11. PERSONALIZING COGNITIVE REMEDIATION INTERVENTIONS: WHAT WORKS AND FOR WHOM?
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The link between cognition and functioning in schizophrenia is well established, and there is a large body of research supporting the efficacy of cognitive remediation (CR) for improving cognitive function in individuals with psychosis. In recent years, the focus of CR research has shifted to better understanding how these interventions work, and factors that influence whether or not an individual is likely to benefit from any such intervention. This line of research is particularly important given the considerable variability in response to this time and labor-intensive intervention, with upwards of 40% of individuals being non-responders. In the current symposium, we present new data exploring specific characteristics of CR interventions, individual participants, and disorder pathology that may influence CR’s impact on outcomes of interest and inform the likelihood of positive response to this intervention.

Mr. Best focuses his talk on the impact of differences in CR approaches. He presents data from a trial directly comparing an executive and perceptual skill-focused CR approach. Neurocognitive, symptom, self-report, functional competence and community function outcomes are evaluated, along with their trajectories after the active intervention phase. EEG data is also presented probing the neurophysiological mechanisms underlying specific effects of these two CR approaches.

Dr. Choi focuses on how the efficacy of CR delivery methods may be augmented by using neurofeedback. He presents data from a trial examining the impact of augmenting standard performance-based CR with pupillometry, which indexes effort expenditure and task engagement, and may thereby offer a more sensitive measure of parameters relevant to optimizing learning. Effects of CR with and without pupillometric feedback are compared on measures of cognitive function and training motivation, and differences in neurofeedback learning algorithms between individuals with chronic schizophrenia versus first episode and clinical high risk are discussed.

Dr. Kurtz focuses on person characteristics that may influence response to CR. He presents data on the influence of demographic factors, cognition, symptoms, and treatment duration/intensity on CR-associated improvements in working memory and functional capacity, and discusses his findings in relation to existing research on predictors of response to CR.

Dr. Penades focuses on the genetic contributions to cognition and CR outcomes. He reviews recent literature on the impact of genetic variables on cognitive function and response to CR, presents new data on the impact of two gene polymorphisms (COMT and BDNF) on cognitive function, and discusses how genetic variability may be used to develop predictive models to optimize outcomes of different CR approaches.

11.1 EXECUTIVE COGNITIVE TRAINING VS. PERCEPTUAL COGNITIVE TRAINING FOR SCHIZOPHRENIA-SPECTRUM DISORDERS: TREATMENT OUTCOMES AND PREDICTORS OF RESPONSE
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Conclusions: Characterizing how and which specific sets of symptoms map to neural circuitry is a key step towards developing targeted and effective treatments for psychiatric disorders. We propose the Neuro-Behavioral Relationships In Dimensional Geometric Embedding (N-BRIDGE) framework as a key step towards unified mapping between the geometry of data-driven behavioral variation and the geometry of data-driven neural variation, thus integrating both categories and continuous dimensions in psychiatry.

Background: Neurocognitive impairments are the best predictors of community functioning for individuals with schizophrenia-spectrum disorders. Cognitive remediation is a psychological intervention designed to improve neurocognitive abilities and community functioning. However, different theoretical approaches have developed without any studies directly comparing them. Additionally, with a movement towards personalizing cognitive enhancing techniques, greater emphasis is being placed on determining predictors of treatment response. The current study is the first to compare the two dominant approaches to cognitive remediation (training of executive skills and training of perceptual skills) and examine predictors of treatment response.

Methods: 70 outpatients with schizophrenia-spectrum disorders were randomized to receive either 6 weeks of executive training (ET) or perceptual training (PT). Electrophysiological activity, neurocognition, functional competence, case-manager rated community functioning, clinical symptoms, and self-report measures were assessed at baseline, post-treatment, and 12-weeks post-treatment.

Results: There were minimal differences between groups at the post-treatment visit. PT improved EEG mismatch negativity amplitude significantly more than ET immediately post-treatment (d = 0.64), however, the effect did not persist at 12-week follow-up (d = 0.01). Examining long-term effects, at 12-week follow-up, ET increased EEG theta power during an n-back working memory task (d = 1.01), neurocognition (d = 0.64), functional competence (d = 0.67), and case manager rated community functioning (d = 0.53) to a greater extent than PT. Larger P300 amplitude (B = .47) and theta power during a working memory task (B = .34) at baseline were significantly associated with larger improvements in neurocognition post-treatment. Baseline mismatch negativity amplitude was not significantly associated with treatment response (B = .17), and no baseline EEG measures predicted functional outcomes.

Conclusions: Both PT and ET improved neurophysiological mechanisms specific to their domains of intervention, however, only ET resulted in improvement in neurocognition and functioning. Improvements in favor of ET did not appear immediately post-treatment but emerged 12 weeks after the end of active treatment. Training executive functioning may prime further cognitive and functional improvements. Executive functions may be more functionally relevant than other cognitive domains and when addressed in treatment lead to better outcomes. Greater P300 amplitude and theta power may be associated with learning-related processes which are important for acquisition and retention of skills during cognitive training programs.

11.2 PUPILLOMETER-BASED NEUROFEEDBACK COGNITIVE TRAINING: OPTIMIZING TASK ENGAGEMENT TO ENHANCE LEARNING IN PRODROME, FIRST EPISODE, AND ESTABLISHED PSYCHOSIS

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Background: Current computerized cognitive training (CT) programs adjust difficulty level solely using a correct or incorrect response. This is the sole method of titrating difficulty because there is only one avenue of input. This is an inherent weakness in how learning is gauged since a correct or incorrect response only conveys one part of the story, so to speak, and does not capture effort expenditure nor level of task engagement, both of which impact performance scores. Neurofeedback provides information about these additional variables and has been used in a number of cognitive therapies to improve domains such as cognitive control in college
students and children with ADHD. Neurofeedback offers CT programs for psychosis a technological step toward maximizing training gains. More specifically, neurofeedback that uses pupillometry can be used as an index of cognitive load and task engagement in CT to generate an algorithm that adjusts task difficulty to remain optimally challenging and arousing while not too frustrating or too easy.  

**Methods:** We compared CT with and without pupillometry-based neurofeedback in three groups of psychosis--established psychosis (n=42), first episode (n=31), and clinical high risk (n=27). This was a double-blind study that used the same tablet-based processing speed training program and the same head-mounted pupillometer but with the pupillometer not syncing with the control box (essentially, turned off), so task difficulty and learning progression were based on either performance (correct/incorrect responses) or pupillometric feedback. CT consisted of sixteen 50-minute sessions over the course of 2 months, with assessments at baseline and post.  

**Results:** The results show a clear advantage when pupillometric neurofeedback is incorporated into the titration algorithm in all three groups. While CT with and without pupillometry improved processing speed, greater gains were noted in the neurofeedback groups on both motorical and non-motorical processing speed. The neurofeedback groups, regardless of psychosis stage, also reported greater motivation/interest for treatment, with 90% completing the entire training compared to just 72% in the group without neurofeedback.  

**Conclusions:** This shows that CT can be quite taxing for people at any stage of psychosis, and correct/incorrect responses do not fully gauge the level of cognitive resources one commits to a task. Pupil dilation betrays underlying neurophysiologic engagement and serves as a precursor to disengagement on a behavioral task. We know that there is a “sweet spot” for the optimal load placed on cognitive resources, in terms of whether a training task is not stimulating enough (constricted pupils), ideally stimulating, or if there is too much information and the task has become overwhelming (dilated pupils). Pupillometry allows us to optimize the training exercises by providing biofeedback to the training software that then uses this information, along with task performance data, to automatically adjust training task parameters and levels for a personalized and efficient training program. In this manner, pupillometric neurofeedback can provide a concise index of how much the person is actively involved in the exercise at that very moment, even before performance can be registered as a correct or incorrect response.

**11.3 PREDICTORS OF RESPONSE TO COGNITIVE REMEDIATION IN SCHIZOPHRENIA**

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**Background:** A growing body of research shows that cognitive remediation (CR) consisting of drill-and-practice and/or strategy training targeted at neurocognitive functions produces small-to-moderate improvements in neurocognition that are durable and generalize to psychosocial function when CR is provided with other rehabilitation interventions (Wykes et al., 2011; Priksen et al., 2018). Despite these positive group findings, results to date reveal substantial individual differences in response to CR interventions. For example, one summary of three CR trials found improvement rates for a mixed group of psychiatric patients that ranged between 40 and 69% for individuals (Medalia and Richardson, 2005). This finding emphasizes the need of determining factors that predict a strong response to CR to effectively match patients to efficacious treatments.  

**Methods:** The current study is a secondary data analysis from two separate, randomized, controlled trials (Kurtz et al., 2007; 2015) that revealed improvements in working memory in response to an extended (6-month), standardized, computer-assisted cognitive remediation intervention when compared to an active, computer-skills control condition. We investigated the relationship between demographic factors (age, education, duration of illness), hours of CR treatment, cognitive skills (crystallized verbal ability, visual sustained attention, verbal learning and memory, and problem-solving), and symptoms (total positive and negative symptoms and general symptoms) measured at study entry, to improvements in working memory skills across these two RCTs.  

**Results:** Results from 58 people with chronic schizophrenia randomly assigned to the CR condition in these two studies (mean age=34.1 years, SD=12.0; mean duration of illness=10.2 years, SD=10.3) revealed that baseline visual sustained attention (partial r=.30, p=.05) and number of hours of training (partial r=.27 p.05) predicted end of trial working memory scores with baseline working memory scores held constant.  

**Conclusions:** These findings will be evaluated with respect to other studies of prediction of response to CR.

**11.4 TOWARDS A MODEL FOR PERSONALIZING COGNITIVE REMEDIATION ON THE BASIS OF GENETIC POLYMORPHISMS**

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**Background:** Cognitive remediation (CR) for schizophrenia is an evidence-based intervention as it has been demonstrated in meta-analytic studies. However, little is known about how individual differences could be affecting responsiveness. Among other variables, genetic variability could help to understand some aspects of the underlying biological mechanisms of cognitive remediation in schizophrenia. Intuitively, genetic variability could be causing different responsivity to cognitive remediation and then, if that would be proved, variability in genetics could help to define new predictors of response and eventually they might allow us to personalize treatments in the near future.  

**Methods:** In this talk we will discuss the literature on genetic factors that may impact response to CR and the results of a systematic review will be presented. Moreover, an exploratory study testing the potential role of two different gene polymorphisms (COMT and BDNF gene) on cognition in a sample of n=110 participants with schizophrenia will be presented. Finally, a tentative model for predicting responsiveness to CR will be presented.  

**Results:** Two different genes have been studied in the context of CR responsiveness. The brain-derived neurotrophic factor (BDNF) has been proposed as a specific marker of cognitive recovery. When samples were divided according to the resulting polymorphisms of the BDNF gene, the carriers of the Met allele behaved totally differently from the rest and no increase in serum BDNF levels was observed, while those without the Met allele did experience an increase in serum levels similar to previous studies. Those data could be potentially reflecting the presence of a negative response marker to cognitive remediation. On the other hand, some studies have shown that other gene polymorphisms, especially those that influence the release of dopamine, could act to influence the response to cognitive interventions in schizophrenia. The most studied is catechol-O-methyltransferase (COMT), which is an important enzyme for the degradation process of dopamine that regulates the availability of dopamine in the frontal cortex. Finally, in our own sample significant differences were found in different COMT polymorphisms in cognitive flexibility (t= 12.81; p = 0.001). In addition, significant differences were also found in measures of verbal learning (t= 11.87; p = 0.04) for different variants of the BDNF gene.  

**Conclusions:** Current data allow us to postulate a provisional model for predicting response to cognitive remediation including the BDNF Val66Met polymorphism and the COMT Val158Met polymorphisms. It seems like those polymorphisms could be accounting for different response to cognitive remediation in different cognitive domains: memory and cognitive flexibility. Eventually, if more new data about different genetic