

# Methodological approaches to outliers in cognitive assessment for schizophrenia: A *post hoc* analysis of the EMERGENT-1 study

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## BACKGROUND

Computerized cognitive batteries (CCBs) provide an alternative to traditional neuropsychological assessment, achieving similar results to standard batteries but without the need for a trained neuropsychologist.<sup>1</sup> However, CCBs may be more susceptible to task non-compliance or non-completion than traditional “pen and paper” assessments. In a recent clinical trial in schizophrenia using a CCB as an exploratory endpoint, greater than 20% of participants had to be excluded due to excessive task errors or non-completion.<sup>2</sup> This high rate of data loss increases variability and can bias results towards the null, making it challenging to detect changes in cognitive performance. In this *post hoc* analysis of cognitive data from the Phase 2 EMERGENT-1 trial (NCT03697252), we present an approach that leverages the highly inter-related nature of performance across cognitive subdomains to identify and censor outliers.

## RESULTS

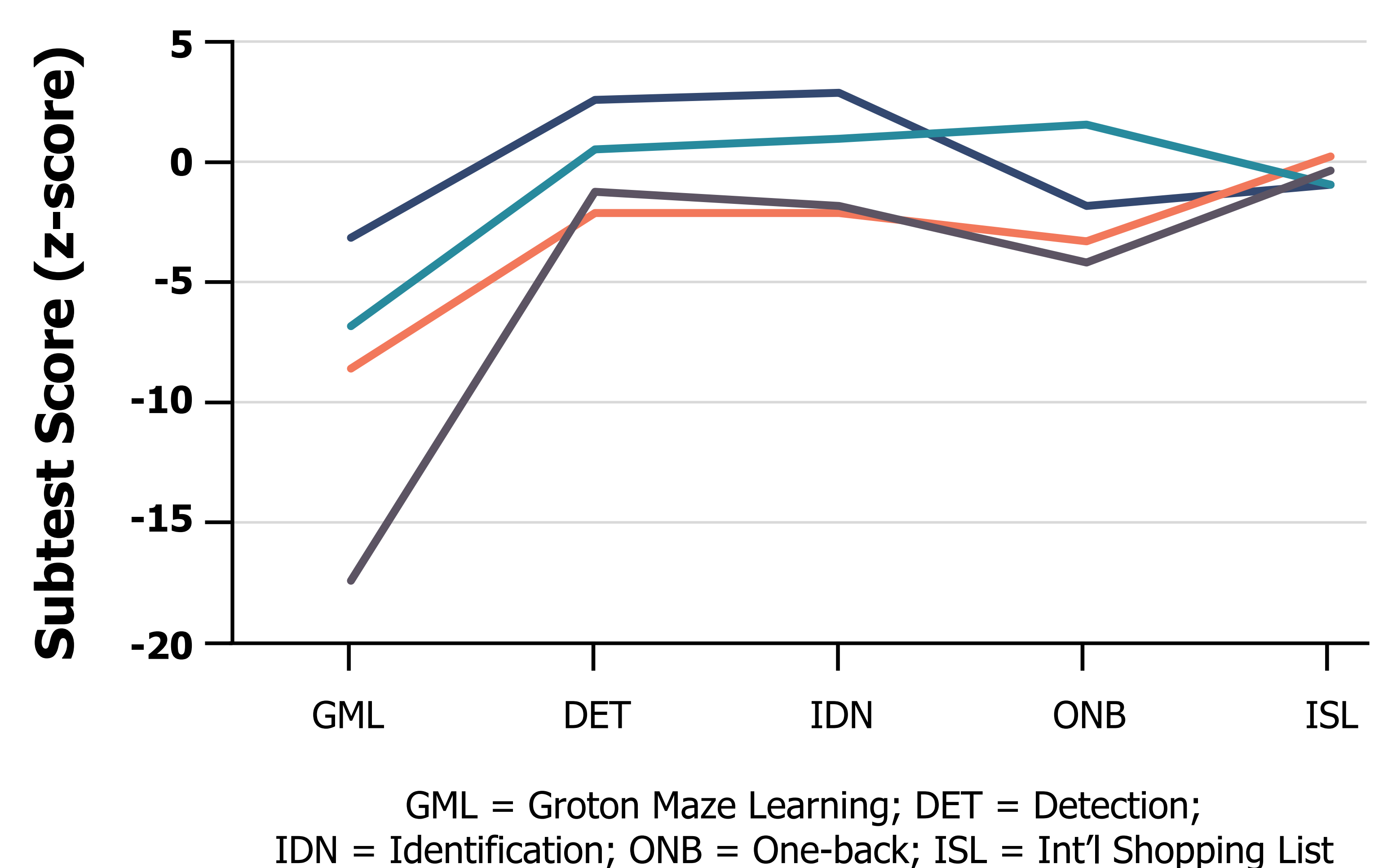
There were no significant differences in demographics or baseline PANSS scores between KarXT and placebo groups in the mITT completers sample. Participants receiving KarXT scored significantly higher on the Detection and Identification subtests compared to placebo, although Cogstate CCB composite scores were similar (see **Table 1**). The average Cogstate CCB intra-individual variability (IIV) at baseline was  $1.3 \pm 0.8$ , suggesting that a participant’s cognitive performance across subtests within a single CCB administration could be expected to vary by 1.3 SDs from their composite score. Eight participants with excessive IIV at baseline (N = 2), week 5 (N = 4), or both timepoints (N = 2) were identified as outliers (IIV > 2.4 at baseline or 2.5 at week 5; the upper limit of 1.5 IQR) and removed from the analysis (see **Figure 1**). IIV-excluded participants had significantly lower Groton Maze Learning and Cogstate CCB composite scores at baseline, reflective of extreme deviations away from the expected performance range in these participants. No other baseline characteristics, including PANSS scores, significantly differed between included vs. excluded participants (see **Table 1**).

**Table 1. Baseline Characteristics by Treatment Arm and Outlier Status**

	mITT Completers			IIV Outlier Comparison		
	KarXT N = 60	Placebo N = 65	p-value	Included N = 117	Excluded N = 8	p-value
Age	45.0 (10.3)	42.5 (9.8)	0.17	43.7 (10.8)	43.8 (10.9)	0.99
Gender, male (%)	48 (80.0%)	45 (69.2%)	0.24	87 (74.4%)	6 (75.0%)	1.00
PANSS Total	96.4 (8.8)	95.7 (7.3)	0.64	96.0 (7.6)	97.5 (13.2)	0.60
PANSS Negative	22.7 (4.4)	22.5 (4.2)	0.67	22.4 (4.3)	25.3 (3.6)	0.07
PANSS Positive	25.8 (3.3)	26.1 (3.5)	0.85	26.0 (3.3)	25.1 (4.5)	0.47
Cogstate CCB Composite	-1.00 (1.00)	-1.25 (0.96)	0.15	-0.41 (0.49)	-2.25 (1.81)	<0.01
Identification	-0.68 (1.55)	-1.57 (1.57)	<0.01	-1.13 (1.55)	-1.26 (2.54)	0.83
Detection	-0.55 (1.59)	-1.26 (1.45)	0.01	-0.90 (1.46)	-1.19 (2.74)	0.61
Groton Maze Learning	-1.52 (1.96)	-1.66 (2.58)	0.75	-1.29 (1.58)	-6.03 (5.27)	<0.01
One-Back	-1.22 (1.63)	-0.85 (1.48)	0.19	-0.97 (1.49)	-1.82 (2.29)	0.14
Int'l Shopping List	-1.03 (0.95)	-0.93 (0.91)	0.55	-0.98 (0.91)	-0.93 (1.23)	0.88

Note: All values reflect group means and (standard deviation) unless otherwise indicated.  
CCB = Cogstate computerized cognitive battery. CCB values reflect z-scores.

**Figure 1. Subtest Score Profile for Individual Cogstate CCB Assessments Excluded at Study Baseline**



**Table 2. KarXT Treatment Effect on Cognitive Performance by Baseline Impairment**

Sample	Treatment	LS Means CFB at Day 35	95% Confidence Interval		Model Results		
		Estimate (SE)	Lower	Upper	t-value	p-value	Cohen's d
mITT Completers	KarXT (N = 60)	0.13 (0.11)	-0.10	0.35	1.13	0.26	0.15
	Placebo (N = 65)	-0.05 (0.11)	-0.27	0.17	-0.48	0.63	0.06
	KarXT vs. Placebo	0.18 (0.13)	-0.08	0.44	1.40	0.16	0.20
mITT Completers (IIV-Outliers Excl.)	KarXT (N = 54)	0.22 (0.12)	-0.02	0.45	1.83	0.07	0.25
	Placebo (N = 63)	-0.05 (0.11)	-0.27	0.17	-0.48	0.63	0.06
	KarXT vs. Placebo	0.27 (0.13)	0.01	0.53	<b>2.05</b>	<b>0.04</b>	<b>0.31</b>

Prior to removal of outliers, there was a non-significant treatment effect for KarXT vs. placebo, with a trend toward greater cognitive improvement in the KarXT group. After removing participants who exhibited excessive IIV at one or more cognitive assessment timepoints, a significant overall treatment effect for KarXT vs. placebo was observed, with greater improvement in the KarXT arm (see **Table 2**).

## METHODS

An abbreviated version of the Cogstate CCB was administered as an exploratory endpoint in EMERGENT-1, a Phase 2 randomized, double-blind, placebo-controlled, 5-week inpatient trial in adults (N = 182) with acute exacerbation(s) of schizophrenia. The abbreviated CCB was administered at baseline and end of study (week 5) and consisted of 5 subtests assessing the following cognitive domains: information processing (Detection), attention (Identification), working memory (One-back), problem solving (Groton Maze Learning), and verbal learning (International Shopping List). Of the 138 study participants that completed the trial and provided valid PANSS scores at all timepoints, 13 were excluded from this analysis (3 at baseline and 10 at week 5) due to missing cognitive data on at least one subtest of the CCB. For the remaining participants in the mITT completers sample (N = 125) intra-individual variability (IIV; the standard deviation of each subject’s normalized subtest z-scores) was calculated for each CCB assessment. Outlier assessments were identified by applying the 1.5 inter-quartile range (IQR) rule to the IIV scores. Composite scores were created per subject by averaging across subtest z-scores. Separate ANCOVA models assessing the treatment effect of KarXT vs. placebo were performed both before and after IIV-driven outlier removal, with covariates of age, sex, site and baseline CCB composite score. Baseline characteristics, including PANSS scores, were compared between treatment groups and IIV-included vs. IIV-excluded participants.

## CONCLUSIONS

- These results suggest that extreme variability in performance across cognitive subdomains, even in a very small proportion of CCB assessments, can substantially bias results toward the null. In this *post hoc* analysis, the censure of data from a few participants (8/125) with high IIV across Cogstate CCB subtests revealed a significant treatment effect for KarXT vs. placebo on cognitive performance.
- The IIV in performance among participants excluded from this analysis was substantially larger than reported in previous studies,<sup>3</sup> and is unlikely to be reflective of true cognitive ability. As seen in Figure 1, IIV-excluded assessments were characterized by large differences in performance across cognitive subtests, which is inconsistent with the interrelated nature of the underlying cognitive functions.<sup>4</sup>
- Excluded participants had lower Cogstate CCB composite scores compared to non-excluded participants, consistent with findings suggesting that high IIV is related to poorer cognitive performance.<sup>5</sup> However, a significant difference in score between these groups was only seen for the Groton Maze Learning task, making it unlikely that extreme IIV is a proxy marker for overall impairment.
- Our findings suggest that IIV may be a useful measure of task non-engagement or non-compliance, and that excluding subjects on the basis of IIV may be a useful method for managing outliers. The prospective application of this method in future trials to exclude participants that are highly variable in their cognitive performance may be warranted.

## REFERENCES & DISCLOSURES

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