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Torenvliet, C.; Groenman, A.P.; Radhoe, T.A.; Agelink van Rentergem Zandvliet, J.A.; Geurts, H.M.

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RESEARCH ARTICLE

One size does not fit all: An individualized approach to understand heterogeneous cognitive performance in autistic adults

Carolien Torenvliet[1] | **Annabeth P. Groenman**[1,2] | **Tulsi A. Radhoe**[1] | **Joost A. Agelink van Rentergem**[1] | **Hilde M. Geurts**[1,3]

[1]Department of Psychology, Dutch Autism & ADHD Research Center, Brain & Cognition, University of Amsterdam, Amsterdam, The Netherlands

[2]Research Institute Child Development and Education, University of Amsterdam, Amsterdam, The Netherlands

[3]Leo Kannerhuis, autism clinic (Youz/Parnassia Group), Amsterdam, The Netherlands

Correspondence
Carolien Torenvliet, Department of Psychology, Dutch Autism & ADHD Research Center, Brain & Cognition, University of Amsterdam, Amsterdam, The Netherlands.
Email: c.torenvliet@uva.nl

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Abstract

Cognitive performances of autistic people vary widely. Therefore, previous group-based comparisons on cognitive aging in autistic adults might have overlooked those autistic adults that are particularly vulnerable for cognitive decline. Multivariate normative comparisons (MNC) statistically assess individual cognitive differences on the entire cognitive profile. Cognitive deviancy as indicated by MNC accurately predicts future cognitive decline, and is therefore sensitive in detecting meaningful cognitive differences. The current study aimed to (1) investigate the applicability of MNC to assess cognitive performance in autism individually, and (2) understand heterogeneous cognitive performance in autistic adults. As pre-registered, we performed MNC in a sample of 254 non-autistic adults, and two independent samples of respectively 118, and 86 autistic adults (20–85 years, mean: 50 years). Cognitive performance was measured on 11 outcomes in six domains (verbal/visual memory, working memory, verbal fluency, Theory of Mind, and psychomotor speed). Using MNC, about twice as many autistic individuals had a deviant cognitive profile (i.e., deviated statistically from the multivariate norm-space) as compared to non-autistic individuals. Importantly, most autistic individuals (>80%) did not have a deviant cognitive profile. Having a deviant profile was significantly associated with higher levels of psychological distress in autistic adults specifically, showing the clinical relevance of this method. Therefore, MNC seem a useful tool to individually detect meaningful cognitive differences in autism. These results are consistent with previous cognitive studies suggesting that most autistic adults show fairly similar cognitive profiles to non-autistic adults, yet highlight the necessity for approaches reflecting the heterogeneity observed in autistic people.

Lay Summary

Aiming to understand cognitive differences between autistic adults, we applied a new statistical method that assesses cognition in a sensitive, and individual manner. Cognitive profiles of autistic adults, and non-autistic adults were, therefore, investigated statistically. About twice as many autistic individuals showed a different cognitive profile (20%) as compared to non-autistic individuals, yet most autistic individuals (80%) did not. Differences were, in part, explained by differences in psychological distress.

KEYWORDS
autism, cognition, heterogeneity, multivariate normative comparisons, neuropsychology

Autism is considered to be highly heterogeneous, resulting in unique behavioral (Fletcher-Watson & Happé, 2019), and cognitive characteristics (Gonzalez-Gadea et al., 2013). This heterogeneity complicates predictions on adult outcomes of autistic individuals, with some individuals growing up to live independently, and others needing assistance all through life. Moreover, with more older individuals recognized as being autistic (Geurts et al., 2021), concerns have been raised about accelerated cognitive aging in autism. These concerns are supported by higher prevalence of age-related disease such as Parkinson's disease/parkinsonism's, and dementia (e.g., Geurts et al., 2022; Hand et al., 2020), and higher rates of self-reported cognitive difficulties in autistic adults (e.g., Klein et al., 2022; Lever & Geurts, 2016). However, in studies on cognitive aging in autism thus far, heterogeneity has been largely ignored.

In the past decade, the literature on cognitive aging in autistic people has developed rapidly. Most cross-sectional studies seem to observe similar age-related effects (i.e., parallel aging) between autistic- and non-autistic adults (Lever & Geurts, 2016; Torenvliet et al., 2021; Tse et al., 2019), yet others have observed evidence for increased age-related effects (i.e., accelerated aging) at least in some domains (Abbott et al., 2018; Baxter et al., 2019; Geurts & Vissers, 2012; Powell et al., 2017). Moreover, advantageous age-related effects have also been observed in which older autistic individuals seemed less prone to age-related effects (i.e., protective aging; Lever et al., 2015; Zivrali Yarar et al., 2020). Scare longitudinal data on cognitive aging in autism also show mixed results, with both parallel (Howlin et al., 2014; Roestorf, 2018), and accelerated patterns of age-related decline (Pagni et al., 2022) – yet modest sample sizes have limited the generalizability of these results. These inconsistencies on cognitive aging in autism might be because group-based comparisons between those with- and without autism do not differentiate between autistic individuals. Given the aforementioned increased incidence of age-related disease, it could well be that, at least for a subgroup of autistic individuals, cognitive aging may be particularly burdensome.

To date, individualized analyses of cognition in autism have been limited to single-test analyses, often named: multiple case series analysis (MCSA; Baez et al., 2012; Crane et al., 2009; Gonzalez-Gadea et al., 2013; Hill & Bird, 2006; Towgood et al., 2009). As expected, studies using MCSA observed inter-individual variability in cognitive performances of autistic individuals (Gonzalez-Gadea et al., 2013; Towgood et al., 2009, but see: Lever & Geurts, 2016). However, the number of false positives in these studies could have been inflated, given the high number of comparisons made (i.e., multiple testing problem), limiting the predictive value of this method. Therefore, additional research is needed to improve individual estimates of cognitive performance within the autistic aging population.

An improved estimate of individual cognitive performance may be obtained using advanced statistical analyses, such as multivariate normative comparisons (MNC; Huizenga et al., 2007). In MNC, cognitive performance is assessed individually, acknowledging the heterogeneity that is known to exist within a certain condition (Huizenga et al., 2007), in this case autism. MNC also model cognition in a multivariate manner, by taking the variance–covariance structure into account. In this way, we can detect deviations in the entire cognitive profile (i.e., a person's pattern of strengths and difficulties on a diverse set of cognitive tests), instead of on separate tests. This enables us to detect not only individuals with deviating scores on single tests, but also individuals with remarkable combinations of test scores (Agelink van Rentergem et al., 2018), bearing more resemblance to clinical assessment than univariate comparisons. For instance, a strength in visual memory combined with difficulties in verbal memory would be salient to a neuropsychologist, and is also detected as statistically deviating by MNC, but not with univariate analyses or even typical multivariate analyses (e.g., MANOVA). As such, using MNC, one can determine whether the cognitive profile of an individual is statistically deviating from a normative sample in a highly sensitive way.

A growing body of literature on cognitive performance in samples with neurodegenerative, and somatic disorders highlights the advantages of MNC. Cognitive impairment classified by MNC was found to be a more precise predictor of further cognitive decline in Parkinson's disease as compared to traditional, univariate approaches (Agelink van Rentergem et al., 2019; Broeders et al., 2013; Muslimović et al., 2009; Smeding et al., 2011). Furthermore, with MNC researchers were able to introduce an improved estimate of cognitive impairment in HIV (e.g., Schouten et al., 2016; Su et al., 2015), meningitis (Schmand et al., 2010), and breast cancer patients (Menning et al., 2016). While these studies demonstrate the value of the MNC method, MNC have not been used to model cognition in autism.

The current study examines the use of MNC in an autistic adult sample. Our two main goals are to (1) assess the applicability of the MNC method in a heterogeneous sample, (2) understand heterogeneity in cognitive performance as indicated by MNC in autistic individuals. As the nature of this study is exploratory, with no previous use of MNC in an autism sample, we use two independent samples of autistic individuals, with the second sample serving as a direct replication of the first sample. We compare the two samples to one non-autistic comparison sample, our normgroup. For each individual in the autism samples, it will be determined statistically whether their cognitive profile lies within the multivariate space of the normgroup (H_0) or outside that multivariate space (H_a). If an individual scores statistically significant outside of the likely multivariate space, this person's cognitive profile will be classified as statistically deviating.

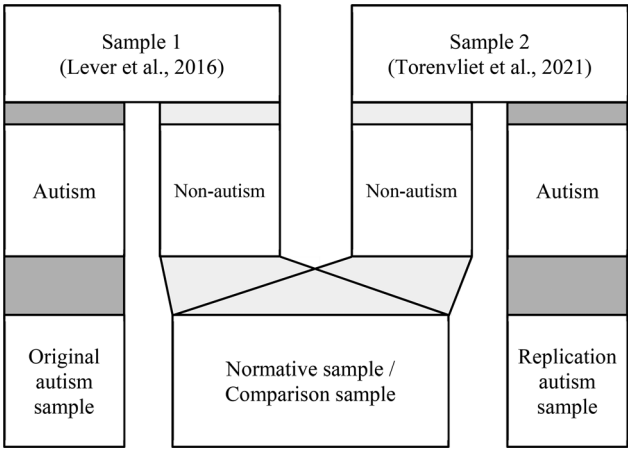

FIGURE 1 Study design

Generally, in non-autistic samples around 5% of individuals show deviating cognitive profile (Huizenga et al., 2007). Based on previous studies, we assume that cognitive performance is more heterogeneous in autism, thus we expect a higher percentage of individuals with deviating cognitive profiles in the autistic samples than in the comparison sample (i.e., >5%). The cognitive test battery includes measures, which are either particularly sensitive to cognitive decline, such as memory and processing speed and/or known to be different in individuals with autism, such as verbal fluency and Theory of Mind. To understand which cognitive tests, contribute to deviating cognitive profiles, test scores of deviating and non-deviating autistic individuals will be compared. We expect that if cognitive heterogeneity is indeed large in autism, cognitive deviations will be scattered across the cognitive profile, on multiple cognitive domains. To assess which autistic individuals show a deviant cognitive profile, we will explore whether cognitive deviancy as indicated by MNC, is associated to certain individual characteristics being age, sex, autistic traits, psychological distress.

METHODS

All data is part of an accelerated longitudinal design study on aging in autism, which includes multiple cohorts at different timepoints (Geurts et al., 2021). For the current study we used published data (Lever & Geurts, 2016; Torenvliet et al., 2021). We analyzed two datasets from the autism group separately, resulting in an *original autism sample*, and a *replication autism sample* (see Figure 1). The normative sample was created by combining participants without autism of the two consecutive cohorts, as for the proposed analyses a large sample size ($n \geq 100$) in the normative sample is preferred (see Huizenga et al., 2007). These data were also used as a comparison sample (see further: Analyses). The study was approved by the ethical review board of the Department of Psychology of the University of Amsterdam (2018-BC-9285).

Participants

Participants in the autism samples were between 20 and 89 years. Hundred-eighteen participants were included in the original sample, 88 were included in the replication sample. The samples were recruited independently (respectively in 2012–2014 and 2019–2020) via several clinical institutions across the Netherlands and (social) media advertisements of autism networks. All participants in the autism samples had a registered diagnosis of autism according to the DSM-III to DSM-5 (American Psychiatric Association, 2013). Exclusion criteria were (1) a history of neurological disorders (e.g., epilepsy, stroke, multiple sclerosis), (2) schizophrenia or having experienced more than one psychosis, (3) scoring below both cut-off of the Autism Diagnostic Observation Schedule (−2) (ADOS cut-off <7, Bastiaansen et al., 2011; Lord et al., 2012), *and* the Autism Spectrum Quotient (AQ <26, Baron-Cohen et al., 2001), (4) Wechsler Adult Intelligence Scale-III/IV IQ < 70 (WAIS III/WAIS IV; Wechsler, 1997, 2003), or Mini Mental State Examination (MMSE; Folstein et al., 1975) < 18[1] (5) current alcohol or drugs dependency.

Participants ($n = 258$) in the normative/comparison sample were between 20 and 89 years old. Participants were recruited via social media, and the social network of the researchers, research assistants, students, and participants. Four additional exclusion criteria in this sample were (1) a history of autism and/or Attention-Deficit/Hyperactivity disorder (AD[H]D), (2) a close family-members with autism and/or AD(H)D, (3) AQ > 32, (4) Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-SR; Kooij et al., 2005) traits in childhood and/or adulthood >6.

Measures

We used 11 cognitive outcome variables measured by seven cognitive tests on the following cognitive abilities: visual episodic memory, verbal episodic memory, verbal fluency, Theory of Mind (ToM), working memory, and psychomotor speed – see Table 1. All measures were considered to have sufficient psychometric properties and have been previously used in aging as well as autism research. An extensive description of the cognitive measures is given in the supplementary materials, and were also described in Lever et al. (2015); Lever and Geurts (2016).

[1]None of our participants scored below 25 on the MMSE.

TABLE 1 Overview of cognitive measures.

Domain	Measure	Outcome	Additional information (score range)
Verbal memory	RAVLT[a]	Verbal Recall I	Sum immediate recall trial 1–5 (0–75)
		Verbal Recall II	Delayed recall (0–15)
		Verbal Recognition	Total correct (0–30)
Visual memory	WMS-III[b]	Visual Recall I	Immediate recall (0–104)
		Visual Recall II	Delayed recall (0–104)
		Visual Recognition	Total correct (0–48)
Visual working memory	N-back[c]	Working memory	Accuracy ratio (−1.0–1.0)
Theory of mind	Faux-Pas[d]	Theory of Mind	Total score (0–38)
Fluency	DAT[e]	Letter Fluency	Nr. of correct words
	GIT[f]	Category Fluency	Nr. of correct words
Processing speed	CRT[g]	Processing speed	Mean reaction time

[a]Dutch version of the Rey Auditory Verbal Learning Task (RAVLT, Rey, 1964; Saan & Deelman, 1986).
[b]Subtest visual reproduction of the Wechsler Memory Scale Third Edition (WMS-III; Wechsler, 1997).
[c]Proportion correct in a 2-back compared to a 0-back condition (in house development, Lever et al., 2015).
[d]Short, Dutch version (9 stories) of the Faux-Pas task (Baron-Cohen et al., 1999; Spek et al., 2010).
[e]Dutch version of the Controlled Oral Word Association Test (COWAT, Benton & Hamsher, 1989; Schmand et al., 2008).
[f]Subtest Word Naming (animals and professions) of the Groninger Intelligence Test (GIT; Luteijn & Barelds, 2004).
[g]2-choice response task, (in house development, Lever et al., 2015).

Next to cognitive tests we used two questionnaires as predictor variables for cognitive deviations being the AQ to measure self-reported autism characteristics (Baron-Cohen et al., 2001), and the Symptom-Checklist-90 (SCL-90; Arrindell & Ettema, 2005) to measure psychological distress. Additionally, we used the Cognitive Failures Questionnaire to measure subjective cognition (Broadbent et al., 1982). These questionnaires have been used previously in both autism, and aging research, and have acceptable (AQ) to good (SCL-90, CFQ) psychometric properties.

ANALYSES

Analyses were pre-registered on AsPredicted.org (#28816) before finishing data collection. Analyses were carried out using R, version 3.6.1. R-Markdowns of the preprocessing steps, and analyses are provided as supplementary materials. To create our normative sample, we performed several pre-processing steps, resembling those taken in the ANDI database, a large project ($n > 5000$) on creating normative data (de Vent et al., 2016). First, demographically corrected outlier scores in the normative sample were removed (3.5 median-derived absolute deviations; MAD; de Vent et al., 2016) on each test, to ensure that standard deviations were not largely inflated by only a handful of extreme test scores. We intended to remove only the most extreme scores, retaining (most) scores within the range of the normal distribution. Indeed, less than 1% of the test scores were removed using this procedure (see Preprocessing Markdown in our Supplementary materials). Outliers were not removed in autism samples. To ensure that this difference in outlier removal (i.e., outliers removed in the normative sample, and not in the autism samples) did not influence group comparisons (autism vs. comparisons), we used data from the normative sample without the removal of individual outlier scores (hereinafter referred to as: the comparison sample) for all analyses. Second, departures from normality were solved using Box-Cox transformations (Box & Cox, 1964), obtained from the healthy participants ANDI dataset (de Vent et al., 2016). For those variables without appropriate ANDI Box-Cox transformations (Faux-Pas, N-back, WMS-III, CRT), most optimal Box-Cox transformations were estimated, based on the data of the current normative sample (Ribeiro & Diggle, 2001). Third, scores were transformed to z-scores using means and standard deviations of the normative sample, with higher scores indicating better task performance. Fourth, for each test separately, demographic corrections for age, biological sex, and education were added using linear parameter estimations (Agelink van Rentergem et al., 2017) with restricted maximum likelihood (REML). This means that each test score was weighted based on one's age, biological sex, and level of education.

We preregistered univariate approaches (MCSA) to estimate cognitive heterogeneity in autism, mainly to compare MNC to existing methods of detecting individual cognitive differences. Next to performing traditional MCSA analyses, we corrected for an increased family wise error rate (FWER, i.e., false positives) in two ways. Details on analyses and results for MCSA are given in the Supplementary materials.

Multivariate normative comparisons

We first tested for multivariate normality, as large deviations from non-normality can result in inflated type-I errors in the MNC statistic, namely Hotelling's T^2. Normality was assessed (R-package: MVN, v.5.8, Korkmaz

TABLE 2 Demographic and symptom characteristics

Measure	Group						
	Norm ($n = 254$)	**Autism original ($n = 118$)**	**Statistics (Norm vs. Autism original)**		**Autism replication ($n = 86$)**	**Statistics (Norm vs. Autism replication)**	
Sex (M/W, M%)	148/106, 58%	83/35, 70%	**$\chi^2 = 4.49$, $p = 0.03$**		53/33, 63%	$\chi^2 = 0.18$, $p = 0.67$	
Education[a]	47/119/88	39/53/26	**$\chi^2 = 11.62$, $p < 0.01$**		24/28/34	**$\chi^2 = 6.18$, $p = 0.05$**	
	Mean (SD) range	**Mean (SD) range**	***t*-value (*p*)**	***d***	**Mean (SD) range**	***t*-value (*p*)**	***d***
Age (in years)	50.4 (16.7); 20–85	47.7 (14.9); 20–80	−1.54 (0.12)	−0.17	55.0 (13.8); 31–85	**2.53 (0.01)**	**0.30**
IQ[b]	113 (16.8); 73–155	114.8 (16.9); 84–155	0.95 (0.34)	0.11	115.2 (15.2); 85–147	1.09 (0.28)	0.14
AQ[c]	13.4 (6.1); 2–30	33.8 (8.3); 8–49	**25.09 (<0.01)**	**3.01**	35.8 (6.4); 15–48	**30.22 (<0.01)**	**3.87**
ADOS(−2)[d]	NA	8.6 (3.1); 1–19	NA	NA	11.5 (3.9); 2–19	NA	NA
SCL-90[e]	115.0 (22.6); 90–213	173.4 (51.3); 95–328	**12.44 (<0.01)**	**1.57**	169.1 (54.6); 95–308	**9.43 (<0.01)**	**1.38**
CFQ[f]	29.4 (10.3); 3–62	46.0 (15.3); 10–80	**10.57 (<0.01)**	**1.27**	47.0 (15.1); 15–84	**10.02 (<0.01)**	**1.36**

Note: M, men; W, Women. Significant differences ($p < 0.05$) are in **bold**. Characteristics of our MCSA subsample are shown in Table S1.

[a]Level of education was determined by the Verhage Coding System (Verhage, 1964), between slashes: junior secondary or practical education/senior secondary education or vocational college/university degree. The five lowest groups were concatenated.

[b]We estimated IQ using two subtests (matrix reasoning and vocabulary) of the Wechsler Intelligence Scale-III and -IV (WAIS-III and WAIS-IV; Wechsler, 1997, 2003).

[c]Autism Quotient (AQ) measured self-reported autism traits.

[d]To measure psychological distress we used the Symptoms Checklist-90 (SCL-90; Arrindell & Ettema, 2005).

[e]To measure subjective cognition we used the cognitive failures questionnaire (CFQ; Broadbent et al., 1982).

[f]To verify autism diagnoses we used the Autism Diagnostic Observation Schedule (Bastiaansen et al., 2011) in autism original, and the ADOS-2 in autism replication (ADOS-2; Lord et al., 2012).

et al., 2014) using Henze-Zirkler's test, and Mardia's test. For MNC, a Hotelling's T^2-statistic was determined for each individual, which indicates whether their cognitive profile deviates from the norm (Huizenga et al., 2007). As we were mainly interested in detecting cognitive profiles that might be indicative of cognitive decline, we specified that one-sided *p*-values (i.e., negatively deviating) of $p < 0.10$ were indicative of a deviant cognitive profile. This results in an expected FWER of 5% as proved by Follmann (1996). Hotelling's T^2 is a multivariate version of a student-t test, which uses a vector of values instead of singular values to estimate deviations from the norm, and a covariance matrix instead of the standard deviation to estimate whether the observed deviations are "truly deviating." As such, the entire "multivariate space" (i.e., cognitive profile) is assessed without increasing the number of false positives. In our analyses, this multivariate space has 11 dimensions, the number of cognitive outcomes included in this study. Furthermore, the covariance matrices are not assumed to be equal, as is the case in MANOVA's, but differences in the correlations between test scores are considered informative to detect whether the cognitive profile of the individual is deviant. In this way, not only individuals with unusual test scores (i.e., extremely low) are indicated as deviant, but also individuals with striking combinations of test scores (i.e., picking up on particular difficulties).

Subsequently, student *t*-tests were used to see which cognitive outcome variables differed significantly between individuals with deviating and non-deviating cognitive profiles as determined by the MNC analyses. For these *t*-tests Holm-Bonferroni corrections were used to correct *p*-values for multiple comparisons.

Finally, logistic regressions were performed to see which factors were significantly associated with cognitive deviancy in the autism samples. Predictors were age, sex, autism characteristics, and psychological distress, the outcome variable was cognitive impairment (yes/no).

RESULTS

Two participants in the replication autism sample were excluded due to (1) missing data on education, (2) sex assigned at birth was neither male nor female (i.e., sex-specific adjustments could not be estimated). Demographic and symptom characteristics of the final sample ($n_{total} = 458$) are shown in Table 2. Compared to the autism samples, the normative sample had higher levels of education. It also consisted of more women than the original autism sample, and average age (in years) was slightly younger than in the replication autism sample. Because test scores were corrected for age, sex, and level of education, the analyses were performed as pre-registered. As expected, the autism samples also had higher average levels of autism characteristics, psychological distress, and self-reported cognitive failures than comparisons.

Majority of autistic adults are not cognitively deviating using MNC

Multivariate normality was violated (HZ = 1.018), yet only skewness was a problem in the data ($z_1 = 361.6$, $p < 0.001$), not kurtosis ($z_2 = -0.1$, $p = 0.913$). We continued using the planned parametric approach, because

TABLE 3 Mean raw test scores, standard deviations, and differences in test scores between deviating and non-deviating autism samples.

		Autism original			Autism replication			Norm
		Deviating	Not deviating		Deviating	Not deviating		
Outcome		Mean (SD)	Mean (SD)	*t*-value	Mean (SD)	Mean (SD)	*t*-value	Mean (SD)
Verbal	Recall I	36.1 (9.1)	50.6 (9.6)	**−5.59****	37.1 (13.9)	46.2 (9.5)	**−3.35***	48.9 (9.7)
	Recall II	6.8 (3.1)	11.2 (2.9)	**−5.11****	6.4 (3.7)	9.7 (2.7)	**−4.42****	10.4 (2.9)
	Recognition	27.2 (4.2)	29.4 (1.0)	**−3.82****	24.9 (4.1)	29.2 (1.2)	**−5.47***	29.3 (1.0)
Visual	Recall I	84.4 (16.9)	92.0 (9.3)	−2.13	79.4 (15.2)	88.5 (10.7)	−2.51	87.2 (11.6)
	Recall II	57.8 (19.3)	81.6 (17.4)	**−5.74****	54.2 (25.0)	76.5 (17.2)	**−3.98****	74.8 (21.2)
	Recognition	42.6 (3.3)	45.6 (2.0)	**−3.92****	43.9 (3.0)	45.0 (2.1)	−1.15	45.2 (2.2)
Working memory		0.9 (0.1)	0.9 (0.1)	−2.24	0.9 (0.1)	0.9 (0.1)	**−3.27***	0.9 (0.1)
Theory of mind		25.0 (4.9)	27.5 (4.8)	−2.17	25.6 (6.6)	27.4 (6.2)	−1.0	29.5 (5.2)
Fluency	Letter	34.8 (11.5)	41.1 (10.8)	−1.96	31.1 (13.1)	38.4 (10.2)	−1.91	41.8 (10.7)
	Category	37.8 (9.4)	45.7 (11.1)	**−3.00***	36.5 (7.9)	42.1 (8.0)	−2.12	45.4 (9.2)
Processing speed		444.1 (63.3)	395.9 (55.3)	**−3.94****	443.3 (96.4)	416.4 (53.0)	−0.78	395.5 (58.2)

Note: SD, standard deviation. *Holm corrected $p < 0.05$, ** = Holm corrected $p < 0.01$. Test statistics corresponding to significant *p*-values are in **bold**. Raw scores are provided instead of z-scores to ease clinical interpretation of the results.

(1) mainly kurtosis biases Hotelling's T^2 (Grasman et al., 2010), (2) removing the most skewed variables generated similar results, and (3) Box-Cox transformations on all cognitive outcome measures yielded similar results. Using MNC, 22 out of 118 individuals (18.6%, CI 12.1–26.9%) in original autism sample, and 17 out of 86 individuals (19.8%, CI 12.0–29.8%) in replication autism sample were indicated as having a deviating cognitive profile (i.e., one-sided *p*'s < 0.10). In the comparison group, 21 individuals (8.3%, CI 5.4–12.4%) had a deviating cognitive profile. Given that the confidence interval of the comparison group is just higher than the expected 5%, the FWER seems somewhat inflated. In both autism samples, about twice as many individuals were indicated as having a deviant cognitive profile as in the comparison sample. The majority (>80%) of autistic individuals did not have a deviating profile. To test the applicability of MNC compared to existing methods, we tested whether MNC was more sensitive (to group differences) than MCSA. As expected using MCSA, rates of cognitive differences were either rather unspecific (i.e., inflated FWER using uncorrected method) or unsensitive (only a handful of deviations detected using correcting methods). In addition, deviations were largely similar between autistic and non-autistic individuals, see Supplementary materials for the exact results.

Deviating- and non-deviating cognitive profiles differ most on verbal memory and least on theory of mind

On average, individuals with deviant cognitive profiles in the autism samples scored significantly lower on all measures of verbal memory, and delayed visual recall compared to autistic individuals with non-deviating cognitive profiles (see Table 3, and Figure 2). Moreover, in the original sample, individuals with deviating cognitive profiles also scored significantly lower compared to those with non-deviating cognitive profiles on visual recognition, and verbal fluency, while this was not the case in the replication sample. In the replication sample individuals with deviating cognitive profiles scored significantly lower on working memory than those with non-deviating cognitive profiles. No significant differences between autistic individuals with deviating and non-deviating cognitive profiles were observed in Theory of Mind, but both groups scored below the normative sample. Between-test correlations are shown in Table S2. Average test scores of individuals with deviating and non-deviating cognitive profiles of the comparison group are shown in Table S3.

Deviation inconsistently associated with self-reported cognition and psychological distress

Having a deviant cognitive profile was not significantly associated with any of the pre-registered variables (i.e., psychological distress, autism characteristics, age, or sex) in the original autism sample. Additionally, we explored whether cognitive deviancy was significantly associated with self-reported cognitive failures, yet this was not the case (see Table 3). In the replication sample, cognitive deviancy was significantly associated with psychological distress, and self-reported cognitive failures. Higher rates of psychological distress, and more self-reported cognitive failures were significantly associated with cognitive deviancy (see Table 4). Other variables did not significantly relate to cognitive deviancy. To further inspect these conflicting results, and increase statistical

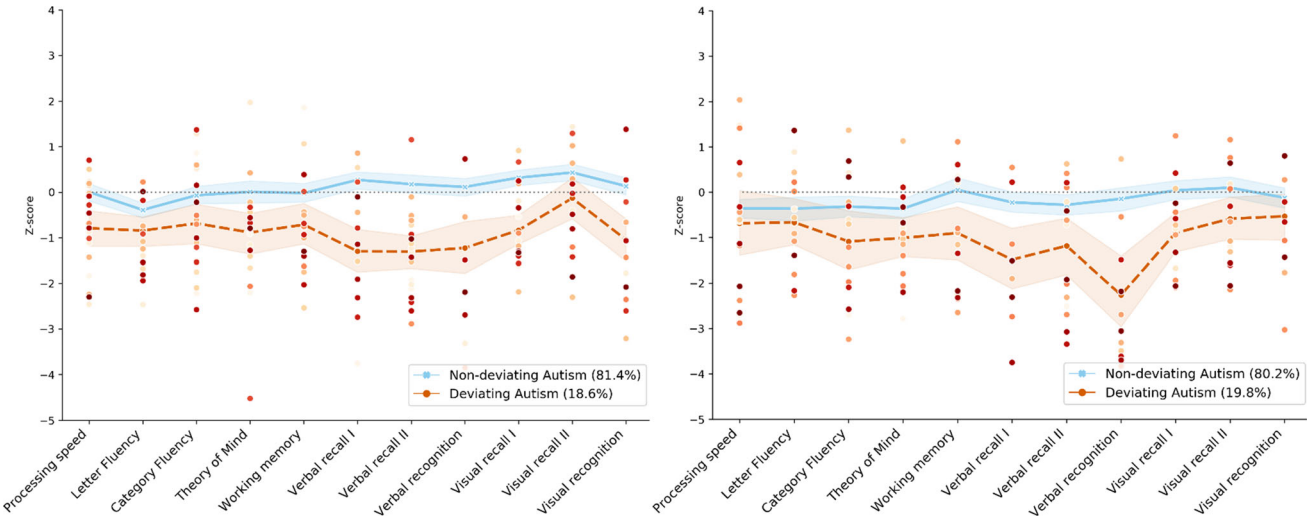

FIGURE 2 Cognitive profiles of the deviating and non-deviating groups in the Autism Original (left) and Autism Replication samples (right). To enhance figural clarity, individual scores (dots) are only displayed for the deviating groups. Individual lines are also omitted, but are shown in Figure S1.

TABLE 4 Regression coefficients for cognitive deviancy with age, sex, AQ, SCL-90, and CFQ as predictors.

	Original autism sample				Replication autism sample			
Predictors	**B (SE)**	***W***	**OR**	**Model fit**	**B (SE)**	***W***	**OR**	**Model fit**
Age	<0.01 (0.02)	−0.07	0.99	$\chi^2 = 4.79$, $R^2 = 0.04$	0.03 (0.02)	1.17	1.03	$\boldsymbol{\chi^2 = 10.46}$*, $R^2 = 0.12$
Biological sex	−0.59 (0.64)	−0.92	0.56		0.70 (0.60)	1.16	2.02	
AQ total	−0.04 (0.04)	−1.14	0.96		0.02 (0.05)	0.39	0.70	
SCL-90 total	<0.01 (<0.01)	1.63	1.01		**0.01 (<0.01)**	**2.33***	**1.01**	
CFQ[a]	<0.01 (0.02)	−0.52	0.99	$\chi^2 = 0.27$, $R^2 < 0.01$	**0.04 (0.02)**	**2.13***	**1.04**	$\boldsymbol{\chi^2 = 5.06}$*, $R^2 = 0.06$

Note: *$p < 0.05$; AQ, Autism Quotient; SCL-90, symptom checklist-90; CFQ, Cognitive Failures Questionnaire; ASC, Autism Spectrum Condition; B, unstandardized beta; SE, standard error; *W*, Wald statistic; OR, odds ratio; R^2, pseudo-R^2 (McFadden, 1973). Test statistics corresponding to significant *p*-values are in **bold**.
[a]CFQ was tested in a separate model, and an exploratory (not pre-registered) analysis.

power, we concatenated the two autism samples. In the two samples combined, cognitive deviancy was significantly associated with psychological distress (B = 0.011, SE = 0.028, $W = 2.976$, $p < 0.001$, *OR*: 1.01, $R^2 = 0.05$), but not with self-reported cognitive failures. In the comparison sample, cognitive deviancy was not significantly associated with any of the aforementioned variables (see Table S4).

DISCUSSION

The current study used a new statistical method to gain further insight into heterogeneous cognitive performances in autism. Concurring with our hypothesis, the extent of cognitive heterogeneity was larger in autistic adults compared to non-autistic adults. Using multivariate normative comparisons (MNC), about twice as many autistic individuals had a deviant cognitive profile (i.e., a pattern of testscores statistically defined as outside the likely normative multivariate space) as compared to non-autistic comparisons, verifying its sensitivity to detect cognitive deviations in heterogeneous samples. Cognitive deviancy as indicated by MNC was significantly associated with higher levels of psychological distress in autistic adults specifically. Finally, unlike existing univariate methods (MCSA), by using MNC we obtained an optimal balance between sensitivity and specificity (FWER near 5%). Therefore, MNC seem a useful tool to detect meaningful cognitive differences in the autistic population.

Several insights can be taken from these results. First, even though a higher number of deviations were observed in the autistic adult groups when using MNC, the majority of autistic adults (>80%) did not have a deviant cognitive profile. Our replication sample further confirmed this observation. This is important, as it is often assumed that autistic adults have a different cognitive profile, characterized by altered cognitive talents and difficulties compared to non-autistic adults (e.g., Bowler et al., 2014; Gaigg et al., 2015; Ring et al., 2016). However, the current results might indicate that in *most* autistic adults, relations between various elements of cognition (for

instance verbal- and visual memory) might be more similar to non-autistic adults than previously expected. Nonetheless, bearing in mind the heterogeneity of cognitive performance between autistic individuals seems crucial in interpreting the previous inconsistent results on cognitive age-related effects (cross-sectional), and cognitive age-related decline (longitudinal) in autism. Given that the number of deviating cognitive profiles was twice as large in our autism samples than in our comparison sample, it may be likely that differences between studies are indeed caused by the heterogeneity of the autistic population.

Second, profile plots of autistic individuals with deviating profiles showed large individual differences, providing corroborative evidence for cognitive heterogeneity within the autism samples. However, comparing deviating and non-deviating cognitive profiles in both the original, and replication autism sample, revealed that some elements of cognition might be more heterogeneous in autism than other elements of cognition. Theory of mind (ToM) performance was lower in individuals with both deviating, and non-deviating cognitive profiles than in comparisons. By contrast, in both samples verbal memory showed the most consistent differences between autistic individuals with deviating and non-deviating cognitive profiles, with individuals with non-deviating profiles performing hardly different or even better than the norm. As such, verbal memory performance seems highly heterogeneous in autistic adults, and indicative of deviant cognitive performance, whereas performance on a ToM task might be more universally impaired, but less indicative of a global deviancy in cognitive performance. On the one hand, this seems to support that ToM is specifically related to autism characteristics (Baron-Cohen, 2000). On the other hand, ToM (at least operationalized using the Faux Pas test) seems randomly related to cognitive functioning in all individuals regardless of autism (also see supplement Table S2) and might not be predictive of overall functioning. In sum, it seems that not all aspects of cognitive functioning are equally heterogeneous and/or indicative of cognitive deviancy. Future research could focus on which cognitive domains are most predictive of differences in future cognitive decline in autism specifically. Based on the current results, verbal memory might be an interesting starting point.

Third, relating cognitive functioning to other aspects of daily life, such as psychological distress or even subjective cognitive functioning, is notoriously difficult (Groenman et al., 2022; Jonker et al., 2000). Interestingly, we observed that deviancy as is indicated by MNC was significantly associated with by elevated levels of psychological distress in autistic adults – although the results of the original and replication sample were not entirely aligned. As this was not observed in non-autistic adults, these results seem complex. One explanation could be that autistic adults show more variation in levels of psychological distress, enhancing the sensitivity of the prediction. This explanation is supported by the larger observed standard deviations of the autism samples on this measure (Table 1). It could also be that with advancing age, MNC becomes more sensitive, as the replication sample was significantly older than both the original autism sample and normative sample, which both did not show this significant association between cognitive deviancy and psychological distress. The observed increased sensitivity of MNC relate to (and possibly predict) daily outcome in comparison to standard cognitive measures is in line with studies describing the use of MNC in samples with neurodegenerative, or somatic disorders. MNC added unique predictive information to the progression of dementia (de Vent et al., 2020), and Parkinson's disease (Broeders et al., 2013; Muslimović et al., 2009; Smeding et al., 2011). Based on the current results, especially given its association to other measures of functioning, MNC might be particularly useful to predict cognitive decline in autism. However, as we are the first to find such an observation in a cross-sectional, autistic sample, the causality, stability, and validity of these results need further investigation.

Given that the current study deals with the typical difficulties of neuropsychological data, some issues need to be addressed. Firstly, (multivariate) normality was violated, which could have inflated rates of Hotelling's T^2 in our results. However, given the relatively low number of individuals with deviating cognitive profiles in the comparison group, this seemed to have not largely impacted the results. Second, MNC are, like any neuropsychological evaluation, impacted by the choice of tasks included in the cognitive test battery. In our case, the cognitive profile highlights specific aspects of memory (i.e., verbal vs. visual; recall vs. recognition), but is limited in the number of tasks focusing on executive functioning. In future research, it might be interesting to explore a broader spectrum of executive functioning tasks. Third, the neuropsychological data collected in the current study excluded those autistic- and non-autistic individuals with neurological history, and underrepresented women, those of oldest age (>70 years), and with less educational years. Consequently, the current results might not generalize to autistic women, and individuals who might be particularly vulnerable for future cognitive decline. Finally, given the cross-sectional nature of the study, we could not predict future (cognitive) functioning. Further assessment of the predictive validity of the MNC approach is, therefore, highly encouraged in future research.

Taken together, the current study showed that MNC are a useful tool to detect and understand heterogeneity in cognitive performance in a diverse population such as autism. Results showed that most autistic adults did not show a deviant cognitive profile, although cognitive heterogeneity was larger than in non-autistic adults. It could well be that those individuals with deviating cognitive profiles are those that might need extra care later in life, although longitudinal research is needed to confirm the predictive value of MNC. MNC advance individualized

cognitive science, and could be extended to other mental health conditions, particularly those, which also show large individual differences in cognitive functioning.

AUTHOR CONTRIBUTIONS

All authors contributed to designing the study, analyses, and pre-registration. Carolien Torenvliet, and Tulsi A. Radhoe were responsible for data collection. Carolien Torenvliet performed the analyses, with help from Joost A. Agelink van Rentergem. Carolien Torenvliet wrote the first draft with input from all authors. Carolien Torenvliet, Annabeth P. Groenman, and Hilde M. Geurts were involved in feedback on subsequent versions. All authors provided feedback on the final version and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ETHICS STATEMENT

The study was approved by the ethical review board of the Department of Psychology of the University of Amsterdam (2018-BC-9285).

ORCID

Carolien Torenvliet https://orcid.org/0000-0002-0865-5154
Annabeth P. Groenman https://orcid.org/0000-0002-8394-6605
Tulsi A. Radhoe https://orcid.org/0000-0001-9271-9503
Hilde M. Geurts https://orcid.org/0000-0002-4824-9660

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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