelioration of psychosocial functioning (Medalia and Saperstein, 2013). Compared to antipsychotic medications, CR is associated with less deleterious side effects, resulting in a less stigmatizing (Morrison et al., 2002), more acceptable treatment (Morrison et al., 2004). For these reasons, CR has become a component of integrated treatments for MPD that is pivotal to ameliorate the course of illness (Fisher et al., 2015), or even to protect the at-risk individual against the onset of a first psychotic episode (Barlati et al., 2016; Loewy et al., 2016).
A wide variety of remediation techniques has been studied over the last twenty years including computer-based training, educational software and therapist-guided strategy coaching in problem-solving tasks (Biagianti et al., 2021). Computer-based training program is the most studied form of CR. Computerized programs either use *neuropsychological principles* to target cognitive processes, such as attention, memory and executive functions, or leverage the mechanisms of *neuroplasticity* to increase the speed and accuracy of auditory and visual processing. While research currently supports the efficacy of both neuropsychology-based and neuroplasticity-based CR in improving targeted cognitive domains (Medalia and Saperstein, 2013), the magnitude of CR-induced cognitive gains greatly varies across patients with MPD, with up to 40% of participants not showing gains in global cognitive performance (Keefe et al., 2011), even after 100 hours of training (Fisher et al., 2010), or with no transfer effects to untrained cognitive outcome measures (Keefe and Harvey, 2012; Murthy et al., 2012).
This is likely due to the high degree of heterogeneity in the neural activation patterns that underlie cognitive endophenotypes, and to inter-individual differences in neuroplastic potential, cortical organization and interaction between brain systems in response to learning. Accordingly, the purpose of this paper is to review studies that used neuroimaging to identify biomarkers that could potentially serve as predictors of treatment response to CR.

METHODS

Search Strategy

Our overarching search strategy involved querying electronic databases (Embase, Elsevier; Scopus, PsycINFO, APA; PubMed, APA) with customized search strings, followed by manual filtering of query results using predefined inclusion and exclusion criteria. In an effort to capture cognition-based interventions whether or not they were labeled as "cognitive remediation", we included key domain terms ("cognitive training" or "cognitive enhancement"). Additionally, we included key domain terms for neuroimaging techniques (such as electroencephalography, "EEG", or Magnetic Resonance Imaging, "MRI"), as well as terms analogous to variations of "psychosis" in our queries. We used Boolean operators (AND, OR) to delineate our results. In addition, references of each included article were carefully scrutinized to further identify other studies of possible interest.

Risk of bias assessment was compliant with recent guidelines from the Agency for Healthcare Research and Quality Evidence-based Practice Center (Viswanathan et al., 2012). Constructs used to assess the risk of bias of individual studies included: Poor or inadequate reporting, Selective outcome reporting, Outcome measures, Study design, Fidelity to protocol, Conflict of interest from sponsor bias, and Applicability/external validity. Whenever risk of bias was deemed not low, and/or for every mismatch in extracted data, all authors discussed until a consensus was reached (Viswanathan et al., 2012).

Eligibility Criteria and Study Selection

We first identified studies by restricting our search to peer-reviewed, English-language journal articles; non-human, review, and meta-analytic reports were excluded. Studies were included according to the following criteria: (a) being an original paper published in a peer-reviewed journal, (b) being an English language paper, (c) recruited and reported data for adults aged 18+ with MPD, and (d) reported findings from randomized controlled trials (RCTs) or single-arm trials of CR; and (e) presented data collected through neuroimaging techniques.

Studies were excluded if they (1) included adolescents or younger children; (2) investigated psychological, psychosocial, or psychoeducational interventions only, without any CR approach or technique. In order to reduce biological confounds due to the heterogeneity of study design and samples, we also excluded studies wherein the independent variables were primarily physiological, e.g., drugs (e.g., Oxytocin, Risperidone, d-Cycloserine), devices (tDCS, rTMS), physical therapy, or biofeedback. Primary and secondary screenings were conducted by two independent reviewers (BB and DB). Consensus for inclusion was reached after discussion with all authors involved.All authors reviewed in full those articles that met inclusion and exclusion criteria. Please see Figure 1 for the PRISMA flow-chart.

RESULTS

We report below a summary of the findings obtained to date on neuroimaging-based biomarkers that can predict response to CR. EEG indexes are presented first, followed by MRI parameters (see Table 1).

Auditory mismatch negativity

We reviewed three studies with a total population of 234 cases that investigated, through clinical trials, whether auditory mismatch negativity (MMN) would predict the response to CR. Mismatch negativity, an index of early auditory processing, is an EEG-derived event related potential (ERP) that is elicited pre-attentively when an infrequent deviant sound violates an established pattern of repeated standard sounds (Näätänen et al., 1992). The MMN response is seen as a negative displacement, in particular at the frontocentral and central electrodes in the difference wave obtained by subtracting the ERP to frequent, "standard", stimuli from that to deviant stimuli (Näätänen et al., 2005). MMN amplitude is thought to signal the prediction error that occurs during implicit perceptual learning when the auditory deviant violates the auditory expectancy (Garrido et al., 2009), therefore

capturing the intersection between perceptual and neurocognitive processes. In support of this theory, Escera et al. (Escera et al., 2003) provided evidence of the involvement of the prefrontal cortex in providing top-down modulation of the deviance detection system in the temporal cortices. Specifically, MMN seems to be sustained by two neural processes, a sensory memory mechanism related to temporal generators and an automatic attention-switching process related to the frontal generators (Garrido et al., 2009; Giard et al., 1990): sensory memory mechanism has been associated with the temporal generators, whereas a cognitive role assigned to the prefrontal generators (Gomot et al., 2000; Maess et al., 2007). Likewise, Rinne et al. (Rinne et al., 2000) demonstrated that the temporal and frontal MMN sources have separate temporal dynamics, even though they interact with each other (Jemel et al., 2002)

MMN is shown to be associated with verbal encoding, working memory, episodic and semantic memory, and psychosocial functioning in normal participants (Light et al., 2007). MMN amplitude, posited to reflect N-methyl-D-aspartate receptor (NMDAR) function (Todd et al., 2013), was found to be reduced in chronic schizophrenia, first episode psychosis, and even individuals at risk for psychosis (Koshiyama et al., 2021; Light and Braff, 2005; Perez et al., 2014). Because it constitutes the most sensitive readout of automatic auditory deviance processing, MMN has been used to predict and track response to CR in MPD patients (Biagianti et al., 2017; Hochberger et al., 2018; Perez et al., 2017). Healthy participants show persistent MMN improvements after auditory CR (Spierer et al., 2007), while patients with schizophrenia –which severely impairs the fronto-temporal networks underlying auditory processing and signal resolution of auditory inputs– do not (Biagianti et al., 2017; Kariofillis et al., 2014). Interestingly, greater MMN deficits (smaller ERP amplitudes) are associated with larger cognitive gains following auditory CR in patients with MPD (Biagianti et al., 2017), suggesting that individuals with the most severe auditory processing deficits may stand to gain the most from targeted auditory CR. Perez et al. found that larger MMN amplitude recorded before CR in MPD was associated with greater gains in auditory perceptual learning (Perez et al., 2017). Finally, initial malleability of MMN, i.e. change from baseline after the initial 1-h dose of CR, predicted improvements in verbal learning as well as decreases in the severity of positive symptoms (Hochberger et al., 2018). Taken together, these findings indicate that MMN appears to be a promising biomarker of treatment response, helping identify individuals who have the greatest potential to benefit from CR, including achievement of greater cognitive gains.

Auditory steady-state response (ASSR)

We reviewed one study with a total population of 42 cases that investigated, through a clinical trial, whether auditory steady-state response (ASSR) would predict the response to CR. Auditory steady-state response (ASSR) is a stimulus-evoked oscillation, generated from primary auditory cortex (Pantev et al., 1993), that can be measured with EEG in response to a sound that is repeated at a fixed rate or frequency. ASSR has been shown to reach its maximum at 40-Hz and this result has been widely replicated (Roach et al., 2013). The 40-Hz ASSR has been shown to be reduced in patients with schizophrenia (Koshiyama et al., 2021; Thun et al., 2016) or other psychosis spectrum disorders, including schizoaffective disorder and bipolar disorder (Zhou et al., 2018), and in individuals at clinical high risk for psychosis (Tada et al., 2016). Recently, Molina and colleagues used an ASSR paradigm to elicit gamma oscillatory power during EEG recordings in MPD patients who underwent CR (Molina et al., 2020). The study found that baseline ASSR predicted cognitive improvement after CR, suggesting that a greater capacity to support gamma oscillations could represent the neural mechanism by which CR induces cognitive gains.

Efference copy corollary/discharge

Efference copy/corollary discharge is defined as a reduced auditory cortical response to self-generated compared to externally generated sounds. During talking, brains automatically generate predictions about the sound of impending vocalizations in order to adjust ongoing speech match intentions. These rapid comparisons help to distinguish between auditory sensations resulting from

our own actions, including overt actions (e.g., speech) and possibly covert actions (e.g., thoughts), and externally generated sounds (Greenlee et al., 2011). In humans, the function of the efference copy/corollary discharge mechanism can be assessed using scalp-recorded EEG and the EEG derived ERPs. Specifically, the auditory N100 (N1) component of the ERP, which emanates from auditory cortex, is reduced in amplitude in response to vocalizations as they are being produced relative to when they are played back (Ford et al., 2016).
Given its clinical relevance and degree of correlation with cognition (Subramanian et al., 2019), efference copy/corollary discharge could represent a reliable biomarker of treatment response to CR for patients with MPD. CR targeting auditory system functioning has the potential to improve the transmission of the efference copy during talking from frontal lobes to auditory cortex, and/or sensory re-afference in auditory cortex (Wang et al., 2014), thus allowing the brain to suppress sensations resulting from its own actions, a hallmark of successful functioning of the mechanism (Roach et al, 2019). While efference copy corollary/discharge has great potential to predict treatment response to CR, Roach et al. (Roach et al., 2019) was unable to show whether baseline N1 suppression abnormalities are necessary for CR to have a positive effect in MPD. In sum, although to date the scientific literature did not explore efference copy corollary/discharge's ability to predict the response to CR, it certainly holds great potential.

Resting state EEG
To date, the scientific literature did not explore resting state EEG as a predictor of response to CR, even though resting state EEG oscillations are certainly great candidates as a biomarker. Cognitive or perceptual tasks require a coordinated flow of information within networks of functionally specialized brain areas, as it has been argued that neuronal oscillations provide a mechanism underlying dynamic coordination in the brain (Fries, 2015; Siegel et al., 2012). These oscillations likely reflect synchronized rhythmic excitability fluctuations of local neuronal ensembles (Buzśaki and Wang, 2012), and may facilitate the flow of neural information between nodes in the network when the oscillations are synchronized between those nodes (Womelsdorf et al., 2007).
In this framework, cognition surfaces as the result of the integration of scattered mosaics of functionally specialized brain regions, and although the mechanisms implicated in large scale integration are still largely unknown, it has been proposed that a possible candidate is the formation of dynamic links mediated by synchrony over multiple frequency bands (Varela et al., 2001).
Resting-state brain activity directly stems from connectivity mechanisms of divergence and convergence that involve oscillations at all frequency bands in association with networks of inhibitory interneurons (Bullmore and Sporns, 2009).
Thus far, EEG resting state has been an important tool to investigate cognitive performance and malleability in older adults (Volf et al., 2018). In elderly individuals at risk for dementia with mild cognitive impairment, it was recently shown that reorganization of beta-band functional connectivity correlated with CR-induced changes (Klados et al., 2016).
In MPD, resting-state EEG abnormalities (such as higher connectivity in delta and theta bands and lower connectivity in alpha band) are often present across the illness' progression to chronic stages (Di Lorenzo et al., 2015; Narayanan et al., 2014). In addition, lower connectivity in alpha band and decreased theta power are commonly observed across parietal regions in individuals vulnerable to psychosis (Di Lorenzo et al., 2015; Zhang et al., 2021). For these reasons, resting state EEG could represent a powerful tool to identify neural endophenotypes and response patterns to cognitive interventions, including CR.

White matter microstructure
We reviewed one study with a total population of 76 cases that investigated through a clinical trial whether white matter microstructure would predict the response to CR. MPD are considered disorders of both functional and structural neural system connectivity, with widespread deficits observed in white matter architecture (Marenco et al., 2012). Disruption of white matter integrity can be evaluated

with an index known as fractional anisotropy (FA), used to characterize the degree of anisotropy, i.e. the degree of water molecules diffusion along the axon (Skudlarski et al., 2010). Reduced white matter integrity, as indexed by decreased FA, has been observed in patients with MPD, relative to healthy control participants, in whole brain white matter, as well as in various regions such as the splenium of the corpus callosum (Foong et al., 2000), the uncinate fasciculus connecting the frontal and temporal lobe, and the cingulum (Kubicki et al., 2003, 2002).
Three tracts have been identified where greater white matter integrity is associated with a significantly better response to CR in MPD patients: 1) the superior fronto-occipital fasciculus, which provides direct connection between frontal and occipital areas, is critical for conveying visual information from occipital sensory cortices to the prefrontal cortex, and was found to predict significant training-induced improvement on attention/vigilance (Subramaniam et al., 2018); 2) medial lemnisci, which contain pathways from the skin via the thalamus to the prefrontal cortex, and are therefore vital for the analyses and integration of sensory-motor information, and were found to predict improved executive functioning after CR (Subramaniam et al., 2018); and 3) the corticospinal tracts, where cortical afferents to frontal motor areas originate from the parietal lobe, the prefrontal cortex, and cingulate cortex (all dedicated to specific sensory-motor executive transformations), and were found to predict improved executive functioning after CR (Subramaniam et al., 2018). Taken together, these findings highlight the potential of FA in predicting the magnitude of cognitive gains following CR.

Gray Matter Morphology
We reviewed three studies with a total population of 144 cases that investigated, through clinical trials, whether gray matter morphology would predict the response to CR. Gray matter abnormalities are commonly observed in patients with MPD and represent a predictor of poorer functional outcomes (Ho et al., 2003; Mathalon et al., 2001). Significant cortical thinning has been found in MPD and even in first episodes psychosis (Crespo-Facorro et al., 2011; Schultz et al., 2010; Venkatasubramanian et al., 2008). Additionally, it has been found that patients with schizophrenia present prefrontal cortical thinning especially in the lateral prefrontal areas (Glahn et al., 2008; Honea et al., 2005), and those reductions are associated with impaired executive functions (Crespo-Facorro et al., 2011).
Cortical thickness has been investigated as a predictor of CR response in MPD patients. Higher gray matter volume at baseline was found to significantly moderate the effects of CR on social cognition (Keshavan et al., 2011), and higher cortical thickness at baseline in frontal, temporal and occipital cortical brain areas was found to be associated with greater improvements in memory after CR (Penadés et al., 2016). Finally, reduced cortical thinning in frontal, temporal, parietal and occipital lobes was found to correlate with improvements in global cognition following CR (Ramsay et al., 2021). These sets of evidence corroborate the validity of using cortical thickness to predict the magnitude of cognitive gains following CR in MPD patients.

Thalamocortical connectivity
To date, despite of its potential, no studies have investigated whether thalamocortical connectivity can be used as a predictor of response. There is, instead, experimental support to hypothesize its role as a biomarker of change. We reviewed one study with a population of 44 cases that investigated, through a clinical trial, whether thalamocortical connectivity could serve as a biomarker of change.
Findings in humans demonstrate that thalamocortical connections influence cognitive functioning across the lifespan (Wang et al., 2012), with positive correlations between thalamo-prefrontal functional connectivity and global cognition (Woodward and Heckers, 2016). Aberrant thalamo-temporal connectivity is associated with increased psychiatric symptoms (Ferri et al., 2018), while disconnections with the prefrontal cortex appear to more closely underlie cognitive dysfunction (Woodward and Heckers, 2016).
Disruption in thalamocortical circuitry has been observed in schizophrenia (Agarwal et al., 2008), characterized by a pattern of both functional and structural hypo-connections between the thalamus

and prefrontal and cerebellar regions, and hyper-connections between the thalamus and auditory, visual, motor, and association cortices (Corradi-Dell'Acqua et al., 2012, Ramsay et al., 2019). These hyper- and hypo-connections are also found to negatively correlate with one another, suggesting that they arise from a common pathophysiological mechanism (Ramsay et al., 2019; Woodward and Heckers, 2016), which appears to be present not only in MPD patients but also in patients at clinical high risk for psychosis (Anticevic et al., 2015).
Given its clinical relevance and degree of correlation with cognitive dysfunction in psychosis (Chen et al., 2019), thalamocortical dysconnectivity has been studied as a potential mechanism of action for CR. Patients after auditory CR show increased thalamocortical connectivity in the left superior temporal gyrus, suggesting that this form of CR evokes intrinsic functional plasticity in auditory processing networks, and may do so by influencing thalamocortical networks (Ramsay, 2019). Additionally, an increase in thalamo-temporal connectivity after auditory CR was found to correlate with improvements in global cognition (Ramsay et al., 2020).

Task-based fMRI
We reviewed seven studies with a total population of 320 cases that investigated, through clinical trials, whether task-based fMRI measures would predict the response to CR.
Patients with MPD show consistently inefficient recruitment of prefrontal neural network resources as cognitive efforts and executive functions are requested (Brissos et al., 2008; Callicott et al., 2000; Minzenberg et al., 2009; Wingo et al., 2009). It has been demonstrated abnormal activation of dorsolateral prefrontal cortex (dPFC) when performing different working memory tasks both in schizophrenia (Barch et al., 2002; Callicott et al., 2000; Carter et al., 1998; Perlstein et al., 2003) and in mood disorders (Garrett et al., 2011; Townsend et al., 2010).
A powerful method of studying the whole-brain correlates of such impairments is functional magnetic resonance imaging (fMRI), especially during n-back tasks that recruit working memory functions (Haut et al., 2010; Royer et al., 2009).
Cognitive improvements have been shown as significantly correlated with dPFC activity changes (Haut et al., 2010; Miskowiak and Petersen, 2019). Because of its pivotal role in studying the neural changes induced by CR (Meusel et al., 2013; Penadés et al., 2013), task-based fMRI has been used to identify potential biomarkers of treatment response to CR in MPD patients (Bor et al., 2011; Subramaniam et al., 2014; Wykes et al., 2002).
The role of dPFC during a working memory task has been studied in remitted patients with bipolar disorder as a predictor of CR treatment efficacy, finding that pre-treatment dPFC hypo-activity during working memory performance predicts greater effects of CR (Miskowiak et al., 2021). Similarly, early change in working memory related neural activity after two weeks of CR was found to predict executive function improvements at treatment completion after 10 weeks (Ott et al., 2020). Therefore, evidence from bipolar patients suggests that task-based fMRI could also be used in MPD to identify neurocircuitry-based biomarkers for pro-cognitive effects upon exposure to CR.

DISCUSSION

1. Summary of findings.

The scope of this narrative review was to identify neuroimaging-based biomarkers with enough scientific rationale and degrees of evidence to be considered as candidate predictors of response to CR. We found sixteen clinical trials investigating the response to CR. Ten studies focused on the identification of *predictors of response* to CR, i.e., indexes whose baseline evaluation has been associated with different magnitude of response to CR, and therefore can be included in CR protocols to determine upfront treatment uptake for a given individual. Six focused on the identification of *biomarkers of change* induced by CR, i.e., neural parameters that change as a result of CR. For such

biomarkers, the magnitude of change after CR is found to correlate with the degree of cognitive gains, suggesting that they can shed light on mechanisms of action of this experimental intervention.

2. Neuroimaging-based biomarkers for cognitive remediation.

Auditory mismatch negativity is a promising predictor of response with the strongest scientific rationale, as we reviewed a total of 7 clinical trials on this matter. We found three studies that support its potential as a predictor and biomarker of early change. Biagianti et al. found that greater MMN deficits are associated with larger cognitive gains following auditory CR in patients with MPD (Biagianti et al., 2017), whereas Perez found that smaller MMN deficits are associated with greater gains in auditory perceptual learning (Perez et al., 2017). These inconsistent findings are further enriched by evidence that changes in MMN after 1 hour of CR predict improvements in verbal learning as well as decreases in the severity of positive symptoms (Hochberger et al., 2018). In sum, more studies are necessary to clarify the contribution that MMN can give as a predictor and biomarker.

The line of work on *auditory steady-state response* is showing great potential, even though is still lacking in experimental support, as we found only 1 study suggesting that gamma oscillatory biomarkers can predict the response to CR. 40-Hz ASSR is a good candidate biomarker of impaired GABAergic and/or glutamatergic neural activity, of early sensory processing, and ultimately of cognitive impairment (Handan et al., 2013). This stems from the notion that 40-Hz ASSR seems to be influenced by fast-spiking, parvalbumin-expressing inhibitory γ-aminobutyric acid (GABA) interneurons and NMDAR glutamatergic signaling in the interneuron-pyramidal neuron microcircuits that generate normal gamma band oscillations (Sohal et al., 2009). Similar to MMN, we can therefore hypothesize that greater ASSR deficits could predict larger response to CR.

Significant correlations exist between *white matter integrity* indexed by FA and cognition in MPD patients. For example, patients with schizophrenia have reduced FA in the anterior limb of the internal capsule (the medial portion of which includes the anterior thalamic radiation), in which better integrity has been associated with better working memory and executive functioning (Mamah et al., 2010). In this review, we found that *the integrity of white matter plays a pivotal role* in predicting the response to CR, in that MPD patients with greater white matter integrity pre-treatment showed larger cognitive gains after CR (Subramaniam et al., 2018). More studies are needed to explore white matter integrity as a potential biomarker of treatment response to CR in psychotic patients.

Research on *gray matter morphology* produced encouraging predictive measures of response to CR, as cortical thickness plays a pivotal role in brain activation patterns. This is because the integrity of cerebral cortices is a fundamental requisite for neural activation (McDonald et al., 2007). On this topic, we reviewed a total of three clinical trials, which elucidated how broad cortical surface area and gray matter reserve, specifically in some brain areas located mainly in regions of frontal and temporal lobes, are associated with greater response to CR (Keshavan et al., 2011; Penadés et al., 2016, Ramsay et al., 2021).

Finally, *task-based fMRI* shows a growing body of evidence for predictors and biomarkers of change after CR, with seven clinical trials reporting aberrant activity in one of the neural substrates of cognition. To date, task-based fMRI measures have been primarily used as biomarker of change, even though preliminary evidence suggests its use also as a predictor of response.
Furthermore, it seems that dPFC, both hyper- and hypo-activate during cognitive tasks. These discrepant conclusions are reconciled in a model proposed by Petersen and Miskowiak, in which dPFC displays hyper-activity when task performance is maintained at a normal level, and hypo-activity when performance declines compared to controls (Petersen and Miskowiak, 2021).

Therefore, modulation of dPFC activity may represent a common systems-level neurocircuitry biomarker model for pro-cognitive effects that arise from CR-related increase in neuroplasticity (Ott et al., 2020).

Thalamo-cortical connectivity is aberrant in psychosis, improves after CR, and is known to serve as a biomarker of change - i.e., the magnitude of its improvements parallels gains in cognitive performance (Ramsay, 2019; Ramsay et al., 2020). These results offer a theoretical basis for the neural mechanisms supporting CR in MPD patients, and provide experimental support for thalamo-cortical connectivity to function both as a biomarker of change as well as a treatment target. For these reasons, we are optimistic about the possibility that thalamo-cortical connectivity could also be used as a predictor of response. Analyses are currently underway to test this hypothesis.

Finally, in light of their relationship with cognition and MPD, *efference copy corollary/discharge* and *resting-state EEG* indexes hold great promise, although no clinical trials have investigated their ability to predict response to CR. The neural generators currently theorized for these two EEG signals greatly overlap with the hypothesized targets for CR (efficiency and connectivity in distributed prefrontal-sensory systems), suggesting that both efference copy corollary/discharge and resting-state EEG could function as predictors of response and as biomarkers of change. Patients with schizophrenia and people at clinical high risk for psychosis show attenuated or absent suppression of auditory cortex in response to self-generated sounds, possibly due to deficits in efference copy/corollary discharge mechanisms (Perez et al., 2012). These deficits, consequently, may underlie the inability to make predictions about the sensory consequences of self-generated actions and to utilize them to adjust behavior and tag experiences as self-generated. Impaired efficiency and connectivity in the distributed prefrontal-temporal auditory systems known to be affected by MPD (Ford et al., 2002) could limit improvements in untrained higher-level cognitive operations after CR (Biagianti et al., 2016). Therefore, efference copy/corollary discharge indexes have great potential to predict treatment response to CR (Subramanian et al., 2019). Analogously, *several lines of evidence support* the potential of *resting state EEG* measures in predicting treatment response. Because 1) neural connectivity patterns during resting wakefulness have been shown to be highly stable for an individual, with up to 90% in heritability in some frequency bands (van Beijsterveldt and Boomsma, 1994); 2) studies have shown that the brain resting state provides a core and intrinsic network architecture that highly overlaps with the network topology of brain task states (Cole et al., 2010; Krienen et al., 2014); and 3) a powerful link exists between resting-state EEG features and cognitive performance (Başar et al., 2001; Geerligs et al., 2015), resting-state EEG is an excellent method to identify cognitive endophenotypes and patterns of response to CR and other cognitive interventions.

In sum, the research conducted to date encourages the tentative implementation in clinical and translational medicine of auditory mismatch negativity, auditory steady-state response, gray matter morphology and white matter microstructure as possible predictors of response. These paradigms have enough evidence to be implemented in translational protocols, so that CR can be delivered in a way that is optimized, personalized and informed through research findings. It is important to note that, while resting state activity, auditory mismatch negativity, efference copy corollary/discharge and auditory steady-state response can be measured through EEG, cortical thickness, white matter microstructure, and thalamo-cortical connectivity measures can be collected using MRI. This has obvious implications on the readiness for implementation in clinical environments, as EEG is exceedingly more affordable and placeable in the clinics than MRI.

3. *Theoretical and clinical implications*

The neural mechanisms underlying many of the EEG and MRI paradigms that we have considered as potential biomarkers point towards a construct of paramount importance when thinking about

response to treatment, that is cognitive reserve. It is now well-established that the concept of cognitive reserve is strictly associated with activation of NMDA receptors, necessary for neuroplasticity (Clem et al., 2008), and that NMDA receptor activity is impaired in MPD (Cho et al., 2016; Coyle, 2006). Indirect proof that intensive CR could in fact enhance synaptic glutamatergic activity in the brain is that increases in serum D-serine, an endogenous co-agonist of NMDA receptors, are associated with gains in cognition upon exposure to CR (Panizzutti et al., 2019). As a matter of fact, the biomarkers we have investigated may capture the neural underpinnings of cortical plasticity mechanisms that occur in the brain, and therefore be measures of "brain reserve". Findings with these biomarkers converge in suggesting that 'a richer brain' – i.e., one with more intact neuroplastic reserve - is potentially more responsive to CR. For example, increased thalamic connectivity was found to correlate with improvements in global cognitive performance, suggesting that plasticity in this circuit relates to training-related generalization to improve cognition (Ramsay et al., 2017). Nonetheless, it is important to note that we identified neuroimaging biomarkers that have little to no correlation with the mechanism of neuroplasticity, as better correlate to the concept of "brain volume reserve", such as gray matter morphology. Based on these findings, the conclusions we can draw for now, although the neurobiological mechanisms of cognitive enhancement remain still largely unknown, are that neuroimaging-based biomarkers offer important information about the mechanisms by which CR may influence the brain's functional architecture. Specifically, certain types of CR may induce neuroplastic changes directly responsible for the treatment-related remediation of the cognitive deficits prevalent in MPD patients, while other CR programs may leverage neural structures where volume-based metrics are able to predict response to CR.

The identification of neuroimaging-based biomarkers has several clinical implications for translational research on CR in psychotic disorders. For example, such identification allows for an in-depth neural characterization of psychotic subpopulations. MPD represent a highly heterogeneous category in which various mechanisms can contribute to the neuropathogenic core underlying cognitive anomalies. In other words, heterogeneity at the level of cognitive endophenotypes seems to be driven by heterogeneity at the level of neural activation patterns. Therefore, investigating at a single-subject level the neural activation patterns known to predict response to CR can provide useful information about the type of CR that is most appropriate for that specific patient, thereby offering a personalized treatment. Secondly, while neuropsychological assessment is certainly more affordable, widely spread, easier to implement, and currently being used to predict response to CR, brain-based biomarkers have the unique ability to capture directly the neural correlates of cognitive function and enhancement, thereby offering and in-depth characterization of cognitive phenotypes in MPD.

LIMITATIONS

The present review has some limitations. First, we reviewed studies that exclusively recruited patients with MPD. Therefore, we may have missed studies that included mixed diagnostic samples of patients. In addition, given the diversity of social, cognitive, and clinical samples used across investigations, as well as the heterogeneity of study designs, outcome findings were incommensurable. Second, considering the dearth of literature on neuroimaging-based predictors of response to CR, we decided to include predictors that have been investigated by only one or two single-arm trials. We are aware that these study types carry a risk of bias and that our conclusions might be influenced by them. However, our aim was to be as inclusive as possible to present an accurate picture of the current state of art of research on CR, without drawing definitive conclusions. At the same time, the dearth of studies may reflect the practical challenges inherent in the conduct of neuroimaging trials of CR, which can be long and intensive in nature, making recruitment and retention of participants particularly difficult. Third, in order to restrict our results to CR for MPD, we did not include several trials where other treatments were delivered in concomitance with CR. The majority of therapeutic advances in the field have been developed for integrated treatments; often

CR-only trials are essentially driven by translational research questions. Fourth, given the heterogeneity in neuroimaging assessments used, and the fact that many studies did not report non-significant outcomes, we are unable to compare outcomes across studies. Future studies should consistently adopt the same set of neuroimaging experiments and repeat such tests at similar time points, in order to facilitate comparisons across datasets. Finally, systematic assessment of study quality was outside the scope of this brief review; however, it is possible that variability in study quality may have influenced findings.

CONCLUSION

In conclusion, while the preliminary findings and sets of evidence presented in this paper merit replication and further investigation in larger samples, they indicate that a systematic evaluation of neuroimaging-based biomarkers –especially of those can be easily assessed in clinical settings (i.e. EEG) – can guide the personalized implementation of CR by identifying those psychotic patients who are more likely to generate neuroplastic enhancement and greater cognitive gains in response to treatment.

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Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases

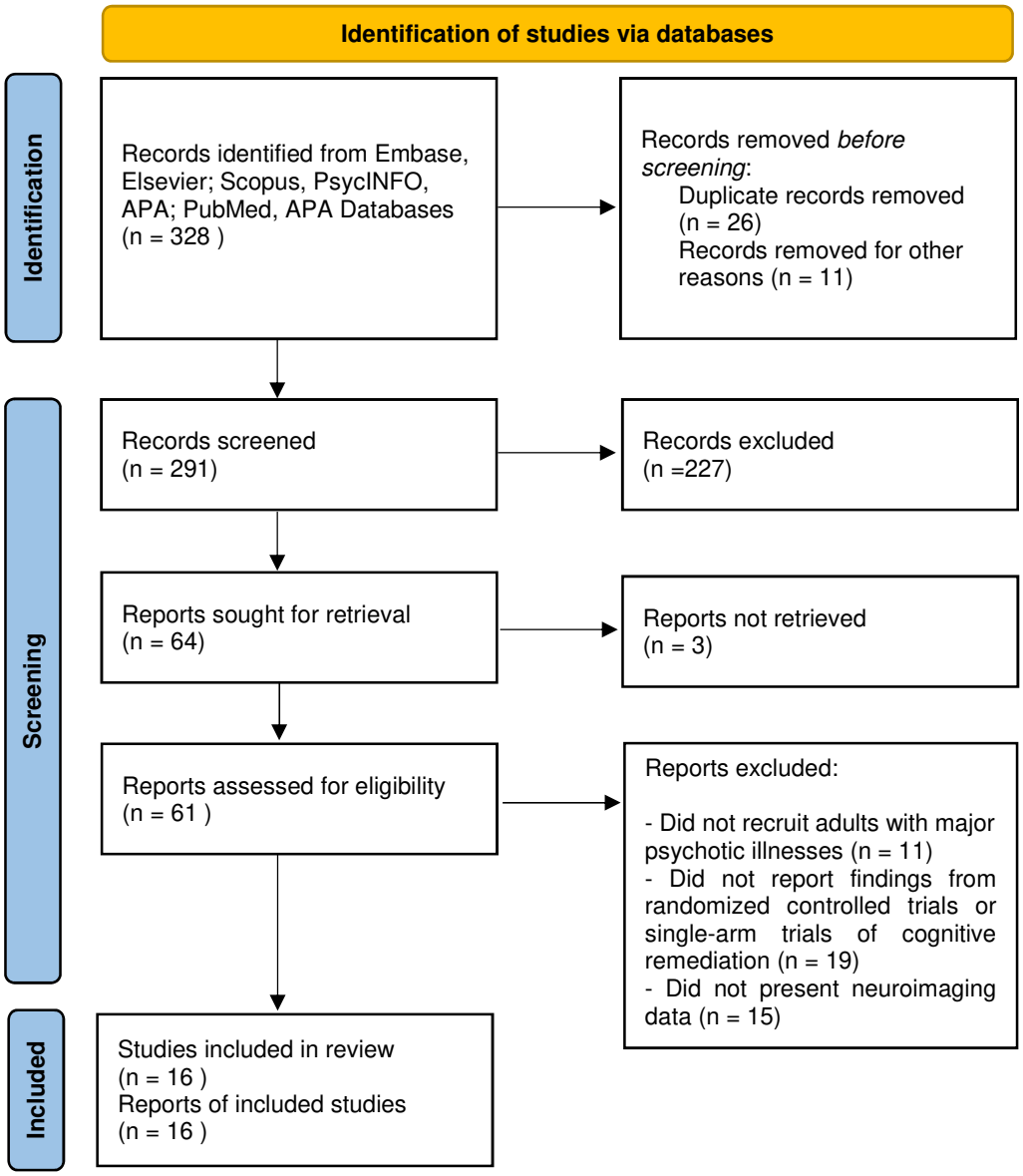

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Table 1. Neuroimaging-based biomarkers that can predict response to CR.

Predictive factor	Number of clinical trials	Population	Readiness for implementation
EEG INDEXES			
Auditory mismatch negativity	**3** (Hochberger et al., 2018; Perez et al., 2017 Biagianti et al., 2017)	234	Promising predictor of response, has identified individuals who have the greatest potential to benefit from CR
Auditory steady-state response	**1** (Molina et al., 2020)	42	preliminary data suggestive of possible prediction of response to CR
Efference copy corollary/discharge	0	/	No studies to date have investigated, but given its degree of correlation with cognition, it has great potential to predict treatment response to CR
Resting state EEG	0	/	No studies to date have investigated, but given its degree of correlation with cognition, it has great potential to predict treatment response to CR
MRI PARAMETERS			
White matter microstructure	**1** (Subramaniam et al., 2018)	76	preliminary data suggestive of possible prediction of response to CR
Gray matter morphology	**3** (Keshavan et al., 2011; Penadés et al., 2016; Ramsay et al., 2021)	144	Promising predictor of response, has identified individuals who have the greatest potential to benefit from CR
Thalamocortical connectivity	1 (Ramsay et al., 2020)	44	No studies to date have investigated whether it can be used as a predictor of response, but evidence shows its role as a biomarker of change
Dorsal prefrontal cortex activity during task based-fMRI	**7** (Miskowiak and Petersen, 2019; Subramaniam et al., 2014; Bor et al., 2011; Haut et al., 2010; Wykes et al., 2002; Miskowiak et al., 2021; Ott et al., 2020)	320	Strong evidence that changes in dPFC serve as biomarker of change. data regarding prediction of response to CR are preliminary