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BACKGROUND

Cognitive impairments are common in individuals with schizophrenia (SZ), schizoaffective disorder (SZA), bipolar disorder (BD) and major depressive disorder (MDD). These disorders also share similar psychopathology and – to some extent – a common polygenic background. Therefore, rather than treating these disorders as distinct categorical entities, a model of an affective-to-psychotic spectrum has been proposed. Previous work has confirmed increasing cognitive impairment on a spectrum from BD to SZA bipolar type, to SZ and SZA depressive type (Lynham et

al., 2018). Findings from genetic studies also support a spectrum from MDD to BD II to BD I to SZA and SZ (Stahl et al., 2019). Using data from the PsyCourse study (Budde et al., 2019), we aim to (1) replicate the finding that cognitive performance decreases on a spectrum from healthy controls over affective to psychotic disorders and (2) explore possible associations of cognitive performance and polygenic risk scores (PRS) for SZ, BD and MDD.

METHODS

Sample

- Adult participants (N=985) from PsyCourse 3.0 dataset
 - Clinical participants with DSM-IV diagnoses of recurrent major depression (MDD), bipolar disorder I and II (BD I and BD II), schizoaffective disorder (SZA), and schizophrenia (SZ)
 - Controls (CON)
- Cognitive data from second study visit (= 6 months after baseline)

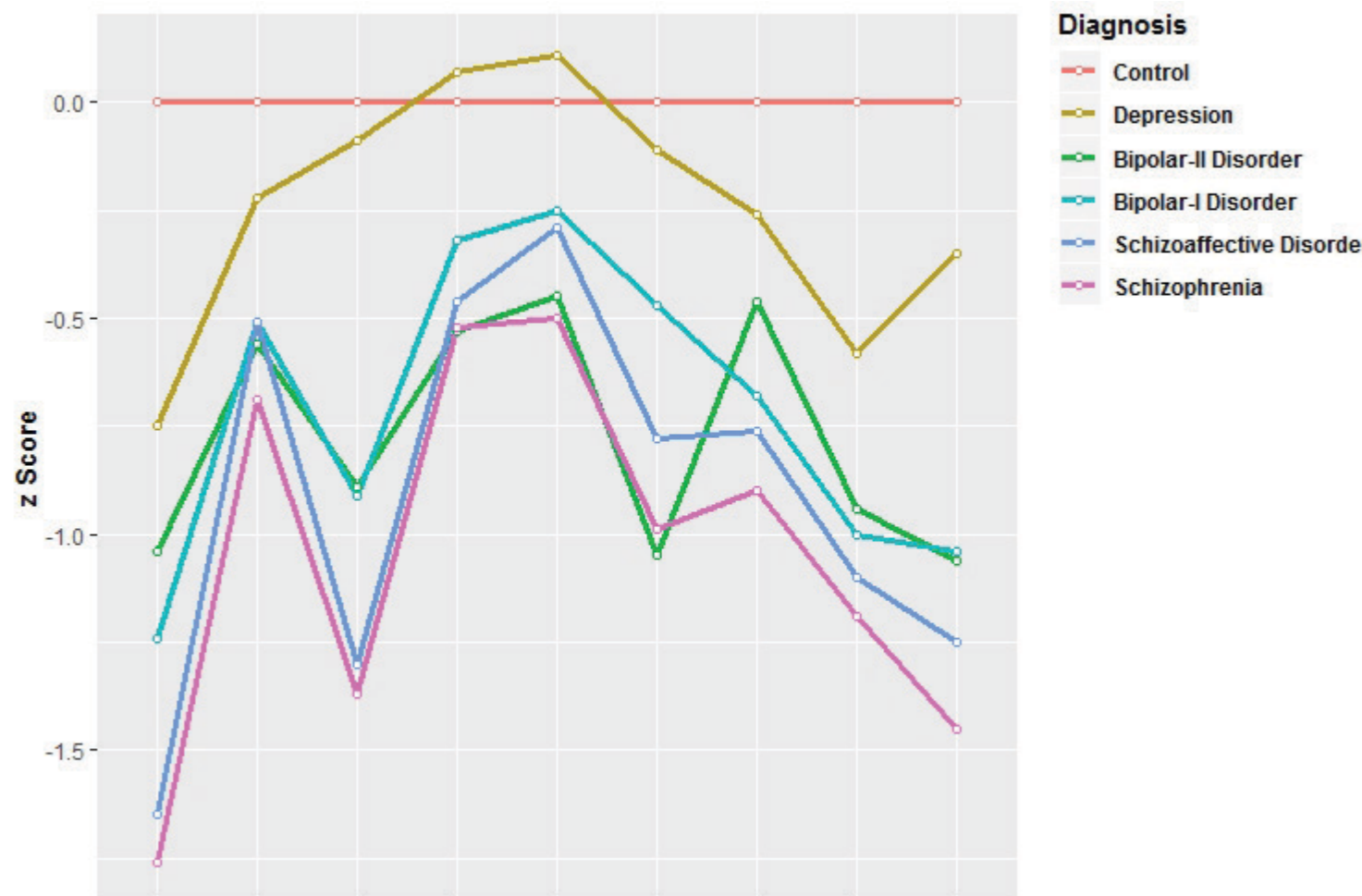


Figure 1. Cognitive Profiles of Diagnostic Groups in Relation to Controls. Z-standardization based on the controls. Displayed are the means of the diagnostic groups without adjustment for covariates. Cognitive domains: 1 = speed of processing, 2 = short term memory, 3 = verbal learning, 4 = consolidation, 5 = long-term memory, 6 = recognition, 7 = working memory, 8 = task shifting, 9 = general cognitive abilities.

Measures

- 8 cognitive test scores (see Table 2) → standardized based on controls
- One score of general cognitive ability (retrieved from principal component analysis)
- Figure 1 shows the **uncorrected mean performance** on the analyzed cognitive domains of clinical participants in relation to controls.

Statistical methods

a) Phenotypic analyses (performed in R version 3.4.2)

- Linear regression models → comparing cognitive performance on single tests between diagnostic groups**
 - Z-standardized cognitive score ~ diagnosis + covariates
 - Reference group: controls
 - Covariates = age, sex, current psychiatric treatment (in- or outpatient treatment), current medication, center
 - Post-hoc pairwise comparisons between diagnostic groups (Tukey's test)
- Linear mixed models → comparing cognitive profiles between diagnostic groups**
 - Z-scores of cognitive performance ~ covariates + diagnosis + cognitive domain + diagnosis*cognitive domain

b) Polygenic risk score analyses of general cognitive ability

- Samples genotyped using Illumina Infinium PsychArray
- Imputation after quality control using SHAPEIT2 and IMPUTE2 (reference panel: 1000 Genomes Project dataset)
- PRS calculated using PLINK 1.90
 - Discovery GWAS for MDD: Wray et al., 2018
 - Discovery GWAS for BD-PRS: Stahl et al., 2019
 - Discovery GWAS for SZ-PRS: Pardiñas et al., 2018
- Linear regression models (N=606) using PRS at 4 thresholds each (5*10⁻⁸, 0.05, 0.1 and 1)**
 - Model 1: general cognitive ability ~ covariates (age, sex, current psychiatric treatment, current medication, center, ancestry principal components 1 and 3)
 - Model 2: general cognitive ability ~ covariates + PRS
- Comparison of adjusted R² between models

Table 1. Sample characteristics and comparison across diagnostic groups

	Total (N=985)	CON (n= 253)	MDD (n= 53)	BD II (n=62)	BD I (n=254)	SZA (n=67)	SZ (n=296)	p
Female sex, n (%)	482 (48.9%)	152 (60.1%)	32 (60.4%)	30 (48.4%)	124 (48.8%)	40 (59.7%)	104 (35.1%)	<0.001
Age at first interview, mean (SD)	42.3 (14.1)	37.4 (15.9)	43.0 (15.1)	48.9 (14.7)	45.2 (13.0)	44.6 (12.0)	42.0 (11.9)	<0.001
Age at onset*, mean (SD)	30.8 (12.0)	-/-	33.2 (14.0)	38.0 (14.8)	32.7 (12.3)	29.7 (10.6)	27.8 (10)	<0.001
Duration of illness*, mean (SD)	13.30 (10.9)	-/-	9.44 (10.0)	11.89 (11.3)	12.98 (11.2)	14.85 (11.0)	14.17 (10.5)	0.03

Table 2. Cognitive Tests

Cognitive Score	Domain
Digit symbol test	Speed of processing
Verbal digit span forward	Short term memory
VLMT sum of correctly recalled words	Verbal learning
VLMT loss after distraction	Consolidation
VLMT loss after time	Long-term memory
VLMT recognition after time	Recognition
Verbal digit span backwards	Working memory
Trail Making Test Part B reaction time	Task shifting

VLMT= verbal learning and memory test

Table 3. Comparison of cognitive performance between clinical participants and controls

Diagnosis	Speed of Processing	Short Term Memory	Verbal Learning	Consolidation	Long Term Memory	Recognition	Working Memory	Task Shifting	General Cognitive Abilities
MDD	#	X	X	X	X	X	X	X	X
BDII	#	X	#	X	X	X	X	X	X
BDI	✓	X	✓	X	X	X	✓	#	#
SZA	✓	X	✓	X	X	X	X	X	X
SZ	✓	X	✓	X	X	X	✓	✓	✓

✓ = significant after FDR correction; # = nominally significant; X= non-significant; reference group: controls; covariates in the model: age, sex, current psychiatric treatment, current medication, center

Table 4. Significant differences in cognitive performance between diagnostic groups

Cognitive Domain	Diagnostic Groups		
Speed of processing	CON	vs.	BDI, SZA and SZ
	BD II	vs.	SZ
	BD I	vs.	SZ
Verbal Learning	CON	vs.	SZA and SZ
Working Memory	CON	vs.	SZ
General Cognitive Abilities	CON	vs.	SZ

Post-hoc pairwise comparisons (Tukey's test), corrected for multiple testing

Table 5. Linear mixed model comparing profiles of cognitive performance

Predictor	F value	P value
Age	230.10	<0.001
Sex	12.61	<0.001
Current psychiatric treatment	4.47	<0.004
Number of antidepressants	0.01	0.94
Number of antipsychotics	9.62	0.002
Number of mood stabilizers	0.01	0.913
Number of tranquilizers	2.94	0.087
Number of other psychiatric medications	2.13	0.145
Diagnostic group	6.06	<0.001
Cognitive domain	49.63	<0.001
Interaction diagnostic group*domain	7.80	<0.001

R² for the model was 24.8%, 95% confidence interval [23.7, 26.8]

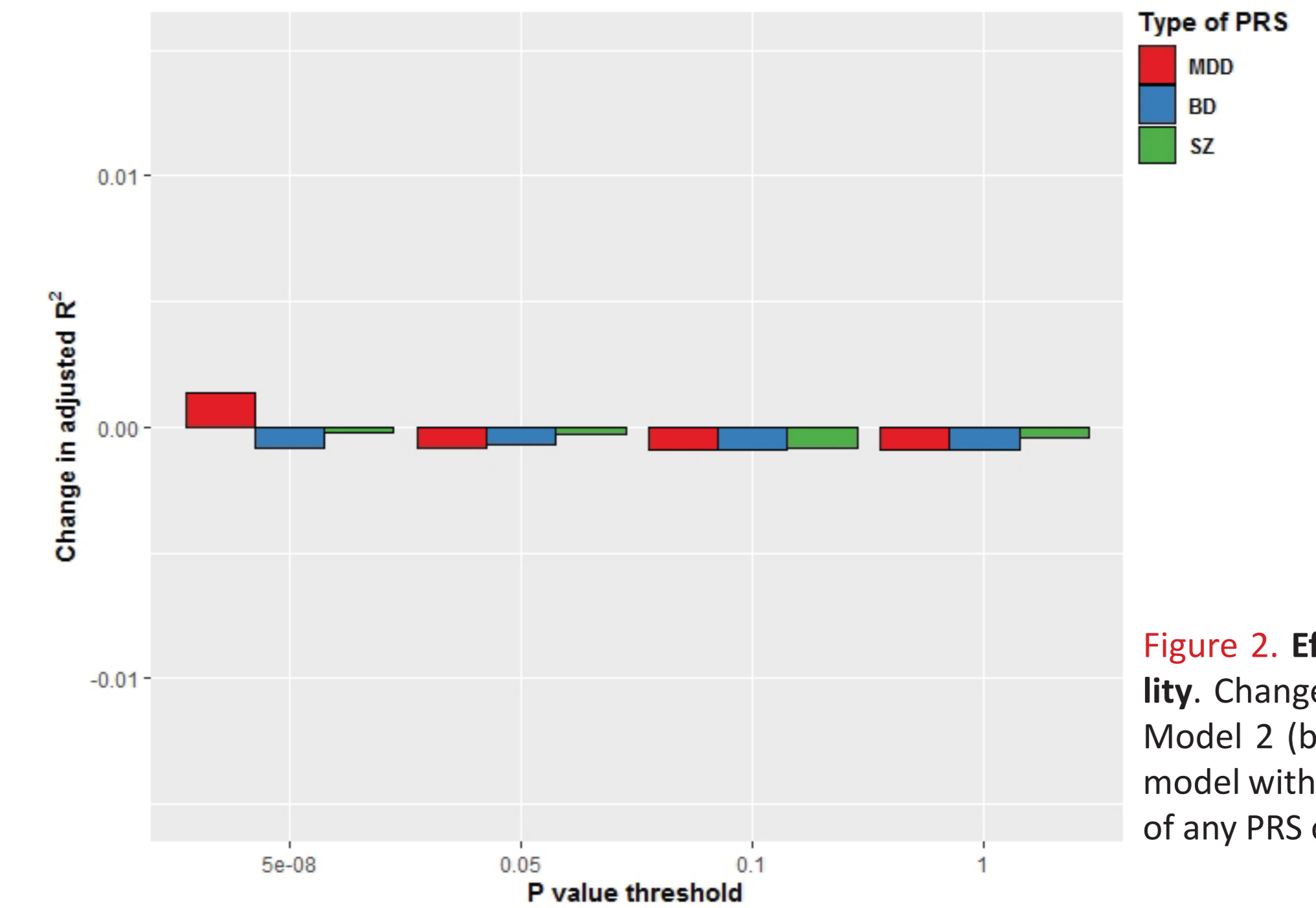


Figure 2. Effects of PRS on general cognitive ability. Change in adjusted R² between Model 1 and Model 2 (baseline model with covariates only vs. model with covariates + PRS). No significant effects of any PRS on general cognitive ability were found.

RESULTS

Performance in the domains speed of processing, verbal learning, working memory, task shifting and general cognitive abilities was significantly poorer in some clinical groups compared to controls (Table 3). However, post-hoc pairwise comparisons did not show significant differences between clinical groups with the exception of speed of processing (Table 4). Nevertheless, there was a significant interaction between diagnostic group (including CON) and cognitive domain in the linear mixed model. This finding supports differences in cognitive profiles between diagnostic groups (Table 5). General cognitive ability was not associated with MDD-, BD- or SZ-PRS (Figure 2).

DISCUSSION

This study replicates the findings from Lynham et al. (2018) on cognitive impairment on the affective-to-psychotic spectrum only partly. Significant differences between clinical participants and controls were observed on five domains, between clinical participants, however, only for speed of processing. Nevertheless, the profiles of cognitive functioning differed significantly. We will explore these profiles further. Possible explanations for non-replication might be the choice of cognitive tests and the very uneven number of participants across diagnostic groups. Also, the subtype of SZA (bipolar vs. depressive) was not assessed in the PsyCourse study, but was important in Lynham et al. (2018). While there are hardly any studies investigating the association between MDD- or BD-PRS and cognitive performance, results from studies with SZ-PRS are mixed (Schaupp et al., 2018). However, the negative findings from the PRS analysis in this study might be due to the comparably small sample size.

GRANTS

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REFERENCES

- Budde et al., PMID: 30070057
 Lynham AJ et al., PMID: 29947606
 Pardiñas AF et al., PMID: 29483656
 Schaupp, SK et al., <https://doi.org/10.20900/jpbs.20180012>
 Stahl EA et al., PMID: 31043756
 Wray NR et al., PMID: 29700475