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Research Paper

Model selection and prediction of outcomes in recent onset schizophrenia patients who undergo cognitive training

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ABSTRACT

Predicting treatment outcomes in psychiatric populations remains a challenge, but is increasingly important in the pursuit of personalized medicine. Patients with schizophrenia have deficits in cognition, and targeted cognitive training (TCT) of auditory processing and working memory has been shown to improve some of these impairments; but little is known about the baseline patient characteristics predictive of cognitive improvement. Here we use a model selection and regression approach called least absolute shrinkage and selection operator (LASSO) to examine predictors of cognitive improvement in response to TCT for patients with recent onset schizophrenia. Forty-three individuals with recent onset schizophrenia randomized to undergo TCT were assessed at baseline on measures of cognition, symptoms, functioning, illness duration, and demographic variables. We carried out 10-fold cross-validation of LASSO for model selection and regression. We followed up on these results using linear models for statistical inference. No individual variable was found to correlate with improvement in global cognition using a Pearson correlation approach, and a linear model including all variables was also found not to be significant. However, the LASSO model identified baseline global cognition, education, and gender in a model predictive of improvement on global cognition following TCT. These findings offer guidelines for personalized approaches to cognitive training for patients with schizophrenia.

1. Introduction

Targeted cognitive training (TCT) of auditory processing and verbal working memory for schizophrenia has shown efficacy for improving cognition (Fisher et al., 2014; Fisher et al., 2009), but little is understood about which patient factors predict positive outcomes. Previous meta-analytic work suggests that symptoms may be predictive of response to cognitive remediation more broadly (Wykes et al., 2011), though other findings suggest that baseline cognition and other treatment factors may also predict response (Kurtz et al., 2009; Fiszdon et al., 2005; Joanna M Fiszdon et al., 2006a, 2006b; Vita et al., 2013; Lindenmayer et al., 2017). In TCT, baseline reward anticipation was associated with improvements in verbal memory as well as global cognition (Fisher et al., 2014), and improvement in auditory processing speed is also a predictor of subsequent cognitive improvements (Biagianti et al., 2016). However, the pre-treatment cognitive and demographic profile of individuals who may benefit from this intervention remains an open question. Efforts to predict treatment outcomes in psychiatric populations including schizophrenia remains a critical goal, especially as psychiatry as a field continues to pursue personalized interventions (McGorry, 2013). However, developing predictive models for psychiatric treatment and outcome poses numerous challenges, and novel analytic tools will likely be required to solve these problems.

Previous work to identify variables predictive of cognitive training outcomes in schizophrenia has been limited by problems with multiple comparisons. Despite numerous clinical trials collecting a wealth of data on measures including cognition, functioning, symptomology, and demographics, there is often insufficient power to test each variable, and few a priori predictions to guide principled analyses. Moreover, building predictive models using linear regression with this type of data raises concerns of "over-fitting," where inflated R^2 values may adequately characterize variance in a single dataset, but hamper its predictive ability in the general population. These challenges have therefore given way to more advanced and iterative statistical procedures, that allow for the inclusion of large numbers of predictor variables, without being penalized for their inclusion.

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Table 1
Baseline statistics, correlations, and linear regression model predicting change in global cognition.

Measure	A) Baseline		B) Correlation		C) Linear regression			
	Mean	SD	*r*-Value	*p*-Value	Estimate	Std. error	*t*-Value	*p*-Value
(Intercept)	–	–	–	–	− 0.84	1.49	− 0.56	0.58
Global cognition	− 0.85	0.74	− 0.31	0.04	− 0.21	0.13	− 1.67	0.11
Symptoms	58.21	12.57	− 0.02	0.89	− 0.001	0.01	− 0.28	0.78
GFR	4.83	2.44	0.03	0.83	− 0.02	0.04	− 0.6	0.55
GFS	5.79	1.39	− 0.1	0.53	− 0.09	0.07	− 1.25	0.22
Strauss	8	2.23	0.02	0.92	0.06	0.05	1.18	0.25
Duration	18.67	15.61	0.06	0.72	− 0.001	0.004	− 0.203	0.84
Age	21.69	3.29	0.04	0.78	− 0.02	0.03	− 0.56	0.58
FSIQ	102.76	12.24	− 0.15	0.33	− 0.003	0.01	− 0.41	0.68
Gender	30 male	–	–	–	0.18	0.16	1.1	0.28
Education	12.88	1.62	0.29	0.06	0.13	0.05	2.53	0.02

Note. Baseline statistics and correlation and linear regression models of all predictors and their relationship to change in global cognition score. (A) Means and standard deviations of all predictors at baseline. (B) No correlations between baseline measures and global cognition were found to be significant after correcting for multiple comparisons (critical $p = 0.005$). (C) The linear regression of all predictors only showed Education to be a significant predictor of change in global cognition score. However, the full model was not significant ($F = 1.61$; $p = 0.15$; *Multiple* $R^2 = 0.34$).

Least absolute shrinkage and selection operator (LASSO) is one such regression procedure that allows for testing large numbers of predictor variables (including when the number of predictors is greater than N) while minimizing the model error as well as minimizing the risk of over-fitting (Tibshirani, 1996). LASSO has been previously used to examine questions regarding genetics (Wu et al., 2009), neuroimaging (Shimizu et al., 2015), and clinical outcomes (Bertocci et al., 2016). The current study seeks to use LASSO to identify a model of baseline cognitive, functional, symptom, and demographic factors that may be predictive of response to TCT in recent onset schizophrenia (SZ); such information could guide personalized treatments for this population. Here we re-examine data from 42 SZ patients who underwent 40 h of targeted cognitive training (TCT) of auditory processing and working memory. Participants were examined at baseline on the basis of global cognition, symptoms, functioning, estimated intelligence quotient (IQ), duration of illness, and demographic variables including age, gender, and education attainment. Previous findings in these participants suggested that the treatment elicited improvement on measures of verbal memory, problem solving, and global cognition (Fisher et al., 2014). We hypothesized that LASSO would more adequately identify a model predictive of global cognitive improvement (measured by the MATRICS Consensus Cognitive Battery) in response to TCT, compared to simple correlation or multiple regression models.

2. Methods

2.1. Participants

Participants in the current study included 43 individuals randomized to the active treatment group (TCT) of a study described previously (Fisher et al., 2014) (Clinicaltrials.gov NTC00694889). Briefly, patients with recent onset SZ were recruited from the Early Psychosis Clinics at the University of California, San Francisco and the University of California, Davis. Participants were required to meet the following criteria: (1) Structured Clinical Interview for DSM-IV (SCID) confirmed diagnosis of SZ or schizoaffective disorder; (2) recent onset of psychotic episode within the last 5 years (M = 18.81; SD = 15.45); (3) good general physical health; (4) age between 14 and 30 years old; (5) fluent and proficient in English; (6) IQ of 70 or greater; (7) no known neurological disorder; (8) no substance dependence in the past year. All eligible participants had achieved outpatient status for at least 3 months, and were stable on psychiatric medications. Participants 18 and older provided informed consent, while participants under 18 provided assent as well as legal parent/guardian consent. All consenting and baseline assessment procedures were conducted prior to random assignment to the training condition. One participant was subsequently removed due to missing clinical data. All study procedures were approved by the IRBs at the University of California, San Francisco and University of California, Davis.

2.2. Training procedure

Participants were loaned a laptop computer to complete the intervention independently at home. Individuals were asked to participate for 40 h over the course of 8 weeks (1 h/day, 5 days/week). Participants were contacted 1–2 times per week by telephone to check in on progress, in addition to offering coaching/support if there were difficulties completing the training. Check-in appointments were also conducted after every 10 sessions, where participants were paid $5 for each completed session, an additional $20 for 10 completed sessions, and $30 after completing 40 h of training. Participants also received $20 for each pre- or post-training assessment. TCT consisted of adaptive computerized exercises designed to improve the speed and accuracy of early auditory processing while engaging in auditory and verbal working memory tasks (Fisher et al., 2009), and was provided by Posit Science, Inc. Exercises are individually adaptive, and designed to dynamically shift the difficulty level to maintain an 80–85% accuracy rate. During a one-hour session, each participant completed four to six exercises, with their compliance monitored via remote upload of their data. Participants completed on average 32.93 h of training (SD = 10.45), over the course of the 8 weeks.

2.3. Assessment procedures

Assessments were conducted blind to group assignment immediately before and after TCT. All assessment staff were trained and monitored by the same senior researcher (M.F.) ensuring cross-site consistency. Assessments included an abbreviated version of the MATRICS Battery to measure global cognition (Nuechterlein et al., 2008), the Positive and Negative Syndrome Scale (PANSS) to measure symptoms (Kay et al., 1987), Strauss Carpenter Outcome Scale to measure social contact, hospitalizations, and engagement in school/work (Heinrichs et al., 1984), the Global Functioning Role and Social Scales, and an estimate of Full-Scale Intelligence Quotient based on verbal reasoning. Means and standard deviations of all predictors are described in Table 1A. Standard demographic variables including age, gender, education, and duration of illness were also collected. Together, 10 total variables were included in the statistical models (summarized in Table 1).