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Personalized Treatment for Cognitive Dysfunction in Individuals with Schizophrenia Spectrum Disorders

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Abstract

Cognitive deficits are a well-recognized issue for individuals diagnosed with schizophrenia spectrum disorders. Despite positive group findings for the use of cognitive remediation (CR) interventions, there are substantial individual differences in response to treatment. In addition, the aggregate CR literature reports low moderate effect sizes for cognitive and functional outcomes. Based on personalized medicine theory, this paper uses extant CR literature to examine the individual characteristics determined to predict treatment response. These characteristics, which fall into the broad categories of cognitive, psychological, and biological can be used as tailoring variables to personalize CR to an individual's unique profile. Personalization through the use of these tailoring variables has the potential to improve the delivery of CR to maximize treatment outcomes.

Keywords

cognitive remediation; neurocognition; personalized treatment; schizophrenia

Introduction

'Personalized medicine' or 'precision medicine' refers to methodical tailoring of medical treatments so that healthcare is customized to the individual recipient. The term primarily refers to the tailoring of treatments according to a patient's genetic content (Hamburg & Collins, 2010), however the concept has been expanded to encompass a variety of personalization measures. In this broader context, the mission of personalization is to find and utilize tailoring variables that capture individual characteristics, needs, and preferences in order to positively impact all stages of care, including prevention, diagnosis, treatment, and follow-up.

In this paper, we discuss the implications and possibilities of applying personalized medicine principles to cognitive remediation (CR) in the treatment of schizophrenia

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spectrum disorders. It is well recognized that schizophrenia spectrum disorders are associated with cognitive deficits that negatively impact essential areas of daily functioning (Green, Kern, Braff, & Mintz, 2000). Evidence of learning-dependent plasticity in the distributed neural systems that underlie perception and cognition, combined with the availability of computerized technology that allows for the delivery of well-defined learning experiences, has opened up a burgeoning field of research in cognitive remediation (CR). While the aggregate literature on CR for schizophrenia indicates that low moderate effect sizes can be obtained for cognitive and functional outcomes (McGurk, Twamley, Sitzler, McHugo, & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011), questions about scalability, and essential training elements remain. Despite positive group findings, there are substantial individual differences in response to CR interventions, with evidence that more than 25% of treated patients do not improve (Murthy et al., 2012; Wykes et al., 2011). Thus key challenges for the field are to: 1) identify the therapeutic techniques that maximally impact neurocognition; 2) understand the mechanisms of generalization of cognitive gains to functional change; and 3) to identify whether particular groups of patients differentially benefit from CR therapies. These issues inform 'personalization', and help determine how CR approaches can be matched to specific clients so that resources can best be utilized for the greatest effect. Current effect sizes for cognition and functional outcomes may remain limited under a moderate ceiling if we do not address personalization, which may be key to maximizing outcomes. By using targeted interventions, tailored to the needs of the patient, we can better address cognitive health.

One task is to examine the types of patient characteristics that are advantageous for tailoring. Research on the development of personalized interventions that adapt the type the intervention based on patient characteristics indicate that the patient characteristics that are best suited to guide personalized treatment should 1) account for a significant amount of the variance in treatment outcome, and 2) characterize a substantial subgroup of the patient population (Collins, Murphy, & Strecher, 2007; Lei, Nahum-Shani, Lynch, Oslin, & Murphy, 2012). The extant literature on restorative cognitive training techniques and on individual differences predicting positive treatment responses may together inform which patient characteristics meet these two criteria and thus may be useful tailoring variables for developing personalized approaches to CR for schizophrenia that lead to more positive outcomes.

CR research informs the choice of tailoring characteristics

The most recent meta-analysis of 40 independent studies of CR for over 2,100 people with schizophrenia indicated a medium effect size (ES) for improving overall cognition (ES = 0.45) and daily functioning (ES = 0.42), with an additional significant but small ES on improving psychiatric symptoms (ES = 0.18) (Wykes et al., 2011). This and previous meta-analytic studies have looked at moderators of ES for cognitive and functional outcomes (Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009; McGurk, Twamley, et al., 2007). Furthermore, there are several studies that have specifically examined predictors of positive responses to CR (Choi & Medalia, 2005; Fiszdon, Cardenas, Bryson, & Bell, 2005; Fiszdon, Choi, Bryson, & Bell, 2006; Kurtz et al., 2009; Medalia & Richardson, 2005; Twamley,

Burton, & Vella, 2011). From this literature we learn that patient and treatment variables intertwine to produce a positive response.

Treatment variables associated with larger ES include supplementing drill and practice with strategy instruction, pairing CR with other psychiatric rehabilitation programs, and treatment intensity (McGurk, Twamley, et al., 2007; Medalia & Richardson, 2005; Wykes et al., 2011). Patient variables known to impact treatment outcome include baseline cognitive profile, (Fiszdon et al., 2005; Fiszdon et al., 2006; Kurtz et al., 2009; Medalia & Richardson, 2005) psychological variables such as clinical stability and motivation, (Choi & Medalia, 2005; Twamley et al., 2011) and biological variables such as age, (Kontis, Huddy, Reeder, Landau, & Wykes, 2013; Wykes et al., 2009), phase of the disorder (e.g., prodromal or chronic) (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014), *COMT* genetic variants, (Bosia et al., 2007; Panizzutti, Hamilton, & Vinogradov, 2013) and anti-psychotic medication and genetic interactions (Bosia et al., 2014). Taken together, this research suggests that the patient characteristics that may productively be used to personalize CR fall into three broad categories: cognitive, psychological, and biological. This paper will discuss the findings of this literature on patient variables and the way in which it may inform the personalization of CR.

Cognitive characteristics as a tailoring variable

The cognitive characteristics of a person refer to the profile of neuropsychological and social cognitive abilities that they present with – for example their attention, memory, processing speed, facial affect recognition, and mentalizing capacity. While it may seem intuitively obvious to use the baseline profile to create a palette and progression of exercises that address those areas of deficit that are most impaired, malleable and hampering attainment of functional goals, in fact CR research often proceeds by administering the exact same exercises to everyone, regardless of their baseline profile, in order to standardize exposure to exercises (Fisher, Holland, Merzenich, & Vinogradov, 2009; Keefe et al., 2012; Vinogradov, Fisher, & de Villers-Sidani, 2012). Research suggests this approach may be compromising effect sizes, and that creating a personalized program of CR based on a person's baseline cognitive profile may lead to better outcomes (Medalia & Richardson, 2005; Murthy et al., 2012).

While people with psychotic disorders present with diverse cognitive profiles, (Heinrichs & Zakzanis, 1998; Joyce & Roiser, 2007; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2004; Saykin et al., 1995) certain domains are more consistently impaired (Dickinson, Ramsey, & Gold, 2007; Kern et al., 2011; Schaefer, Giangrande, Weinberger, & Dickinson, 2013) and correlate more with functional outcome (Green et al., 2000; Kern et al., 2011; Nuechterlein et al., 2008). We can look to the CR literature to discern what baseline cognitive characteristics account for a significant amount of the variance in impact of CR on cognitive and functional outcomes, and characterize a substantial subgroup of the patient population.

Attention

Several studies indicate that people with schizophrenia who have more impaired baseline attention have worse cognitive and functional outcomes following CR (Fiszdon et al., 2005; Kurtz et al., 2009; Medalia & Richardson, 2005). One interpretation is that a certain level of attention is necessary to successfully focus on the tasks, thereby limiting specific and generalized cognitive skill gains. This finding is not unique to schizophrenia; in other disorders that cause attention impairment (e.g., ADHD, Depression) there is evidence that attention facilitates acquisition of cognitive and other skills (Mausbach, Harvey, Goldman, Jeste, & Patterson, 2007; Mayes & Calhoun, 2007). Thus the cognitive profile that is predictive of a diminished response to CR is one that is marked by more severe attention impairment, a problem evident in a substantial subgroup of the patient population that participates in CR (Fiszdon et al., 2005; Kurtz et al., 2009; Medalia & Richardson, 2005).

The foreseeable implication of this is using baseline attention to tailor CR, as those with more impaired baseline attention may first require exercises to address those deficits, whereas others may be able to directly tackle higher-level cognitive tasks. The baseline cognitive profile could thus be used to craft a package of restorative exercises that are tailored to the individual's cognitive needs. Appropriately scaffolding treatment to ensure success as they move to more advanced tasks may in turn enhance motivation to stay in treatment. This process of personalizing treatment has the potential to enhance CR outcomes.

Information Processing

Many CR programs that use restorative computer-based exercises deliver cognitive exercises in a hierarchy, building from attention and processing speed to working memory, verbal learning and memory and problem solving. However some programs begin the hierarchy at an earlier level of information processing, first targeting early sensory information processing in the auditory, verbal, and visuospatial domains, followed by practice on exercises that incorporate working memory, verbal learning and memory. This approach is guided by data indicating prevalent and large effect size deficits in sensory perceptual information processing in schizophrenia when measured neurophysiologically and behaviorally (Gold et al., 2012; Javitt, 2009; Javitt, Shelley, & Ritter, 2000; Jonsson & Sjostedt, 1973; Rabinowicz, Silipo, Goldman, & Javitt, 2000). Deficits in early sensory information processing may affect the fidelity of information encoding, and the appropriate selection or filtering of task-relevant versus irrelevant stimuli which feed forward, rendering complex higher level functions (e.g. working memory, problem solving) inefficient and impaired. Proponents of this restorative approach posit that degraded processing of lower perceptual information must first be improved in order to drive improvements in those cognitive processes that are more proximal to daily functioning (Adcock et al., 2009; Vinogradov et al., 2012). There is some evidence that training on exercises that place implicit, increasing demands on auditory perception and accurate aural speech reception improve the speed and accuracy of auditory information processing, and that these effects generalize to higher order verbal memory performance (Adcock et al., 2009; Fisher et al., 2009). Another research group, using the same restorative computerized cognitive remediation training package in a larger sample, could not replicate these findings, yet found

important subgroup differences in who benefited from the treatment. Patients who made greater gains in auditory processing speed also made improvement in cognition across the training period (Murthy et al., 2012). Together these studies 1) indicate that training in sensory perceptual processing can be beneficial for higher-level cognition for some patients, and 2) highlight the importance of looking beyond group differences in order to customize CR treatments.

The possibility of personalized CR

A sizeable number of patients have significant information processing impairments, and neurophysiological data suggest that this subset of patients may benefit from training in basic sensory information processing to allow for changes in higher order cognitive abilities to occur (Adcock et al., 2009; Fisher et al., 2009). However, since not all patients have sensory deficits, it may be inefficient CR practice to universally employ training on sensory/perceptual processes.

We have pilot data from 34 outpatients, ages 18–65, with schizophrenia/schizoaffective disorder that supports this (Medalia, Saperstein, Javitt & Lee, 2016). Participants were first stratified by impaired or intact baseline performance on an auditory Tone Matching Test (TMT), (Gold et al. 2012; Rabinowicz, Silipo, Goldman, & Javitt, 2000) a behavioral measure of auditory perception and discrimination in schizophrenia and then randomly assigned to either “Brain Basics” (N = 17), or “Brain Training” (N = 17). These two CR treatments were identical except for one key feature: Brain Basics included training in sensory information processing to enhance basic perception before moving to higher-level cognitive tasks, while Brain Training trained directly on higher-level cognitive skills. Participants were assessed for change in global neurocognition (MATRICS Consensus Cognitive Battery; MCCB; Nuechterlein, 2008) and functional capacity (UCSD Performance-Based Skills Assessment- Brief; UPSA-B (Mausbach et al., 2007)) from baseline to post treatment and at 3-month follow-up.

There was a significant interaction between baseline TMT status (intact versus impaired) and CR treatment type, with those classified as TMT impaired showing greater cognitive ($F = 4.11$, $p < 0.052$) and functional ($F = 6.69$, $p < 0.015$) benefit from receiving the CR that included sensory processing training. Within the TMT impaired group, 85% of subjects who received “Brain Basics” improved 5+ points on the MCCB while only 20% of those exposed to Brain Training showed a 5+ improvement. There was no added benefit to giving sensory processing training to subjects with baseline intact TMT, who responded similarly to the two CR approaches.

These pilot data suggest there is merit to tailoring treatment according to baseline cognitive profile. We used auditory processing as the tailoring variable because many but not all individuals have these deficits, (Rabinowicz et al., 2000) and when present they impact treatment response (Murthy et al., 2012). The reported interaction effects lend support for further investigation of our hypothesis that patients are unlikely to benefit equally from receiving the same cognitive training exercises. Importantly, these findings suggest that personalization using a cognitive tailoring variable has the potential to impact both cognitive and functional outcomes.

Psychological characteristics as a tailoring variable

Psychological variables such as depressed mood, anxiety, low intrinsic motivation and doubts about self-efficacy are prevalent in schizophrenia and have been linked to lower scores on cognitive tests (Medalia & Richardson, 2005; Tas, Brown, Esen-Danaci, Lysaker, & Brune, 2012; Ventura et al., 2014). Several studies have investigated how CR can be optimized by addressing intrinsic motivation to learn (Choi, Fiszdon, & Medalia, 2010; Choi & Medalia, 2010). In the following section, we focus on motivation as a tailoring psychological variable.

Motivation

Impaired motivation is a core feature of people with prominent negative symptoms of schizophrenia. Intrinsic motivation, which refers to behavior driven by internal rewards (e.g. value, interest, enjoyment) has been identified as an important factor for cognitive gains in individuals with schizophrenia (Saperstein & Medalia, 2015). Specific psychological variables that contribute to intrinsic motivation to learn are delineated in the MUSIC model (Jones, 2009) which incorporates Expectancy Value and Self Determination theories of motivation (Deci, 1985; Eccles & Wigfield, 2002) into a single model of 5 main psychological variables: *e*Mpowerment, Usefulness, Success, Interest, and Caring. These five variables have been demonstrated to impact motivation and learning of cognitive skills in people with schizophrenia. *Empowerment*, encompassing autonomy, choice, and perceived control, has been found to contribute to overall levels of intrinsic motivation to learn in schizophrenia (Choi et al., 2010) and when enhanced, is associated with greater learning outcomes (Choi & Medalia, 2010). *Usefulness*, or task value, and *interest* are also shown to be important factors in supporting intrinsic motivation and learning in schizophrenia (Choi et al., 2010). Several studies have suggested a strong link between *success* or perceived competency and learning. Choi, Fiszdon and Medalia (2010) found greater expectation of success and perception of competence to be the most important factors in explaining how much was learned during and retained after a CR intervention (Choi et al., 2010). Huddy et al. (2012) found *caring*, or the quality of the CR therapist-patient relationship to impact length of therapy and improvements on clients' main target complaint (Huddy, Reeder, Kontis, Wykes, & Stahl, 2012).

The systematic identification of the mechanisms within individual clients that are working to motivate and demotivate may lead to stronger personalization of instructional interventions during CR. For example involving client participation in planning the course of CR exercises based on their needs and personal learning style is an instructional technique that can increase participant empowerment. Similarly, tailoring a learning activity to the interests or goals of an individual can help promote interest and perceived usefulness. In addition, 'contextualization' or making material meaningful by presenting it in a real-world context can also enhance interest and usefulness. Cognitive-behavioral strategies can be provided one-on-one or during Bridging groups to change negative self-appraisals or doubts about self-competency, and promote 'success' beliefs. Finally, the role of the therapist in CR can impact motivation by gratifying the need for a supportive, caring relationship. Future research could examine if need for caring interpersonal relationships is a useful tailoring

variable when choosing whether to use a therapist-mediated versus largely computer-based CR intervention. Conceivably someone with a large need for supportive relationships would be more motivated and show more cognitive improvement when doing CR with a therapist, while others may thrive in a largely computer-based and/or home-delivered CR intervention.

Biological characteristics as a tailoring variable

Biological tailoring of CR treatment relies upon discerning the factors that most affect neuroplasticity in individuals with schizophrenia. The CR literature has identified a number of factors, which contribute to cognitive gains and functional outcome including genetic variability, age, and cognitive reserve.

Genetic Variability

Catechol-O-Methyltransferase (COMT) is one of the major enzymes involved in dopamine and norepinephrine metabolism in the prefrontal cortex, and is specifically associated with prefrontal cognition. Variability in the COMT gene has been linked to cognition in schizophrenia-spectrum disorders (Diaz-Asper et al., 2008; Egan et al., 2001) and to cognitive intervention response (Bosia et al., 2007; Bosia et al., 2014; Panizzutti et al., 2013; Pieramico et al., 2012). With regard to CR for schizophrenia, one study linked single nucleotide polymorphisms (SNPs) in the COMT gene and differential improvement in cognition following 50 hours of computer-based cognitive remediation (Panizzutti et al., 2013). A second set of studies focused specifically on the COMT Val158Met polymorphism. While the Val allele is consistently linked to lower baseline cognitive performance, there is evidence to suggest that Met carriers show greater cognitive improvement following computer-assisted CR than Val homozygotes (Bosia et al., 2007). While negative findings on the effect of the Val158Met polymorphism have also been reported, (Greenwood, Hung, Tropeano, McGuffin, & Wykes, 2011; Twamley et al., 2014) further investigation has yielded new insights into the role of COMT variability, indicating a potential interaction effect between COMT genotype and antipsychotic medication. Bosia and colleagues (2014) reported a significant difference between genotypes among patients treated with more prominent D2 receptor blocking antipsychotics, such that Met carriers obtained a significantly greater effect size following computer-assisted CR added to standard rehabilitation therapy (Bosia et al., 2014). Specifically, Met carriers showed significant cognitive improvement, while Val/Val genotypes improved when receiving clozapine, yet no mean improvement when treated with other antipsychotic drugs. Although multiple mechanisms for this synergistic effect are hypothesized, these data suggest that COMT genotype may inform the tailoring of cognitive intervention for some schizophrenia-spectrum patients through the pairing of appropriate pharmacological intervention.

Phase of illness, age, cognitive reserve

There is some evidence that phase of illness impacts cognitive gains from CR. A meta-analysis of CR in first episode patients (Revell, Neill, Harte, Khan, & Drake, 2015) found a similar pattern but lessor degree of improvement in cognition, symptoms and functioning than the Wykes et al (2011) meta-analysis found with older, chronic patients. However, a direct comparison of CR response in early versus chronic phase patients by Bowie et al.

(2014) found an inverse relationship between duration of illness and improvements in neurocognition and real-world skills following CR. Specifically, early-phase patients (within 5 years of first episode) had larger improvements in executive functioning and processing speed as compared to long-term patients (15 years of illness). Closely related phase of illness is the issue of age. While studies have reported no baseline differences in cognitive ability across age groups, when CR is delivered as a time limited number of sessions, it has been found to be less effective in older patients with schizophrenia, with those ages 40 to 45 and older achieving more limited cognitive improvement (Kontis et al., 2013; McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007; Wykes et al., 2009). It remains to be seen whether older patients simply require more sessions to show the benefit younger patients more quickly achieve, or if there is an age associated improvement ceiling.

In neuropsychiatric disorders, there is evidence to suggest that high cognitive reserve is a protective factor against the development or expression of neurological conditions, and in schizophrenia, pre-treatment brain structural alterations in prefrontal and temporal cortex have been found to impact response to antipsychotic drug treatment. Pretreatment cognitive reserve has therefore been investigated as a moderator of CR treatment response. In one study, Keshavan and colleagues (2011) examined whether pre-treatment cortical volumetric measures predicted the effects of Cognitive Enhancement Therapy (CET) versus an enriched supportive therapy control on neurocognition and social cognition in a sample of early course schizophrenia-spectrum disorder patients (Keshavan et al., 2011). In this study, individuals with greater pretreatment cortical surface area and higher gray matter volume demonstrated more rapid social-cognitive response to CET with small ($d = .19$) and medium ($d = .58$) effect sizes, with a specific effect of temporal lobe volumetric measures on social-cognitive improvement. However, no differential effect was found for neurocognitive response.

In a similar line of investigation, Kontis and colleagues (2013) investigated the impact of proxy measures of cognitive reserve, defined by premorbid IQ and vocabulary knowledge, on neurocognitive outcome following CR (Kontis et al., 2013). Although higher premorbid IQ was associated with better post-treatment memory performance in younger participants, the effect was not specific to CR, and in older patients greater cognitive reserve did not mitigate the negative impact of older age. Thus, the impact of cognitive reserve appears limited and these data underscore the impact of age on CR outcome. Taken together with data from Bowie and colleagues as well as animal model data, (Lee et al., 2012) research suggests the possibility of an early, critical window of time for cognitive intervention in schizophrenia-spectrum disorders, when neuroplasticity may be more pronounced. Duration and/or intensity of CR may thus need to be personalized to account for age and phase of illness.

Knowledge of the biological factors that impact CR outcomes has important implications for personalizing cognitive intervention through the tailoring of adjuvant treatments to enhance neuroplasticity among those who may be less likely to benefit. Personalization may include the careful selection of atypical antipsychotic medications to support the neural mechanisms underlying learning and/or the concurrent use of interventions such as repetitive transcranial magnetic stimulation (Ziemann, 2005) or transcranial direct current stimulation (Mondino,

Haesebaert, Poulet, Suaud-Chagny, & Brunelin, 2015) to enhance cortical plasticity. In addition, CR outcomes may be enhanced by tailoring the use of behavioral techniques including strategy coaching and compensatory skills training (Twamley, Savla, Zurhellen, Heaton, & Jeste, 2008) to support cognitive learning and enhance generalization. The latter options may be more acceptable or tolerable, especially among those for whom biological therapies may be unavailable or contraindicated.

Conclusion

We have considered the application of personalized medicine principles to cognitive remediation for schizophrenia spectrum disorders, using the broader concept of personalization that encompasses a variety of measures beyond genetic variability. Research suggests that the patient characteristics that may productively be used to personalize CR fall into three broad categories: cognitive, psychological, and biological. Within these categories, a number of specific variables bear consideration as tailoring variables: baseline cognitive profile, intrinsic motivation to learn, genetic variability, and age. CR is a low risk, well tolerated and accepted intervention that addresses a core impairment of psychosis associated with functional outcome. Current CR research methodologies typically employ fixed treatment protocols, and this may have created an effect ceiling, given the evidence that there are substantial individual differences in response to CR interventions (Murthy et al., 2012; Wykes et al., 2011). Therefore, we suggest that future CR research attend to the heterogeneity of subjects by designing studies informed by a personalized approach to cognitive treatment. A within-subjects design may better elucidate the mechanisms for cognitive improvement, as subjects' response to CR can be evaluated based on the variability within their specific cognitive profile without comparison to a larger, diverse group. The design of tailoring strategies may follow from the elucidation of specific mechanisms of treatment effect. Randomized controlled trials can directly attend to personalized approaches by using a Sequential Multiple Assignment Randomized Trial (SMART) design. A SMART design allows for testing of an adaptive, as opposed to fixed, treatment strategy, which aims to maximize individual outcomes based on both baseline patient characteristics and intermediate measures of treatment response (Nahum-Shani et al., 2012). By addressing personalization, there is the potential to maximize outcomes and better address cognitive health.

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