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Predicting response to cognitive training for schizophrenia using results from two studies with different outcomes

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Abstract

Background: Collaborative data sharing between research groups provides an opportunity to explore the basis for the heterogeneity in cognitive training outcomes reported in the schizophrenia literature. The current analyses focused on the contribution of site and participant characteristics to these heterogeneous outcomes.

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Contributions

Below are details of the contributions to this manuscript made by each author:

Alice Saperstein took primary responsibility for organizing the data for analysis, manuscript writing and production.

Jean Choi conducted data analyses and assisted with manuscript writing.

Carol Jahshan was a principal investigator of the original, referenced study from which data were drawn, and assisted with data preparation for the current study.

David Lynch participated in data interpretation and contributed to the developing manuscript.

Melanie Wall oversaw statistical methods, participated in data interpretation and manuscript writing.

Michael Green was a principal investigator of the original, referenced study from which data were drawn, conceptualized the current study and contributed to manuscript writing.

Alice Medalia was the principal investigator of the original, referenced study from which data were drawn, conceptualized the current study, contributed to data interpretation and manuscript writing.

All authors critically read, contributed to, and have approved the final manuscript.

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Conflict of Interest Statement

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Methods: Data from two independent studies, from New York (NY) and Los Angeles (LA), were combined to yield a sample of 132 outpatient adults with schizophrenia/schizoaffective disorder. While similar treatment doses, cognitive exercises and outcome measures were used, sites differed in use of coaching, group discussion and compensation. Between-site differences in participant demographic and baseline clinical characteristics were tested. Regression examined predictors of change in cognition (MCCB) and functional capacity (UPSA) which could explain site differences in treatment effects.

Results: Medium to large treatment effect size differences in MCCB and UPSA favored the NY site over LA. When the studies were combined, the effect of site was significant for both outcomes with a medium effect size difference. After controlling for background characteristics, the effect of site was reduced for both outcomes, but remained significant for cognition. Improvement in UPSA was associated with better baseline MCCB ($p<0.001$), lower baseline UPSA ($p<0.001$) and younger age ($p=0.019$). The overall model with site, baseline scores, and participant background characteristics explained about 30% to 40% of the variance in outcomes.

Discussion: Participant and treatment characteristics are both predictive of outcomes, but treatment characteristics may be more consequential to cognitive gain, while participant characteristics may be more consequential to change in functional capacity.

Keywords

Cognitive remediation; cognitive training; neurocognition; schizophrenia; functional capacity

1. Introduction

Schizophrenia-spectrum disorders are associated with deficits in several areas of neurocognition such as attention, memory, speed of processing, and executive functioning. Such impairments are prevalent, pervasive, persistent (Bora et al., 2010; Reichenberg et al., 2009), and significantly contribute to functional disability (Bowie et al., 2008; Green et al., 2015). Cognitive training interventions have the potential to significantly improve cognitive outcomes as well as social and vocational functioning when provided in the context of psychiatric rehabilitation (McGurk et al., 2007; Wykes et al., 2011). Despite these positive group-level findings, there is significant variability in individual-level responses with a proportion of participants exhibiting little or no benefit (Murthy et al., 2012; Wykes et al., 2011).

Participant characteristics are recognized as significant predictors of CR outcome. However, there is disagreement in the literature about how factors such as age (Corbera et al., 2017; McGurk and Mueser, 2008; Vita et al., 2013; Wykes et al. 2009), duration of illness (Bowie et al., 2014), baseline abilities and cognitive profile (DeTore et al., 2019; Fiszdon et al., 2006; Lindenmayer et al., 2017; Medalia et al., 2019; Twamley et al., 2011) impact treatment outcomes. Regarding treatment characteristics, comparisons of bottom-up to top-down cognitive training ascribe benefits to both (Adcock et al., 2009; Best et al., 2019), without definitive conclusions regarding the superiority of one over the other. Treatment context, on the other hand, shows a more robust effect in that cognitive interventions integrated with psychosocial rehabilitation evidence better outcomes than cognitive training

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alone, and that the use of transfer techniques (e.g. strategy coaching) bolsters this effect (Wykes et al., 2011). Further investigation of person-level factors and treatment characteristics that significantly and reliably impact training outcomes may inform the delivery of personalized cognitive interventions that maximize opportunity for individual cognitive and functional gains.

With that goal in mind, this study combined the datasets from two recent cognitive training trials, one from New York City (Medalia et al., 2019) and the other from Los Angeles (Jahshan et al. 2019), that examined the overall and relative efficacy of two cognitive training approaches and mechanisms of treatment effect. While the two studies shared multiple design elements, overlapped in the use of similar cognitive training software, and drew from similar diagnostic populations, very different results were reported. Medalia and colleagues (2019) reported large pre/post effect size gains in neurocognition and functional capacity across treatment conditions, but Jahshan and colleagues (2019) reported no significant pre/post treatment gains. Pooling the datasets afforded us the opportunity to investigate the relative contributions of participant characteristics (e.g. age, baseline abilities) versus site characteristics (e.g. treatment context) to the differential outcomes. This investigation overcomes the limitations of previous studies that used smaller, more homogeneous samples, or merged data sets encompassing studies with different training doses and outcome measures, allowing for a more robust investigation of factors that predict response to cognitive training for schizophrenia.

2. Methods

The New York study was conducted at Columbia University Irving Medical Center with oversight from the New York State Psychiatric Institute Institutional Review Board (NCT01945333), while the Los Angeles study was conducted within the Veterans Affairs Greater Los Angeles Healthcare System (NCT01891721). Study design elements that were similar or that distinguished one from the other are summarized below. Full intervention protocols are detailed in their respective publications (Jahshan et al., 2019; Medalia et al., 2019). A unified database was created by merging participant demographic characteristics and data from overlapping measures collected at baseline and post-treatment. When variables from similar outcome measures differed between studies, raw data were used to recalculate scores, thereby harmonizing the data (see Assessment Measures). Data harmonization and analyses were conducted at the NY site. Research team members from each site collaborated in the discussion of results and formulation of conclusions.

2.1 Study Characteristics

Studies at both sites employed a randomized parallel group design. Both included computer-based cognitive exercises delivered in a small group format by trained research personnel over 12 to 15 weeks at a rate of 3 sessions per week. In each study, two treatment approaches were compared, one which emphasized training on bottom-up operations in the auditory system inclusive of working memory and verbal learning and memory (Brain Basics in NY and Brain Fitness (Posit Science, San Francisco) in LA), and one which provided training across a range of cognitive skills such as attention, memory, reasoning and

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executive functioning, without targeting the auditory system directly (Brain Training in NY and Cogpack (Marker Software, Ladenburg, Germany) in LA). The computerized learning programs provided regular individualized feedback and adjusted the level of difficulty based on the individual's performance during the session to support motivation and drive learning. Participants continued to receive their designated mental health services and were maintained on their current psychoactive medications. Assessments of neurocognition, psychiatric symptoms, and functional capacity were assessed by raters blind to treatment condition.

While both studies provided technical instruction and support during cognitive training, only the NY site incorporated individualized strategy coaching and manualized group-based discussions based on the concept of bridging (Medalia et al., 2017) within each session. Furthermore, the NY study was conducted at participants' clinics, incorporated within the context of recovery services including individual case management and skills training groups whereas cognitive training in the LA study was offered in a campus building apart from other rehabilitative services. Participants in the LA study were compensated for sessions and assessments while participants in the NY study were compensated for assessments only. Only the LA study design included a placebo control group.

2.2 Participants

All participants were clinically stable outpatients with schizophrenia or schizoaffective disorder living in the community. Common exclusion criteria included having an estimated premorbid IQ below 70 based on reading ability, having an identifiable neurological disorder, seizures or history of serious head injury with loss of consciousness, meeting criteria for substance dependence, or insufficiently fluent in English. The NY study also excluded individuals who participated in cognitive remediation in the 12 months prior to study entry. The unified dataset consisted of 132 unique individuals with pre and post-treatment assessment data (LA: n=65, NY: n=67). Participants from the LA study assigned to the control group were not included in the analyses.

2.3 Assessment Measures

2.3.1 Neurocognition—Neurocognition was assessed with the NIMH MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008). Since the NY study used a normed neurocognitive composite T score while the LA study calculated an average T, normed neurocognitive composite T scores were generated for the LA sample to harmonize the outcome measure. The neurocognitive composite T score is based on measures of working memory, attention/vigilance, verbal learning, visual learning, processing speed, and reasoning and problem solving.

2.3.2 Functional Capacity—The UCSD Performance-based Skills Assessment (UPSA; Patterson et al., 2001) was administered to evaluate functional capacity. The UPSA is comprised of a series of role-play tasks with props that are performed to simulate situations that a person is likely to encounter in the community. Because the LA study used the full UPSA while the NY study used the Brief version (UPSA-B; Mausbach et al., 2007) only the

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raw scores from the finance and social/communications subscales were used to generate a harmonized UPSA total score which ranges from 0 to 100.

2.3.3 Symptom Severity—Clinical symptoms in the LA study were evaluated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984). Clinical symptoms in the NY study were evaluated using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1992). To harmonize symptom variables, SANS Total scores were converted to a PANSS Negative score (van Erp et al., 2014) and BPRS Total scores were converted to a PANSS Total Score (Leucht et al., 2013). The PANSS Total and PANSS Negative scores were used in data analyses to capture symptom severity.

2.3.4 Motivation—Both studies administered the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR; Choi et al., 2010) at baseline. Raw scores were used to calculate an IMI Total Score and Enjoyment, Choice, and Value subscale scores.

2.4 Statistical Analyses

The harmonized MCCB and UPSA outcomes used in the present analysis differed slightly from the outcomes summarized in the original publications, hence we performed within site tests of change from pre to post treatment separately for the active treatment arms i.e., Brain Basics and Brain Training in NY, and Brain Fitness and Cogpack in LA. T-tests assessed whether the pre/post change scores within each arm were significantly different from zero and whether arms differed within each site. Given no differences in pre/post change were found between active treatment arms within sites, all subsequent analyses collapsed the arms within sites.

Background characteristics of study participants were summarized using descriptive statistics and compared between sites using two-sample t-tests and chi-square tests. Differences found in baseline MCCB and UPSA between site were further interrogated by testing whether site differences persisted after controlling for other sociodemographics using linear regression with baseline MCCB and UPSA as outcomes.

Preliminary regression analyses examined simple associations between baseline participant characteristics and outcome measures. To examine site differences in treatment outcomes, linear regression models were performed predicting change in MCCB and UPSA separately. First, we fit a model including only site as the predictor to obtain unadjusted site differences in treatment effects. Then, a second model was fit including site plus all available background participant characteristics: baseline MCCB, baseline UPSA, age, gender, race/ethnicity, education, PANSS Negative, PANSS Total, and IMI-SR score. Because of collinearity between the IMI scores, only the one that provided the best overall R-square value was used. Percent change in the site differences before versus after controlling for participant characteristics was calculated and provides a useful summary of how much of site differences in outcomes can be explained by differences in background characteristics of participants. Standardized regression coefficients are reported to facilitate comparisons across predictors and outcomes.

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3. Results

3.1 Within site treatment effects on cognition and functional capacity

In the NY study, change scores on the MCCB neurocognitive composite improved for Brain Basics (Mean change=5.27, SD=4.60, p<.001) and Brain Training (Mean change=3.91, SD=5.03, p<.001) with no significant difference between the two (p=0.25). In the LA study, within group MCCB neurocognitive composite change scores did not reach statistical significance for Brain Fitness (Mean change=−1.00, SD=5.46, p=.324), nor Cogpack (Mean change=0.37, SD=6.14, p=.722) and these active arms in LA did not differ from one another (p=0.349).

The NY study found change score improvements on the UPSA for both treatment arms: Brain Basics (Mean change=11.04, SD=11.41, p<.001) and Brain Training (Mean change=6.61, SD=11.76, p=.002), while the LA study did not: Brain Fitness (Mean change=2.03, SD=7.64, p=.162), Cogpack (Mean change=3.24, SD=10.11, p=.075). Differences were not found between active treatment arms for UPSA within NY (p=0.123), nor LA (p=0.602).

Collapsing across the two active treatment arms within site, MCCB scores significantly improved in the NY study (Mean change=+4.58, SD=4.83, p< 0.001) but not in the LA study (Mean change=−0.26, SD=5.83, p=0.72), and UPSA scores significantly improved in both the NY (Mean change=+8.79, SD=11.72, p<0.001) and LA (Mean change=+2.68, SD=8.99, p=0.02) studies.

3.2 Comparison of background characteristics between sites

Background characteristics of participants are summarized and compared by site in Table 1. Study participants were similar between sites in proportions of males/females and psychiatric symptom severity (PANSS). The LA sample was significantly older and had more years of education, while the NY sample included a greater proportion of participants identifying as Black/African American and as Hispanic/Latinx. The NY sample reported higher levels of baseline intrinsic motivation.

Importantly, study participants at baseline in LA compared to NY had substantially (over a full standard deviation) better neurocognition (MCCB: LA, M(SD)=35.4(12.2) vs. NY, 20.7 (12.2)) and functional capacity (UPSA: LA, 76.4(12.7) vs NY 54.1(16.6)). These baseline site differences in neurocognition and functioning persisted even after controlling for age, gender, education and race (site effect: b=9.82, p<0.0001 MCCB; b=18.2, p<.0001 UPSA).

3.3 Comparison of neurocognitive outcomes by site

The unadjusted site difference (+4.8 points) on the MCCB favoring NY was statistically significant (p<0.001) representing a medium effect size difference (Cohen’s d=4.8/14.2 = 0.34). After controlling for all background characteristics, the adjusted site difference remained significant (p=0.026) but decreased to 3.1 points, suggesting that 35% of site differences in MCCB change were explained by differences in participant background characteristics.

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3.4 Comparison of functional capacity by site

The unadjusted site difference (+6.1 points) on the UPSA favoring NY was statistically significant (p=0.001), a medium effect size (Cohen's d=6.1/18.5 = 0.33). After controlling for all background characteristics, the adjusted site difference (−0.64 points, p=0.790) was no longer statistically significant and indicated UPSA improvement was fully explained by differences in participant background characteristics.

3.5 Predictors of outcome

Multiple linear regression models examining the effects of site and participant background characteristics on change in MCCB and UPSA are summarized in Table 2.

For improvement on the MCCB, the overall model R-squared was 28.8%. Although none of the predictors other than site reached statistical significance using p<0.05, two predictors had standardized regression coefficients >0.20 indicating a small but potentially meaningful effect. First, lower UPSA at baseline (B=−0.074, SE=0.044, p=0.092) was associated with greater improvement in MCCB. Second, race/ethnicity was associated with cognitive outcome (p=.064) such that non-Hispanic Whites evidenced greater MCCB gain than non-Hispanic Black/African Americans (B=2.52, SE=1.21, p=0.040). Of note, in a preliminary analysis, lower baseline MCCB was associated with greater MCCB change (Supplemental Table 1), but it was not a significant predictor of MCCB change in the overall model.

For improvement on the UPSA, the overall R-squared was 39.9%. We found significant effects of baseline MCCB (B=0.35, SE=0.09, p<0.001), baseline UPSA (B=−0.52, SE=0.07, p<0.001) and age (B=−0.20, SE=0.08, p=0.019), such that participants with better baseline neurocognition, lower baseline UPSA performance, and younger age demonstrated more improvement on the UPSA.

4. Discussion

This study harmonized datasets from two distinct cognitive intervention trials conducted with people with schizophrenia spectrum disorders. We took advantage of the multiple design elements the two studies shared to explore the factors contributing to the discrepant findings as they were previously reported. By harmonizing outcome variables and reanalyzing the data, we examined the relative impact of site versus participant characteristics on change in neurocognition and functional capacity. This investigation speaks to the larger issue of heterogeneity in outcomes observed across the published cognitive intervention studies to date (Reser et al., 2019) and efforts to identify characteristics of individuals and/or elements of our interventions that can inform personalization.

In the regression analyses, participant characteristics played a predictive role in both cognitive and functional outcomes, though to differing degrees. MCCB change was partially explained by participant characteristics, most notably baseline functional capacity and race which trended towards statistical significance. Similar to a recent analysis of 14 randomized controlled trials (Seccomandi et al., 2021), this set of analyses did not find that age predicted cognitive change. Site differences were reduced by 35% after controlling for participant

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characteristics, however, site accounted for the greater proportion of variance in MCCB change. In contrast, participant characteristics, not site differences, predicted who gained the most from cognitive interventions to improve their functional capacity. For the UPSA, greater improvement was significantly associated with three participant characteristics - younger age, better baseline cognitive functioning and lower baseline UPSA scores.

Since site differences played a significant role in the prediction of neurocognitive improvement, it is important to consider how the interventions differed. The four active training conditions overlapped in their use of some but not all exercises and software programs: Brain Basics in NY and Brain Fitness in LA overlapped heavily, Brain Training in NY shared some of the same exercises with the addition of those that targeted executive functions, whereas Cogpack in LA was completely unique. However, despite the overlap noted in the two most similar conditions, Brain Basics achieved significant neurocognitive gains while Brain Fitness did not. Further both studies in their original publications demonstrated relationships between training progress, specifically with respect to the auditory processes trained, and cognitive outcome, yet still achieved different outcomes. It therefore makes sense to consider intervention elements beyond software selections to explain the effect of site.

Unique features of the NY study were the integration of cognitive intervention with broader psychosocial programming and enhanced in-session opportunity for interaction with the clinician through individualized strategy coaching as well as with other group members during the bridging discussions. These features as well as the content of bridging groups intended to reinforce skill development, promote transfer of training, and support intrinsic motivation and engagement in learning. Prior research suggests that the differences in use of strategy coaching and bridging groups may contribute to varied outcomes in cognitive remediation research (Medalia and Bowie, 2016; Medalia and Freilich, 2008). Further, there is evidence that embedding cognitive remediation in recovery services may promote better outcomes (McGurk et al., 2007; Wykes et al., 20011). Although we cannot disentangle the impact of specific design features on treatment outcome, in this set of analyses site differences significantly predicted variability in cognitive but not functional capacity gain. Without the explicit use of clinician-mediated learning enhancement and transfer strategies, the LA study was similar to those of Dickinson et al. (2000) and Gomar et al. (2015) which did not yield significant treatment gains, and contrasts with the NY study which did.

Aggregating data from two sites resulted in a racially and ethnically diverse sample. While the category of race/ethnicity trended toward significance as a predictor of neurocognitive gain, we found specifically that participants who identified as non-Hispanic Black or African American benefited significantly less compared to their White non-Hispanic peers. This finding has not been reported in other studies of predictors of cognitive training and we are cautious in our interpretation. However, it is important to consider the potential impact of race and ethnicity on assessment and treatment response, particularly given the more systemic finding that such factors are markers of disparities in health care, independent of other factors such as education or socioeconomic status (Lewis-Fernandez et al., 2013; Williams, 1996). We still have much to learn about the role of race, culture, and ethnicity in cognitive interventions specifically.

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This investigation has limitations. First, the unexplained variance indicates the potential importance of participant and treatment variables which were not measured. Second, analyses were restricted to a completer sample for both sites, which precluded entering treatment adherence as a potential predictor of outcomes. Third, the NY study lacked a control group with which to assess the specificity of predictors for CR outcome. It remains clear that there is no one-size-fits-all approach to treating cognition and this set of analyses indicates that both participant and treatment characteristics contribute to treatment outcomes in meaningful ways. Additional cross-site analyses may help to identify patterns of treatment response that can guide personalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Background characteristics in active treatment groups across sites

	Total (N=132)	NY (N=67)	LA (N=65)	
Variables	**Mean (SD) or % (n)**	**Mean (SD) or % (n)**	**Mean (SD) or % (n)**	**p-value**
Age	47.7 (11.6)	44.2 (12.5)	51.4 (9.3)	**<.001**
Sex				0.275
Female	25.8% (34)	29.9% (20)	21.5% (14)	
Male	74.2% (98)	70.1% (47)	78.5% (51)	
Race/Ethnicity				**<.001**
Black/African American (non-Hispanic)	46.2% (61)	50.7% (34)	41.5% (27)	
White (non-Hispanic)	25.0% (33)	11.9% (8)	38.5% (25)	
Hispanic/Latinx	22.7% (30)	34.3% (23)	10.8% (7)	
Asian (non-Hispanic)	3.0% (4)	0.0% (0)	6.2% (4)	
Multi-Racial/Other (non-Hispanic)[a]	3.0% (4)	3.0% (2)	3.1% (2)	
Education (years)	12.3 (2.1)	11.5 (2)	13 (1.9)	**<.001**
PANSS Total	54.4 (13.5)	53.4 (12.8)	55.4 (14.2)	0.405
PANSS Negative	14.8 (4.8)	14.7 (5.2)	14.9 (4.4)	0.900
IMI Enjoyment	40.7 (7.0)	42.6 (6.7)	38.7 (6.9)	**0.002**
IMI Choice	39.1 (7.6)	39.3 (8.1)	39 (7.2)	0.849
IMI Value	42.7 (6.9)	43.9 (7.4)	41.4 (6.2)	**0.035**
IMI Total	122.5 (17.7)	125.7 (16)	119.1 (18.8)	**0.031**
Baseline MCCB	27.9 (14.2)	20.7 (12.2)	35.4 (12.2)	**<.001**
Baseline UPSA Brief	65.1 (18.5)	54.1 (16.6)	76.4 (12.7)	**<.001**

[a]One participant missing race/ethnicity was recoded as Other

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Table 2.

Multiple Regression Models of Change in Cognition and Functional Capacity from Pre to Post Cognitive Training

	MCCB Change (R square 28.8%)			UPSA Change (R square = 39.9%)		
Effect	**B(SE)**	**Standardized B**	**p-value**	**B(SE)**	**Standardized B**	**p-value**
Site (LA vs. NY)	−3.048 (1.348)	−0.521	0.026	0.636 (2.379)	0.058	0.790
Baseline MCCB	−0.015 (0.054)	−0.037	0.778	0.35 (0.093)	0.455	<.001
Baseline UPSA-B	−0.074 (0.044)	−0.234	0.092	−0.523 (0.074)	−0.888	<.001
Age	−0.021 (0.049)	−0.041	0.676	−0.201 (0.084)	−0.213	0.019
Sex (Male vs. Female)	−0.287 (1.144)	−0.049	0.803	−1.073 (1.96)	−0.098	0.585
Race/Ethnicity [a] (vs. Black (non-Hispanic))			0.064			0.542
Hispanic	0.107 (1.306)	0.018	0.935	−2.615 (2.25)	−0.240	0.248
White (non-Hispanic)	2.517 (1.21)	0.430	0.040	1.587 (2.111)	0.146	0.454
Education (years)	−0.084 (0.259)	−0.030	0.746	−0.04 (0.445)	−0.008	0.928
PANSS Negative	−0.022 (0.133)	−0.018	0.870	−0.005 (0.231)	−0.002	0.981
PANSS Total	−0.052 (0.043)	−0.120	0.233	−0.082 (0.073)	−0.102	0.267
Motivation IMI [b]	0.112 (0.074)	0.132	0.136	−0.16 (0.123)	−0.103	0.198

[a] Race/ethnicity categories tested are the 5 shown in Table 1 including also Asian and Mixed/Other but estimates for those groups with less than n=5 are not shown due to small sample sizes.

[b] For MCCB outcome IMI measure is Value, for UPSA outcome IMI measure is Enjoyment, each chosen respectively as they showed highest model R-square.

Note: Standardized regression coefficients scale the B estimate by the standard deviation of the outcome and the predictor.