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Transdiagnostic Predictors of Everyday Functioning: Examining the Relationships of Depression and Reinforcement Learning

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***Background and Hypothesis*: Impairments in function (ie, the ability to independently accomplish daily tasks) have been established in psychotic disorders. Identifying factors that contribute to these deficits is essential to developing effective interventions. The current study had several goals: examine potential differential relationships across domains of neurocognition, assess whether reinforcement learning is related to function, identify if predictors of function are transdiagnostic, determine whether depression and positive symptoms contribute to function, and to explore whether the modality of assessment impacts observed relationships. *Study Design*: Data from 274 participants were examined with schizophrenia/schizoaffective disorder (SZ; *n* = 195) and bipolar disorder (BD; *n* = 79). To reduce dimensionality, a PCA was completed on neurocognitive tasks which resulted in 3 components. These components and clinical interview data were used to investigate predictors of functional domains across measures of function (self- and informant-report SLOF and UPSA). *Results*: Two components, working memory/processing speed/episodic memory (βs = 0.18–0.42), and negative/positive reinforcement learning (β = −0.04), predicted different functional domains. Predictors of function were largely transdiagnostic with two exceptions: reinforcement learning had a positive association with self-reported interpersonal relationships for SZ and a negative association for BD (β = 0.34), and the negative association between positive symptoms and self-reported social acceptability was stronger for BD than for SZ (β = 0.93). Depression robustly predicted self-reported but not informant-reported function, and anhedonia predicted all domains of informant-reported function. *Conclusions*: These findings imply that reinforcement learning may differentially relate to function across disorders, traditional domains of neurocognition can be effective transdiagnostic targets for interventions, and positive symptoms and depression play a critical role in self-perceived functional impairments.**

Key words: schizophrenia/bipolar disorder/psychosis/neurocognition

Introduction

Psychotic disorders are among the most disabling illnesses worldwide.[1] This disability extends across multiple functional domains, including social (eg, interpersonal communication and relationships), occupational (eg, employment/work skills), and community functioning (eg, activities of independent daily living). Identifying the factors that are associated with, and possibly contribute to, these functional deficits is essential to inform effective interventions. However, there are still several open issues in the literature. This study focuses on clarifying the transdiagnostic relationships of neurocognition and symptoms with domains of function in schizophrenia and bipolar disorder.

There is robust evidence demonstrating that neurocognitive impairments in domains such as processing speed, working memory, and attention are core features of schizophrenia.[2] Further, neurocognition has been shown to play a crucial role in functional outcomes for individuals with schizophrenia.[3] Studies have robustly demonstrated small-to-medium effect sizes between general neurocognition and function.[4,5] To the contrary, there is

a lack of strong and consistent evidence for differential relationships between function and domain-specific components of neurocognition.[6–8] Notably, however, the relationship between neurocognition and function broadly defined has been largely shown to cut across cognitive domains, and a number of studies have examined composite measures of neurocognition in relation to function.[4,5]

Generally, the literature is most robust in linking work function to neurocognition.[3,9–12] This is likely due to the fact that cognitive skills such as memory and executive function may be more important for work than most aspects of social or community functioning. Yet, the findings regarding the relationships between neurocognition and other domains of function are mixed.[13] Several studies found that general neurocognition is significantly related to social function,[5,8,9,14] while others reported no significant association between neurocognition and social function.[7,15] This dichotomy is present for the domain of community function as well. The majority of studies have demonstrated relationships between community function and general neurocognition,[7,16] with two meta-analyses reporting small-to-medium effect sizes.[4,5] However, this is in stark contrast with studies that found no relationship between community function and neurocognition.[17,18] This inconsistency in the literature might be a by-product of the significant heterogeneity present in schizophrenia and suggests the influence of other contributing factors, such as introspective accuracy.[19]

In contrast to the literature on schizophrenia, less work has been done to investigate the factors that are associated with function in bipolar disorder. Like schizophrenia, studies have demonstrated neurocognitive deficits in bipolar disorder,[20–22] predominantly in episodic memory, attention/concentration, and executive functions.[2,23] Additionally, these deficits have been associated with functional outcomes in bipolar disorder[24–30] and persist outside the context of active symptoms.[23,29,31] Although the cognitive and functional impairments in bipolar disorder are generally less severe than in schizophrenia,[21,32] the literature suggests that the relationships between neurocognition and function are present across both disorders.[23,25,29] Still, it is less clear whether the strength and pattern of these relationships across domains of cognition and function are the same across disorders.[17,23] Identifying the transdiagnostic nature of these deficits and relationships could inform interventions that are beneficial for both schizophrenia and bipolar disorder.[17]

The majority of the research described above focuses on what is often referred to as "cold" cognition, which does not include the domain of reinforcement learning. There are multiple elements of reinforcement learning, including implicit (ie, outside of conscious awareness) and explicit (ie, including the use of explicit representations about potential reward associations), as well as both positive reinforcement (ie, learning about actions that lead to reward) and punishment components (ie, learning to avoid actions that lead to loss).[33] Given that the bulk of the literature has centered on standard neurocognitive domains, there is less evidence about the potential role of reinforcement learning in functional outcomes across psychotic disorders. However, several recent studies have linked reinforcement learning to effort allocation, anticipated pleasure and motivation, and everyday function in schizophrenia and schizoaffective disorder.[34–36] Furthermore, there are hints that these relationships are transdiagnostic across the spectrum of psychotic disorders, in that more severe motivation and pleasure deficits are related to worse explicit reinforcement learning performance across diagnoses of schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis.[33] Thus, investigating the relationships between reinforcement learning and function in psychotic disorders could help inform future transdiagnostic interventions.

The role of negative symptoms in functioning in psychotic disorders has also been widely supported.[17,37] Several studies found that negative symptoms are the most robust predictor of everyday function in schizophrenia.[38–42] Only a small body of research has investigated depression as a separate contributing factor from negative symptoms. This work has suggested that depression is associated with function and quality of life across psychotic disorders, but the magnitude of this relationship is unclear.[6,43] In bipolar disorder, depressive symptoms have been found to be more strongly correlated with functional impairments than manic symptoms.[44,45] On the other hand, while some studies reported that depression is more associated with function than psychotic symptoms in schizophrenia,[46,47] other studies found the contrary.[48,49] Moreover, the impact of positive symptoms has mixed support.[17] Much literature suggests that positive symptoms are less associated with general function than negative symptoms in schizophrenia and are related to different domains of function.[6,50] Also, while psychotic symptoms are not as prevalent in bipolar disorder, there is evidence that they contribute to disability.[51] Overall, more work is needed to investigate the presence, strength, and patterns of transdiagnostic relationships between symptoms and functional domains.

There is also a need to investigate whether these predictors differ across different modalities of assessment. Individuals with schizophrenia often have deficits in introspective accuracy, ie, self-evaluating their illness and function.[52–56] Due to this, informant reports of function and performance on functional competence tasks are often used as alternative measures. Generally, prior work suggests that patients overestimate their function compared to informant-reported function. Variability in symptoms may influence the degree to which patients are able to accurately report their own function. Ermel[52] found that depression is related to the underestimation of interpersonal function and the magnitude of discrepancy between self- and informant-reported function. In

contrast, Harvey[53] demonstrated that participants with higher self-reported depression more accurately report their function, while participants with very low self-reported depression tend to overestimate their function.

To address the gaps in the literature described above, the study focused on the following questions: (1) Are there differential relationships between neurocognition and function across functional domains? (2) Is reinforcement learning related to function? (3) Are the predictors of function transdiagnostic? (4) Are depression, independent of negative symptoms, and positive symptoms related to function? and (5) Does the modality of assessing function impact the observed relationships? Based on prior work, we predicted that traditional domains of neurocognition will be significantly associated with work and community functioning, presumably to a larger degree with work functioning. Yet the mixed research support led us to infer that traditional domains of neurocognition might not be associated with social functioning. Furthermore, we predicted that reinforcement learning will be related to function, though it is uncertain whether this relationship will differ across functional domains. Importantly, given the literature cited above, we hypothesized that the predictors of function will be broadly transdiagnostic. We also predicted that depression and positive symptoms will be independently linked to function, though the literature suggests strong associations with depression and fairly weak associations with positive symptoms. Lastly, we expected the predictors of function, particularly depression, to differ between self- and informant-reported function due to research on disrupted introspective accuracy in psychosis, as previously described.

Methods

Participants

Participant data (see below for final sample sizes) were collected from two studies with identical recruitment and assessment procedures conducted by the Cognitive Neuroscience Task Reliability And Clinical applications for Serious mental illness (CNTRaCS) Consortium, which is comprised of 5 sites: University of California, Davis; Maryland Psychiatric Research Center; Rutgers University; University of Minnesota; and Washington University. Group differences in data from the first study are reported in Barch et al.,[33] Gold et al.,[57] and Moran et al.,[58] and group differences in data from the second study are reported in Pratt et al.[59] Participants provided written informed consent based on the specific recruiting and informed consent procedures approved by each site's local Institutional Review Board. See Supplementary Material for exclusion criteria.

Procedure

A masters-level clinician conducted or supervised assessments using the Structured Clinical Interview for DSM-IV-TR, the 24-item Brief Psychiatric Rating Scale (BPRS), and the Clinical Assessment Interview for Negative Symptoms (CAINS) (table 1).

Participants and individuals with information about the participants' function (eg, family members, therapists) were asked to complete the Specific Levels of Functioning Scale (SLOF).[68] The SLOF assesses four domains: Interpersonal Relationships (eg, effectively communicating), Social Acceptability (eg, inappropriate or abusive behavior), Activities of Community Living (eg, managing household responsibilities), and Work Skills (eg, employable skills). Each domain is scored from 1 to 5, with higher scores indicating better function.

Participants also completed the UCSD Performance-Based Skills Assessment (UPSA),[69] a performance-based measure of functional capacity. Participants were asked to perform various tasks, including manipulating money, making routine and emergency calls, and performing shopping tasks. The UPSA total score used in this analysis is on a 0 to 100-point scale, with higher scores indicating better function.

Participants completed two cognitive testing sessions within one month. The cognitive tasks (table 1) were Working Memory Change Detection and Change Localization, Running Span, Explicit Probabilistic Incentive Learning Task (E-PILT), and a Reversal Learning Task. Three subtests of the MATRICS Consensus Cognitive Battery were also administered: BACS Symbol Coding, Hopkins Verbal Learning Test (HVLT), and Letter Number Sequencing (LNS).

Data Analysis

Data Cleaning and Final Participant Totals Data were analyzed from 274 participants, comprised of 195 individuals with a diagnosis of schizophrenia or schizoaffective disorder (SZ; 113 M 82 F), and 79 individuals with a diagnosis of bipolar disorder with psychosis (BD; 30 M 49 F). See Supplement for details on outliers. Numerical variables were standardized to have a mean of 0 and a standard deviation of 1. Data from 165 participants were used for the informant-report analyses (42 BD; 123 SZ).

Principal Component Analysis A principal component analysis with an oblique rotation was conducted with all 13 neurocognitive variables (table 1) to reduce the dimensionality of the neurocognitive data and focus on dissociable domains of cognition. A Catell's Scree Test was used to determine the optimal number of components. This procedure is described in more detail in the Supplementary Materials.

Prediction Both-direction stepwise linear regressions were used to explore the predictors of UPSA total score and of the four SLOF self-report and informant-report scales (this method is described in more detail

Table 1. Procedure

Name	Reference	Domain	Brief Description	Variable
Symptoms				
Brief Psychiatric Rating Scale (BPRS)	(Overall & Gorham, 1962)[60]	General Psychiatric Symptoms	The depression subscale assesses despondency in mood, sadness. The positive symptom subscale assesses grandiosity, suspiciousness, hallucinations, and unusual thought content.	• Depression Subscale • Positive Symptoms Subscale
Clinical Assessment Interview for Negative Symptoms (CAINS)	(Kring et al., 2013)[61]	Negative Symptoms	The anhedonia subscale measures interest and frequency of motivated behavior, frequency of pleasure and frequency of expected pleasure over the past week. The blunting subscale assesses facial expressivity, vocal expressivity, and body gestures.	• Anhedonia - Motivation and Pleasure (MAP) Subscale • Blunting Subscale
Neurocognition				
BACS Symbol Coding	(Keefe, 2004)[62]	Processing Speed	Participants are asked to quickly write the symbol associated with a given number within 90s.	• T-Score
Hopkins Verbal Learning Test (HVLT)	(Brandt, 1991)[63]	Episodic Memory	Participants are read a list of words and asked to repeat those words across three trials.	• T-Score
Letter Number Sequencing (LNS)	(Gold, 1997)[64]	Working Memory	Participants listen to a string of intermixed letters and numbers and then are asked to restate the sequence in numeric and alphabetical order.	• T-Score
Change Detection	(Gold et al., 2019)[57]	Working Memory	Participants are asked to encode a 5-item array, and after a short delay are presented with a 5-item test with either 0, 1, 2, or 5 items that differ from the original array, then are prompted to indicate whether they detect any changes.	• Percent accuracy
Change Localization	(Gold et al., 2019)[57]	Working Memory	Participants are presented with a single change on the test array and are asked to identify the location of the changed item.	• Percent accuracy
Running Span	(Broadway & Engle, 2010)[65]	Working Memory	Participants are presented with a string of letters and are asked to recall the last X letters.	• Original Operation - # of items remembered in their correct position • Adaptive Operation - # of items remembered in their correct position
Probabilistic Reversal Learning	(MacDonald et al.)[66]	Reversal Learning	Adapted from Cools and colleagues (2002). Participants selected one of two abstract images, with one item reinforced for 80% and 90% of the time, and then were told whether their choice was correct.	• Average Trials to Initial Acquisition • Average Trials to First Reversal
Explicit Probabilistic Incentive Learning Task (E-PILT)	(Gold, 2012)[67]	Reinforcement Learning	Participants are presented with various picture stimuli that are reinforced at different contingencies (80% or 90%) and asked to learn which images are associated with gain or avoiding loss.	• W80 - # of correct responses in gain and 80% condition • W90 - # of correct responses in gain and 90% condition • L80 - # of correct responses in loss and 80% condition • L90 - # of correct responses in loss and 90% condition

in the Supplementary Materials). Each model included the following independent variables: age, sex, diagnosis, symptom variables, scores from the 3 neurocognitive PCA components, and interactions of each variable with diagnosis. Each final model was selected with Bayesian Information Criterion because this approach penalizes more complex models and is likely to select a "true" model with large datasets.

Follow-up analyses were implemented to test whether depression was more significantly associated with self- or informant-reported function. Specifically, a series of three linear regressions were conducted on the domains of function that were significantly predicted by depression in the main analyses. These models included depression as the dependent variable and self- and informant-report SLOF scales as independent variables.

Results

Descriptives

The racial and ethnic composition of the groups is shown in Supplementary figures 1 and 2. SZ participants had higher BPRS positive symptoms, CAINS Anhedonia (Motivation and Pleasure Sympotoms), and CAINS affective blunting scores than BD participants but did not differ on any other variables (table 2).

Principal Component Analysis

The Catell's Scree Test results suggested using three components, which cumulatively explained 51% of the total variance (table 3). The first principal component was comprised of 7 neurocognitive variables—Running Span Original, Letter Number Sequencing, BACS Processing Speed, Running Span Adaptive, Hopkins Verbal Learning, Change Detection, and Change Localization. This component can be viewed as a composite of Working Memory, Processing Speed, and Episodic Memory (WM-PS-EM). The second principal component was comprised of the 4 EPILT neurocognitive variables—W80, L90, L80, and W90. This component can be viewed as a composite of positive and negative Reinforcement Learning (PosNegRL). The third principal component was comprised of both Reversal Learning neurocognitive variables—Reversal Learning First Reversal and Reversal Learning Initial Acquisition and EPILT W90. The component scores were used in the following analyses.

Regression

UPSA Seventeen percent of the variance in functional competence was accounted for by age and WM-PS-EM (table 4, Supplementary figure 3). A 1 standard deviation unit (SDU) increase in age was associated with a 20% increase in UPSA score, and a 1 SDU increase in WM-PS-EM performance was associated with a 43% increase in UPSA score.

Specific Levels of Functioning Scale: Self-Report

Interpersonal Relationships. Thirty-one percent of the variance in self-reported interpersonal relationships was accounted for by depression, positive symptoms, anhedonia, blunting, diagnosis, PosNegRL, and the interaction of diagnosis with PosNegRL (table 4, supplementary figure 4). A 1 SDU increase in depression score was associated with a 31% decrease in self-reported interpersonal relationships score, a 1 SDU increase in positive symptoms score was associated with a 15% decrease in self-reported interpersonal relationships score, a 1 SDU increase in anhedonia was associated with a 24% decrease in self-reported interpersonal relationships, and a 1 SDU decrease in blunting was associated with a 14% decrease in self-reported interpersonal relationships. Regarding the significant interaction effect, for SZ, a 1 SDU increase in PosNegRL was associated with a 13% *increase* in self-reported interpersonal relationships holding all other variables at 0. In contrast, for BD, a 1 SDU increase in PosNegRL was associated with a 21% *decrease* in self-reported interpersonal relationships.

Social Acceptability. Eighteen percent of the variance in self-reported social acceptability was accounted for by depression, positive symptoms, diagnosis, and the interaction of positive symptoms and diagnosis (table 4, Supplementary figure 4). A 1 SDU increase in depression was associated with a 16% decrease in self-reported social acceptability. The significant interaction effect reflects that for SZ, a 1 SDU increase in positive symptoms was associated with a 22% decrease in self-reported social acceptability, but a 114% decrease in self-reported social acceptability for BD holding all other variables at 0.

Activities of Community Living. Seven percent of the variability in self-reported activities of community living was accounted for by anhedonia and WM-PS-EM (table 4, Supplementary figure 4). A 1 SDU increase in anhedonia score was associated with a 17% decrease in self-reported activities of community living, and a 1 SDU increase in WM-PS-EM was associated with a 18% increase in self-reported activities of community living.

Work Skills. Fourteen percent of the variability in self-reported work skills was accounted for by depression and anhedonia (table 4, Supplementary figure 4). A 1 SDU increase in depression was associated with a 29% decrease in self-reported work skills, and a 1 SDU increase in anhedonia was associated with a 20% decrease in self-reported work skills.

Specific Levels of Functioning Scale Informant-Report

Interpersonal Relationships. Seventeen percent of the variance in informant-reported interpersonal relationships was accounted for by anhedonia and blunting (table 5, Supplementary figure 5). A 1 SDU increase in anhedonia was associated with a 29% decrease in informant-reported interpersonal relationships, and a 1 SDU increase in blunting was associated with a 20% decrease in informant-reported interpersonal relationships.

Social Acceptability. Six percent of the variance in informant-reported social acceptability was accounted for by anhedonia and blunting (table 5, Supplementary figure 5). A 1 SDU increase in anhedonia score was associated with a 24% decrease in informant-reported social acceptability, and a 1 SDU increase in blunting score was associated with a 26% increase in informant-reported social acceptability.

Activities of Community Living. Five percent of the variability in informant-reported activities of community living

Table 2. Descriptives

	Mean		SD		Min		Max		Skew		Kurtosis		*T*-test	
	BD	*SZ*	*BD*	*SZ*	*BD*	*SZ*	*BD*	*SZ*	*BD*	*SZ*	*BD*	*SZ*	*Stat*	*P*
Age	36.70	37.16	10.42	10.92	18.42	18.04	55.72	56.69	0.22	0.16	−1.08	−1.23	−0.32	1.00
BPRS Depression	9.91	9.16	4.16	4.10	4.00	3.00	20.00	22.00	0.50	0.69	−0.77	−0.22	1.36	1.00
BPRS Positive Sym	4.47	8.13	1.99	4.15	3.00	0.00	11.00	20.00	1.59	0.54	1.73	−0.60	−7.50	.00
CAINS Anhedonia	8.39	11.61	5.27	6.39	0.00	0.00	19.00	28.00	0.24	0.46	−0.79	−0.28	−3.95	.00
CAINS Blunting	1.18	3.23	1.97	2.94	0.00	0.00	9.00	12.00	2.12	0.70	4.20	−0.29	−5.70	.00
UPSA Total	84.38	79.97	10.69	12.48	40.40	43.94	100.00	100.00	−1.29	−0.84	2.22	0.31	2.75	.16
Interpersonal[a] (Inf.)	3.84	3.65	0.75	0.82	2.00	1.57	5.00	5.00	−0.54	−0.40	−0.52	−0.43	1.33	1.00
Social [a](Informant)	4.35	4.53	0.50	0.49	2.67	2.17	5.00	5.00	−0.84	−1.72	0.95	4.04	−2.13	.77
Community[a] (Inf.)	4.77	4.65	0.45	0.51	3.82	3.00	6.36	6.00	0.70	−1.08	2.55	1.79	1.39	1.00
Work[a] (Informant)	4.10	3.91	0.76	0.87	2.33	1.83	5.00	5.00	−0.42	−0.56	−0.99	−0.78	1.23	1.00
Interpersonal (Self)	3.76	3.56	0.83	0.84	1.57	1.14	5.00	5.00	−0.61	−0.33	−0.22	−0.44	1.75	1.00
Social (Self)	4.39	4.48	0.49	0.45	2.83	2.33	5.00	5.00	-0.90	-1.35	0.36	2.63	-1.38	1.00
Community (Self)	4.72	4.63	0.35	0.49	3.55	1.82	5.18	5.36	−1.15	−2.14	0.75	6.70	1.52	1.00
Work (Self)	4.17	4.14	0.69	0.72	2.17	2.00	5.00	5.00	−0.76	−0.83	0.00	0.21	0.37	1.00
BACS	42.53	41.76	10.95	11.96	21.00	20.00	71.00	80.00	0.42	0.34	−0.07	−0.09	0.49	1.00
HVLT	44.29	41.50	8.44	9.01	24.00	24.00	72.00	70.00	0.60	0.67	0.62	0.42	2.36	.45
LNS	46.42	43.53	9.81	9.85	23.00	20.00	68.00	68.00	−0.07	−0.07	−0.40	−0.37	2.20	.66
Change Detection	0.65	0.66	0.13	0.14	0.40	0.26	0.90	0.96	−0.24	−0.29	−0.96	-0.46	−0.58	1.00
Change Localization	0.61	0.62	0.14	0.16	0.27	0.12	0.83	1.00	−0.40	−0.21	−0.80	−0.09	−0.70	1.00
Running Span O	68.91	60.88	19.82	19.99	25.00	10.00	113.00	118.00	0.05	0.20	−0.79	−0.30	3.02	.08
Running Span A	41.99	38.55	17.84	17.84	1.00	1.00	83.00	84.00	0.20	0.25	−0.70	−0.52	1.45	1.00
Rev Learning IA	−18.06	−19.03	5.59	7.17	−35.00	−42.50	−10.00	−10.00	−0.83	−0.89	0.70	0.25	1.08	1.00
Rev Learning FR	−19.10	−19.58	7.10	6.54	−45.00	−45.00	−10.00	−10.00	−1.53	−1.28	2.34	1.79	0.54	1.00
EPILT W80	0.80	0.76	0.17	0.21	0.20	0.00	1.00	1.00	−1.55	−1.31	2.47	1.39	1.72	1.00
EPILT W90	0.79	0.78	0.16	0.19	0.30	0.10	1.00	1.00	−1.07	−1.08	0.78	0.54	0.46	1.00
EPILT L80	0.79	0.74	0.18	0.21	0.30	0.10	1.00	1.00	−1.00	−0.85	0.42	0.05	1.59	1.00
EPILT L90	0.77	0.75	0.18	0.19	0.10	0.10	1.00	1.00	−1.15	−1.06	1.33	0.77	0.87	1.00
			Median		Min		Max		Mann–Whitney Test					
			BD	*SZ*	*BD*	*SZ*	*BD*	*SZ*	W					*P*
Years of Education			14	14	8	3	21	22	9426.5					.09
Mother's Years of Education			14	13	7	0	24	23	7429.0					1.00
Father's Years of Education			14	13	9	7	22	23	6263.5					1.00
			Proportions						Chi-square Test					
			BD		*SZ*				χ^2					*P*
Gender			38% male	62% female	58% male		42% female		8.21					.011

P-values are adjusted with the Holm–Bonferroni correction. All numerical variables are standardized.
[a]$N = 165$

Table 3. PCA of Neurocognitive Variables

Variable	First Principle Component (WM-PS-EM)	Second Principle Component (PosNegRL)	Third Principle Component (RevLearn)
Running Span Original	0.791	.	
Letter Number Sequencing	0.784		
BACS Processing Speed	0.741		
Running Span Adaptive	0.730		
Hopkins Verbal Learning	0.638		
Change Detection	0.549		
Change Localization	0.523		
EPILT W80		0.719	
EPILT L90		0.718	
EPILT L80		0.694	
EPILT W90		0.466	0.307
Reversal Learning First Reversal			0.777
Reversal Learning Initial Acquisition			0.674

Note: Only loadings above 0.3 are shown for clarity.
PosNegRL, Positive and Negative Reinforcement Learning; RevLearn, Reversal Learning; WM-PS-EM, Working Memory, Processing Speed, and Episodic Memory.
The values in italics are the 95% CI's.
*** $P < .001$; ** $P < .01$; * $P < .05$

Table 4. UPSA and Self-Report Regression Results: Standardized β Coefficients, 95% CIs, and Model Fit

	UPSA	Interpersonal Relationships	Social Acceptability	Activities of Community Living	Work Skills
Age	0.20 *** *[0.08, 0.31]*	-	-	-	-
Depression	-	−0.31 *** *[−0.42, −0.20]*	−0.16 ** *[−0.28, −0.04]*	-	−0.29 *** *[−0.41, −0.18]*
Positive Symptoms	-	−0.15 * *[−0.27, −0.03]*	−0.68 *** *[−0.90, −0.46]*	-	-
Anhedonia	-	−0.24 *** *[−0.36, −0.13]*	-	−0.17 ** *[−0.29, −0.05]*	−0.20 *** *[−0.31, −0.08]*
Blunting	-	−0.14 * *[−0.25, −0.03]*	-	-	-
WM-PS-EM	0.43 *** *[0.31, 0.54]*	-	-	0.18 ** *[0.06, 0.30]*	-
PosNegRL	-	−0.04 *[−0.16, 0.08]*	-	-	-
Diagnosis	-	0.04 *[−0.22, 0.30]*	0.95 *** *[0.59, 1.32]*	-	-
Positive Symptoms × DX	-	-	0.93 *** *[0.50, 1.35]*	-	-
PosNegRL × DX	-	0.34 ** *[0.10, 0.58]*	-	-	-
Adjusted R^2	0.17	0.31	0.18	0.07	0.14
BIC	745.45	719.37	751.51	777.35	754.54
F-test	$F(2, 271) = 29.27$***	$F(7, 266) = 18.30$***	$F(4, 269) = 16.08$***	$F(2, 271) = 11.16$***	$F(2, 271) = 23.89$***

Note: Dashes (-) illustrate that the final model does not include that predictor.
PosNegRL, Positive and Negative Reinforcement Learning; WM-PS-EM, Working Memory, Processing Speed, and Episodic Memory.
The values in italics are the 95% CI's.
*** $P < .001$; ** $P < .01$; * $P < .05$

was accounted for by anhedonia (table 5, Supplementary figure 5), with a 1 SDU increase in anhedonia associated with a 23% decrease in informant-reported activities of community living.

Work Skills. Twenty percent of the variability in informant-reported work skills was accounted for by anhedonia and WM-PS-EM (table 5, Supplementary figure 5). A 1 SDU increase in anhedonia was associated with a

Table 5. Informant-Report Regression Results: Standardized β Coefficients, 95% CIs, and Model Fit

	Interpersonal Relationships	Social Acceptability	Activities of Community Living	Work Skills
Anhedonia	−0.29 *** *[−0.45, −0.13]*	−0.24 ** *[−0.40, −0.07]*	−0.23 ** *[−0.39, −0.08]*	−0.37 *** *[−0.51, −0.22]*
Blunting	−0.20 * *[−0.36, −0.05]*	0.26 ** *[0.10, 0.43]*	-	-
WM-PS-EM	-	-	-	0.21 ** *[0.07, 0.35]*
Adjusted R^2	0.17	0.06	0.05	0.20
BIC	455.28	475.68	473.22	449.79
F-test	$F(2, 162) = 17.57$***	$F(2, 162) = 6.10$**	$F(1, 163) = 9.50$**	$F(2, 162) = 20.90$***

Note: Dashes (-) illustrate that the final model does not include that predictor.
WM-PS-EM, Working Memory, Processing Speed, and Episodic Memory.
The values in italics are the 95% CI's.
*** $P < .001$; ** $P < .01$; * $P < .05$.

37% decrease in informant-reported work skills, and a 1 SDU increase in WM-PS-EM was associated with a 21% increase in informant-reported work skills.

Depression in Relation to Self- Versus Informant-Reported Function As reported above, depression was consistently related to self-reported but not informant-reported function. Linear regressions for each of these domains of function indicated that when self and informant are in the same model, only self-report significantly related to depression (Supplementary table 2).

Discussion

We found that two neurocognitive components, one comprised of working memory, processing speed, and episodic memory, and the other comprised of negative and positive reinforcement learning, selectively predicted different domains of function. Additionally, the relationships were largely transdiagnostic with two exceptions: the association between positive and negative reinforcement learning and self-reported interpersonal relationships, and the relationship between positive symptoms and self-reported social acceptability. Furthermore, our results demonstrated that depression was robustly associated with self-reported but not informant-reported function. On the contrary, anhedonia predicted all domains of informant-reported function.

The literature indicates that traditional domains of neurocognition are robustly associated with occupational functioning.[9–13] We found that the neurocognitive component, defined as a composite of working memory, processing speed, and episodic memory, was positively associated with informant-reported work skills but was unassociated with self-reported work skills. The lack of association between neurocognition and self-reported work skills deviates from the prior literature. Yet, the discrepancy between self- and informant-reported results aligns with research that suggests individuals with psychosis may not accurately self-evaluate their functional capacities.[53] Further, given that self-reported work skills were predicted in part by depression, these results may reflect that depression skews self-reported ratings of work skills functioning,[52,53] as discussed in more detail below.

While the existing literature supports a relationship between work skills and neurocognition, evidence regarding the relationship between neurocognition and social functioning is unclear. We found that the working memory, processing speed, and episodic memory component was not associated with social functioning based on either self or informant report. However, the component reflecting positive and negative reinforcement learning was associated with self-reported interpersonal relationships, though it interacted with diagnosis. Specifically, better positive and negative reinforcement learning predicted increased self-reported interpersonal relationships in SZ but decreased self-reported interpersonal relationships in BD. While this finding was unexpected, it implies that the pathways linking disrupted reinforcement learning to social function might vary as a function of diagnosis. Previous work has suggested that reinforcement learning is linked to motivation and apathy across psychotic disorders.[34,35] This lends itself to the possible interpretation that individuals with poor reinforcement learning may fail to learn cues predicting positive social engagements. In contrast, reinforcement learning has also been associated with hyper-reward responsivity in BD,[70,71] which could be related to socially inappropriate behavior. Though in the current analyses, we did not find significant correlations between anhedonia and reinforcement learning across both groups (Supplementary figure 6). Therefore, this finding is in need of replication before further interpretations can be proposed.

As noted above, we found that some aspects of reinforcement learning were related to interpersonal function but no other components of function. Moreover, the component comprised of reversal learning was not significantly associated with any domains of function across modalities of assessment. At this point, it is not clear

whether this is due to construct-related differences (ie, reversal learning engages differential processes) or different psychometrics of the reversal learning task compared to the other reinforcement learning tasks.

Broadly, the existing literature has yet to come to an agreement on whether the patterns and strength of relationships between domains of neurocognition and function are transdiagnostic.[17,23] Here, we found that the neurocognitive component comprised of working memory, processing speed, and episodic memory was related to self-reported community living, UPSA, and informant-reported work skills similarly across disorders. This suggests that interventions that target the link between neurocognition and function could be effective across diagnoses. Specifically, this result supports previous claims that cognitive rehabilitation, which has been shown to improve function in schizophrenia by ameliorating cognitive deficits, might be equally beneficial in bipolar disorder.[17,72,73] On the other hand, as discussed above, we found that the relationship of reinforcement learning to self-reported interpersonal relationships differed by diagnosis. This finding is in need of replication, but if confirmed, it suggests potentially different intervention approaches across schizophrenia and bipolar disorder in terms of the role of reward learning in function.

Similar to neurocognition, negative symptoms have been robustly associated with deficits in function.[17,37–42] In the current study, anhedonia predicted all informant-reported domains of function and self-reported interpersonal relationships, activities of community living, and work skills. In addition, affective blunting was associated with self- and informant-reported interpersonal relationships. In contrast to prior literature, we found that an increase in blunting was related to an increase in informant-reported social acceptability, an unexpected finding that warrants further evaluation. However, the anhedonia findings are consistent with prior studies that have highlighted the importance of interventions to target negative symptoms as a mechanism for treating functional impairments.[74]

The current findings suggest that depression plays a critical role in self-reported everyday function across diagnoses. An increase in depression was significantly associated with worse self-reported function in all domains except activities of community living. In contrast, depression was unassociated with any informant-reported functional domain, with follow-up analyses corroborating a significantly stronger relationship between self-reported function and depression. These results demonstrate that depression impacts self-perceived function and can be contextualized by prior literature that linked depression to introspective inaccuracy in schizophrenia, namely the underestimation of interpersonal function.[52,53] Thus, while targeting depression in psychotic disorders in and of itself may not improve functioning, it may improve accuracy in the perception of functional impairments and could potentially lead to an improved willingness to engage in activities. Above all, these results strongly suggest that depression should be further investigated as a contributing factor to function and taken into account when evaluating assessments with patients. Moreover, although introspective accuracy can impair the objectivity of self-report measures,[52,53] self-report measures can still provide insight into a patient's functional deficits that cannot be captured in informant-report measures and index how a person thinks about their own level of function, which may impact behavior whether or not it is wholly accurate. For that reason, both self-and informant-report measures should be utilized when conceptualizing a patient's functional ability and the sources of their functional impairments.

The literature has suggested that positive symptoms are less and differentially associated with function than negative symptoms, though this may reflect the difficulties of recruiting individuals with severe psychotic symptoms and capturing fluctuating positive symptoms at a single time point.[6,50,75] In our study, positive symptoms were negatively related to self-reported but not informant-reported, social acceptability across disorders, and to a significantly larger degree for BD. This points toward the possibility that positive symptoms impact an individual's self-perceived social acceptability rather than how others perceive their social acceptability. Ultimately, the key takeaway from these results is that positive symptoms should not be overlooked when considering the predictors of social function, especially for BD.

There are several limitations to this study. First, we did not assess introspective accuracy and we could not formally determine whether it is linked to depression. Second, there were fewer participants with informant- than self-report measures, which might have impacted power in the informant-report analyses. Third, the study sample included medicated patients with predominantly nonactive symptoms, so the distribution of positive symptoms was skewed. Fourth, the BD sample was significantly smaller than the SZ sample. Lastly, the data were collected using a cross-sectional research design, and we were unable to evaluate causal relationships.

On the whole, the present findings provide evidence that neurocognition and symptoms have mostly comparable associations with functioning across SZ and BD, reinforcement learning plays a small role in daily functioning, depression largely impacts self-perceptions of functional ability, and informant-report measures provide markedly different perspectives of function than self-report measures. Overall, these findings highlight the importance of examining depression and utilizing different modalities of assessment in research on function across psychotic disorders. Further, they emphasize the need for future work to investigate reinforcement learning

as a predictor of function and imply that traditional domains of neurocognition and symptoms may be effective transdiagnostic targets for future interventions.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Author Contributions

N.D. had full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis. N.D. performed the data analysis. All authors developed the study concept and design and aided in interpretation and provided critical revisions. All authors approved the final version of the paper for submission.

Conflict of Interest

N.D. and E.M. have no conflicts to report. D.M.B. has received grants from the Brain & Behavior Research Foundation and the National Institutes of Health (NIH), and is a consultant for Pfizer on studies related to the treatment of negative symptoms in schizophrenia. C.S.C. has received research grants from the National Institutes of Health (NIH), the Brain and Behavior Foundation, the Burroughs Wellcome foundation, GlaxoSmithKline, and the Robert Wood Johnson Foundation and has been an external consultant for Lilly, Merck, Pfizer, Roche, and Servier. J.M.G. has received grants from National Institutes of Health (NIH), receives royalty payments from Brief Assessment of Cognition in Schizophrenia, and has acted as a consultant to Amgen, AstraZeneca, GlaxoSmithKline, Hoffman LaRoche, Merck, Pfizer, and Solvay. S.L. has received research grants from the National Institutes of Health (NIH) and the National Science Foundation. A.W.M. has received research grants from the National Institutes of Health (NIH) and the Brain & Behavior Research Foundation. J.D.R. has received research grants from the National Institutes of Health (NIH), the Brain & Behavior Research Foundation, the EJLB Foundation, and the Robert Wood Johnson Foundation. S.M.S. has received research grants from the National Institutes of Mental Health (NIMH), The Brain & Behavior Research Foundation, the van Ameringen Foundation, the Jacob and Valeria Langaloth Foundation, the Patrick P,. Lee Foundation, the Chernowitz Medical Research Foundation, the New England Research Institutes, the New York State Office of Mental Health, the New Jersey Division of Mental Health and Addiction Services, The Lavelle Fund for the Blind, diaMentis, Inc., Janssen Pharmaceutica, AstraZeneca, and Pfizer.

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