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RESEARCH ARTICLE

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Abstract

Objective: The aim of this study was to characterise the association between the cognitive profile and weight restoration in children and adolescents with anorexia nervosa.
Methods: The study was a longitudinal, matched case–control, multicentre study. An assessment of cognitive functions was conducted by using the Wechsler Intelligence Scale for Children–III/the Wechsler Adult Intelligence Scale–III, the Test of Memory and Learning–second edition, Trail Making Tests A and B, the Rey–Osterrieth Complex Figure Test and the Cambridge Neuropsychological Test Automated Battery.
Results: One hundred twenty individuals, 60 patients with anorexia nervosa with mean age of 14.65 (SD 1.820) years and 60 healthy controls with mean age of 14.76 (SD 1.704) years, participated. No association was found between weight recovery and cognitive functions. However, a significant increase in motor speed was found in Trail Making Test A ($p = 0.004$), Reaction Time (RTI) five-choice movement time ($p = 0.002$) and RTI simple movement time ($p = 0.011$), resulting in a normalisation corresponding to that found in healthy controls. Furthermore, a significantly lower score in the perceptual organization index ($p = 0.029$) was found at follow-up.
Conclusions: Weight recovery appears not to be associated with cognition. Copyright © 2016 The Authors European Eating Disorders Review published by Eating Disorders Association and John Wiley & Sons Ltd

Introduction

Anorexia nervosa (AN) is characterised by restrictive eating behaviour, a refusal to maintain normal body weight, a disturbed body image and an intense fear of becoming fat or gaining weight (American Psychiatric Association, 2013). The lifetime prevalence of AN is 0.16–0.30% (Bulik et al., 2006; Hudson, Hiripi, Pope, & Kessler, 2007; Raevuori et al., 2009a; Raevuori, Niemela, Keski-Rahkonen, & Sourander, 2009b; Woodside et al., 2001), and the standardised mortality ratio in severe AN is 8.1 (95% CI = 1.6–23.6) in men and 10.6 (95% CI = 7.6–14.4) in women (Gueguen et al., 2012).

Cognitive inefficiencies have been identified in adult patients with AN, particularly with regard to set-shifting abilities and central coherence, that is, the ability to switch between tasks, and a detailed information processing style and difficulty in seeing the big picture (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Lang, Lopez, Stahl, Tchanturia & Treasure, 2014b; Tchanturia et al., 2004; Tchanturia et al., 2011; Tchanturia et al., 2012).

In contrast, the picture is less clear with respect to the cognitive profile of children and adolescents with AN. Several studies have found no evidence of cognitive inefficiencies (Buhren et al., 2012; Calderoni et al., 2013; Lang, Stahl, Espie, Treasure & Tchanturia, 2014a; Sarrar et al., 2011), while some have found

inefficiencies in visuoconstruction set-shifting abilities, sensory-motor speed, reaction time and nonverbal intelligence of patients with AN (Andres-Perpina et al., 2011; Hatch et al., 2010; Kjaersdam Telleus et al., 2015; Lange & Tchanturia, 2014; Lang et al., 2015; Rose, Frampton, & Lask, 2013; Stedal, Frampton, Landro, & Lask, 2012).

A mean full-scale intelligence quotient (FSIQ) of 101.1 (SD 16), which is close to the normative population mean of 100, was found in the largest study of cognitive functions in children and adolescents with AN to date (Kjaersdam Telleus et al., 2015). Thus, this study showed no evidence of an elevated IQ above the normal mean in the AN group, which is consistent with the results of several other studies (Bayless et al., 2002; Buhren et al., 2012; Gillberg, Gillberg, Rastam, & Johansson, 1996; Lang et al., 2015; McDowell et al., 2003).

There are inconclusive findings on differences in cognitive functions between the AN subtypes. In a systematic review, Van Autreve and Vervaet (2015) found that group differences in central coherence and set shifting between AN-restricting type and AN-bingeing/purging type were not strong enough to draw definitive conclusions.

Longitudinal studies of cognitive functions in adult patients with AN have been conducted. Cavedini et al. (2006) found that decision-making performance in inpatients with AN did not improve significantly from admission to discharge. Likewise, Bodell et al. (2014) found no significant difference in decision-making performance from baseline to weight restoration in a sample of AN patients. However, a significant improvement after weight restoration was found in the subgroup of patients with AN who were poor performers at baseline (Bodell et al., 2014). In a longitudinal study on young adults, Zwipp et al. (2014) found that motor speed increased with weight gain in patients with AN.

Only a few follow-up studies of cognitive functions in children and adolescents with AN have been conducted (Buehren et al., 2011; Buhren et al., 2012; Hatch et al., 2010). In a follow-up study conducted among juvenile patients with AN, it was found that when patients with AN had a low body weight, they performed significantly worse than control participants in tests of motor speed; these inefficiencies appeared to normalise with weight gain (Hatch et al., 2010). Another study showed an increased reaction time when engaging in set-shifting tasks and a reduced error rate across time (Buhren et al., 2012).

Consequently, there is limited knowledge about how the cognitive profile of children and adolescents with AN progresses over time. As children and adolescents undergo cognitive maturation, it is important to examine how the cognitive status and development of children and adolescents with AN progress and to expand our knowledge of the impact that low body weight and other AN symptoms may have on cognition. Likewise, it is relevant to enhance our knowledge regarding the cognitive profile in children and adolescents with AN in comparison with that found in adult patients with AN.

Expanding our understanding of how cognitive development is affected as patients with AN recover or become chronic is best achieved by using longitudinal studies.

The aim of this study was to characterise the development of cognitive functions in children and adolescents with AN. Another aim was to examine the association between cognition and weight recovery in AN patients. This aim was accomplished through the re-examination of children and adolescents with AN 1 year after baseline, when the patients were first assessed in the study. The hypotheses of the study were as follows.

1. The maturation of cognitive function, that is, intelligence and specific cognitive functions, in children and adolescents with AN is significantly reduced compared with that of matched healthy controls (HCs).
2. The change in intelligence and specific cognitive functions of patients who recover weight is significantly different from that of patients who do not recover normal body weight at 1 year follow-up.
3. The baseline cognitive profile is a predictor of weight recovery operationalised by obtaining a body mass index (BMI) above the AN threshold, that is BMI above the WHO 15th percentile, corresponding to a BMI of 18.5 or above at age 18.

Methods

Participants

Study recruitment of patients with AN at baseline took place between January 2009 and December 2011, while recruitment of HCs at baseline was completed in December 2012. One-year follow-up assessment was completed in December 2013. At baseline, patients were recruited after being diagnosed with AN in accordance with the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) (American Psychiatric Association, 2013).

The inclusion criterion for patients was less than 18 years of age and diagnosed with AN in one of the participating centres. The exclusion criterion for patients was cognitive exam with the Wechsler Intelligence Scale for Children (WISC) or the Wechsler Adult Intelligence Scale (WAIS) within the last year. The inclusion criterion for HCs was less than 18 years of age. The exclusion criterion for HCs was cognitive exam with the WISC or WAIS within the last year and/or known psychiatric illness.

At baseline, the AN group and the HCs were matched 1:1 for gender and age (i.e., within 1 year). A total of 188 age- and gender-matched participants were originally recruited for the study: patients with AN (N = 94) and HCs (N = 94). Of these participants, 60 matched pairs, a total of 120 individuals, participated 1 year later in the follow-up study. Thus, the follow-up participation rate was 64%. Of the 120 participants, 110 were female and 10 were male. The main reason that patients dropped out of the study was that they left treatment and wanted no additional contact with mental health services. This article includes the baseline and follow-up data on these 60 matched pairs. Between baseline and follow-up, the patients received treatment consisting of specialised psychotherapeutic eating disorder intervention. The study was conducted in accordance with the Declaration of Helsinki. It was approved by the local Research Ethics Committee (file number: N-20080060MCH) and authorised by the local Data Protection Agency. Participation was voluntary. Patients were informed that nonparticipation would not affect their treatment. Written and oral information about the study was provided before recruitment, and written informed consent was obtained in all cases.

A detailed description of the recruitment is included the paper of Kjaersdam Telleus et al. (2015).

Measures

Baseline

Assessment battery

AN symptomatology was assessed by using Eating Disorder Examination (EDE) version 16 (Cooper, Cooper, & Fairburn, 1989; Williamson, Barker, Bertman, & Gleaves, 1995). A structured examination of each patient's somatic condition was also conducted. This examination involved a collection of clinical observations and patient-reported somatic symptoms according to generally recognised somatic complications in AN (Hebebrand & Bulik, 2011; Mitchell & Crow, 2006), including electrocardiogram recordings and clinical and paraclinical assessments, that is biochemical laboratory tests.

A parental interview was conducted to collect anamnestic data. Assessment of comorbidity was conducted by using the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (Cooper et al., 1989; Kaufman, Birmaher, Brent, Ryan, & Rao, 2000; Wilfley, Schwartz, Spurrell, & Fairburn, 2000), in addition to the Autism Screening Questionnaire (Ehlers, Gillberg, & Wing, 1999).

The healthy controls were screened for indications of psychiatric disorders during recruitment by using the Autism Screening Questionnaire (Ehlers et al., 1999) and the Strengths and Difficulties Questionnaire (Goodman, 1997), which is a brief behavioural screening questionnaire.

The assessment of cognitive functions was conducted by using a comprehensive neurocognitive assessment battery. The HCs and the patients with AN were assessed with an identical cognitive assessment battery in a fixed order. The neurocognitive assessment battery included the Wechsler Intelligence Scale for Children–III (WISC-III) (Wechsler, 1991) or the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997), depending on age, both Danish versions. The Rey–Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995), pen-and-paper version, and Trail Making Tests A (TMT-A) and B (TMT-B) (Lezak, 2012; Reitan & Wolfson, 1985), pen-and-paper version, were also administered.

Nine subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Lowe & Rabbitt, 1998) and four subtests from the Test of Memory and Learning–second edition (TOMAL-2) (Reynolds & Bigler, 1994) were also administered. A detailed description of the assessment battery used in the study is included in the paper of Kjaersdam Telleus et al. (2015).

Follow-up

At 1 year follow-up, the AN group was assessed by using EDE version 16 (Cooper, Grocutt, Deepak, & Bailey, 2007; Wilfley et al., 2000) to obtain the diagnostic status of the eating disorder. The AN group and the HCs were assessed by using the complete identical neuropsychological test battery from baseline.

Data analysis

Statistical analysis

Initially, a comparison was performed between the group of patients with AN who participated in the follow-up study and the group of patients with AN who dropped out before the follow-up. The two groups were compared at baseline with regard to age, gender and neurocognitive measures. Gender was compared by using Fisher's exact test, owing to the small proportion of males. The remaining variables were compared by using either the two-sample *t*-test or, if distributional assumptions were not met, its nonparametric equivalent, the Wilcoxon rank-sum test.

Furthermore, the patients with AN and the HCs were compared on all neurocognitive measures at baseline. Likewise, the two groups were compared regarding change from baseline to follow-up on the same neurocognitive measures. The tests were conducted by using the paired *t*-test or, if distributional assumptions were not met, the nonparametric equivalent, the Wilcoxon signed-rank test. Effect sizes were calculated by taking the dependence structure of the data into account by adjusting for correlation within the matched pairs.

In order to investigate whether there were any differences in change between AN patients with comorbidity and patients without comorbidity, a two-sided unpaired *t*-test was performed on all neurocognitive measures comparing these two groups.

Predictors of weight recovery were investigated by using logistic regression analyses, which were performed on only the patients with AN. As mentioned, a good outcome was defined as obtaining a body mass index (BMI) above the WHO)15th percentile, that is, corresponding to a BMI of 18.5 or above at age 18 of years, at follow-up (Cole & Lobstein, 2012; World Health Organization, WHO), whereas the second group consisted of patients with AN who had not achieved normal body weight, that is weight below the AN cut-off BMI of 18.5 (American Psychiatric Association, 2013). A separate regression model was generated for each of the neurocognitive variables, by using these as explanatory variables while controlling for gender and age. The explanatory variables included only baseline data. To determine whether the control parameters had any impact on weight recovery, an additional logistic regression model was used that included only gender and age as explanatory variables.

Finally, BMI was considered. The same method as that described earlier was used, that is the patients with AN were distributed into two groups. One group had a BMI higher than the WHO's 15th percentile at follow-up, and the other group had a BMI lower than the WHO's 15th percentile at follow-up (World Health Organization, WHO). The high BMI group was compared in terms of changes in neurocognitive measures with those patients with a low BMI at follow-up. Likewise, those in the higher BMI group were compared with their matched controls with regard to changes in neurocognitive measures. The comparisons were performed as explained above, again differentiating between paired and unpaired comparisons.

A *p* value lower than 0.05 was considered to be statistically significant. All analyses were performed in STATA 13 (StataCorp, 2013; College Station, TX).

Inter-rater reliability

Fully trained clinical psychologists performed the assessments of cognitive functions and the EDE-16. Psychiatric doctors and medical doctors conducted the somatic assessment. Ongoing corating, supervision and retrospective inter-rater reliability tests were conducted. The retrospective inter-rater reliability tests were conducted on the WISC-III/WAIS-III in 14 cases. The observed inter-rater reliability of the FSIQ in this study was satisfactory at 0.985, indicating a high uniformity rating. A detailed review of actions taken to obtain a high degree of reliability was described previously (Kjaersdam Telleus et al., 2015).

Results

Sixty of the 94 matched pairs from baseline participated at follow-up. In general, the dropout group and the follow-up group did not significantly differ from one another in regard to background information. Likewise, average BMI, weight, height and illness duration did not differ significantly between the two groups. However, there was a significant difference in age ($p = 0.005$), with patients in the dropout group having a mean age of 15.6 years and patients in the follow-up group having a mean age of 14.5 years. With regard to cognitive functions, there was a significant difference between the two groups in verbal intelligence quotient (VIQ) ($p = 0.048$), with patients in the dropout group performing significantly poorer (VIQ mean = 99.9) than those in the follow-up group (VIQ mean = 107.7). In the remaining measures of cognitive functions and IQ, no significant differences were found.

The average age at baseline in the 60 patients of the AN group was 14.7 years (SD 1.8), with a range of 10.6–17.9 years. The mean illness duration at baseline, measured by self-reported duration of changes in eating behaviour, was 1.2 years (SD 1.2), with a range of 0.1–5.3 years.

At baseline, 98.3% of the patients met the diagnostic criteria for AN. One patient did not fully meet the diagnostic weight criteria for AN but did meet the diagnostic criteria for Other Specified Feeding or Eating Disorder, Atypical AN. Among the patients, 88.3% had the AN-restricting subtype. whereas 11.7% had the AN-bingeing/purging subtype. At baseline, the patients with AN had an average BMI of 15.7 (SD 1.8) and a mean resting pulse of 60.1 (SD 13.8); lanugo hair was found in 45.6% of the patients and peripheral cyanosis in 33.9%. Among the patients, 36.7% had symptoms of comorbidity, 23.3% had symptoms of affective disorder, 21.6% had anxiety, 6.6% had psychotic symptoms and 6.6% had symptoms of autism spectrum disorder at baseline; 25% of the patients had one comorbid disorder, 11.6% of the patients had two comorbid disorders and 3.3% of the patients had three comorbid disorders.

Of the patients with AN, 33.9% had a family history of eating disorders. At follow-up, 36.6% of the patients had fully recovered from AN symptomatology, that is BMI, and both psychological criteria; 15% of the patients with AN did not obtain weight recovery.

As shown in Table 1, no significant difference was found between groups for the increase in test scores from baseline to 1-year follow-up, with the exception of motor speed. A significant improvement in motor speed, as measured by TMT-A [difference (diff) = −6.5, $p = 0.004$, Effect Size (ES) = −0.262), RTI five-choice movement

time (CANTAB) (diff = −62.55, $p = 0.002$, ES = −0.633) and RTI simple movement time (CANTAB) (diff = −77.05, $p = 0.011$, ES = −0.511), indicated a greater development in the AN group than in the HCs. However, at baseline, thee patients performed significantly worse than the HCs in all three subtests: TMT-A (diff = 8.2, $p = 0.004$, ES = 0.181), RTI five-choice movement time (CANTAB) (diff = 67.71, $p = 0.001$, ES = 0.638) and RTI simple movement time (CANTAB) (diff = 58.52, p = 0.018, ES = 0.431). Thus, the significant greater improvement of motor speed represents a normalisation of performance in patients with AN.

The patients with AN and the HCs had a nonsignificantly different change in development in FSIQ (diff = −1.5, $p = 0.951$, ES = −0.012) as the AN patients improved an average of 4.9 points (SD = 12.8) and the HCs improved an average of 6.6 points (SD = 6.6).

As shown in Figure 1, a significant difference in the perceptual organization index (POI) was found, with the patients with AN performing significantly worse than the HCs at follow-up (diff = −4.7, $p = 0.029$, ES = −0.382); however, at baseline, the difference was nonsignificant (diff = −4.3, $p = 0.120$, ES = −0.286). Likewise, a significant difference in VIQ was found at baseline (diff = 5.4, $p = 0.025$, ES = 0.388) (Figure 1) but not at follow-up (diff = 2.4, $p = 0.441$, ES = 0.152).

As seen in Figure 2, a significant difference in IQ scores was found, with the patients with AN having a significantly larger difference in IQ scores between VIQ and performance intelligence quotient (PIQ) as well as between verbal comprehension index (VCI) and POI than the HCs. Thus, a significant difference in IQ scores between VIQ and PIQ was found both at baseline (diff = 8.8, $p = 0.002$, ES = 0.594) and at follow-up (diff = 6.6, $p = 0.016$, ES = 0.432). Likewise, a significant difference in IQ scores between VCI and POI was found both at baseline (diff = 10.1, $p = 0.001$, ES = 0.624) and at follow-up (diff = 9.4, $p = 0.002$, ES = 0.588).

As shown in Table 2, there was a significant association between age at baseline and weight recovery (OR 0.57, CI 0.35–0.94, $p = 0.027$), indicating that the odds of weight recovery were diminished with age in the patients with AN. Other than age, no significant associations were found between weight recovery of BMI and the remaining baseline variables, that is gender, intelligence or specific cognitive functions (see Table 2).

Furthermore, no association between BMI and change in cognition was found. Thus, the study results do not indicate any association between weight recovery of BMI and changes in intelligence or specific cognitive functions (Table 3).

With respect to an association between change in cognition and comorbidity in patients with AN, no significant associations were found besides in POI. Here a statistical significant difference was found in the change between the AN group without and with comorbidities (diff = 9.7, $p = 0.0200$) in favour of the latter.

Discussion

To our knowledge, this is the largest follow-up study of cognitive functions conducted in children and adolescents with AN. A high degree of credibility was obtained through the use of a large number of participants, a comprehensive neuropsychological test battery and a high inter-rater reliability.

Table 1 Mean difference between test scores at baseline and at 1 year follow-up

60 Matched pairs	Change						Paired diff	Paired diff	Paired ES
	Patients			Controls					
	Mean	SD	*p* value	Mean	SD	*p* value	Mean	*p* value	
WISC-III/WAIS-III									
Full-scale IQ (FSIQ)	4.9	12.8	0.001	6.6	6.6	<0.001	-1.5	0.951	-0.012
Verbal IQ (VIQ)	2.3	12.1	0.098	4.6	7.7	<0.001	-2.3	0.340	-0.202
Performance IQ (PIQ)	6.4	13.2	<0.001	7.7	8.9	<0.001	-1.0	0.929	0.016
Difference (VIQ - PIQ)	-4.1	12.9	0.021	-3.1	12.1	0.114	-1.3	0.378	-0.162
Verbal comprehension index (VCI)	4.3	12.9	0.009	4.5	8.0	<0.001	0.0	0.686	0.090
Working memory index (WMI)	-0.9	16.0	0.870	2.1	8.7	0.068	-3.3	0.103	-0.274
Perceptual organization index (POI)	6.7	14.5	0.001	7.6	10.1	<0.001	-0.6	0.772	0.051
Processing speed index (PSI)	4.4	15.3	0.021	4.5	16.2	0.081	1.0	0.702	0.070
Difference (VCI - POI)	-2.4	13.8	0.194	-3.1	13.5	0.348	0.6	0.820	0.044
Rey Osterreith Complex Figure Test (RCFT)									
Copy	-0.9	3.2	0.063	-0.6	4.0	0.432	-0.3	0.675	-0.082
Time to copy	-47.0	81.5	<0.001	-49.3	61.8	<0.001	-0.7	0.778	-0.062
Immediate recall	1.7	5.5	0.028	1.3	5.2	0.115	0.2	0.590	0.108
Delayed recall	1.2	5.8	0.079	1.1	5.3	0.179	0.0	0.747	0.065
Trail Making Tests (TMT)									
A	-9.3	12.2	<0.001	-2.8	7.9	0.016	-6.5	0.004	-0.262
B	-6.2	41.8	0.003	-3.0	20.3	0.329	-0.7	0.356	-0.087
Difference (B - A)	2.9	39.0	0.811	-0.1	18.5	0.962	5.4	0.418	0.101
TOMAL-2									
Memory for stories	1.4	8.0	0.209	0.1	6.3	0.516	1.7	0.174	0.233
Memory for stories—delayed Recall	1.7	8.9	0.196	2.0	6.1	0.013	0.0	0.999	0.000
Word-selective reminding	3.2	10.4	0.019	1.1	6.3	0.064	2.3	0.379	0.184
Word-selective reminding—delayed recall	0.5	2.5	0.246	0.4	1.5	0.028	0.3	0.808	0.054
Cambridge Neuropsychological Test Automated Battery (CANTAB)									
Intra-Extra Dimensional Set Shift (IED) stages completed	0.3725	1.7772	0.174	0.1579	0.8407	0.247	0.2083	0.894	0.028
Intra-Extra Dimensional Set Shift (IED) total errors adjusted	-10.0196	40.0592	0.025	-7.0351	19.4853	0.011	-3.6042	0.984	0.005
Intra-Extra Dimensional Set Shift (IED) EDS errors	-0.5098	11.0587	0.423	-2.5088	10.4542	0.022	1.8750	0.377	0.203
Recognition Memory (PRM) number correct	0.4200	2.4082	0.405	0.2632	1.7781	0.115	0.0638	0.777	-0.055
Spatial Recognition Memory (SRM) number correct	0.2000	2.0898	0.410	-0.1579	2.1111	0.580	0.3617	0.219	0.258
Simple and Choice Reaction Time (RTI) five-choice movement time	-37.68	87.49	0.012	26.01	78.69	0.017	-62.55	0.002	-0.633
Simple and Choice Reaction Time (RTI) five-choice reaction time	-33.49	197.12	0.214	-3.48	46.51	0.782	-31.71	0.621	-0.109
Simple and Choice Reaction Time (RTI) simple movement time	-44.79	142.69	0.026	20.05	118.41	0.099	-77.05	0.011	-0.511
Simple and Choice Reaction Time (RTI) simple reaction time	-21.15	115.61	0.174	-2.73	47.27	0.625	-16.56	0.856	-0.044
Information Processing (RVP) A	0.2271	0.4280	0.001	0.2755	0.4601	0.000	-0.0102	0.977	0.006
Stockings of Cambridge (SOC) problems solved in minimum moves	1.5102	2.2091	0.000	0.8070	2.0392	0.006	0.7826	0.116	0.301
Stockings of Cambridge (SOC) mean initial thinking time 5	3226.75	8541.43	0.009	435.31	4578.06	0.412	2008.03	0.150	0.289
Stockings of Cambridge (SOC) mean moves 5	-1.1047	1.8454	0.001	-0.4330	1.4836	0.032	-0.5641	0.158	-0.288
Stockings of Cambridge (SOC) mean subsequent thinking time 5	-566.27	1541.41	0.314	17.40	928.35	0.902	-202.65	0.650	-0.161
Spatial Span (SSP) span length	0.3023	1.3190	0.181	-0.0877	1.2995	0.763	0.3000	0.183	0.264
Spatial Working Memory (SWM) strategy	-1.4583	5.7721	0.143	-2.4912	4.1796	0.000	0.7333	0.512	0.135
Spatial Working Memory (SWM) total errors	-5.1875	15.5134	0.083	-4.6491	12.0052	0.017	-1.0222	0.915	-0.025

One hypothesis of the study was that the development of cognitive functions in children and adolescents with AN would be significantly different from that of matched HCs. However, a similar nonsignificant statistical difference in cognitive development was found in all cognitive domains, with the exception of motor speed. Thus, both intelligence and specific cognitive functions developed uniformly. The study findings thus suggest that AN does not influence cognitive development in children and adolescents over a period of 1 year, contrary to the original hypothesis.

The significant differences in nonverbal intelligence, that is the significant difference in POI between the patients with AN and the HCs found at follow-up, were similar to those differences found in the baseline study (Kjaersdam Telleus et al., 2015). This result is consistent with the results of a study by McCormick et al. (2008), where patients with AN performed significantly worse than controls in PIQ (*p* = 0.000).

The uniform development in cognitive functions resulted in an unaltered significant difference, indicating that inefficiencies in nonverbal intelligence in patients with AN do not normalise over
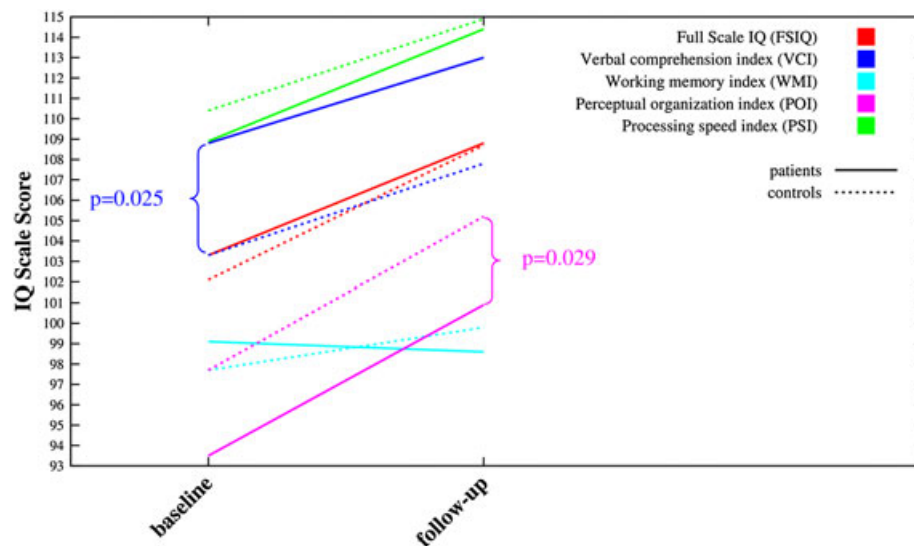
Figure 1. Patients with AN and HC IQ scores, scores for processing speed and working memory at baseline and follow-up
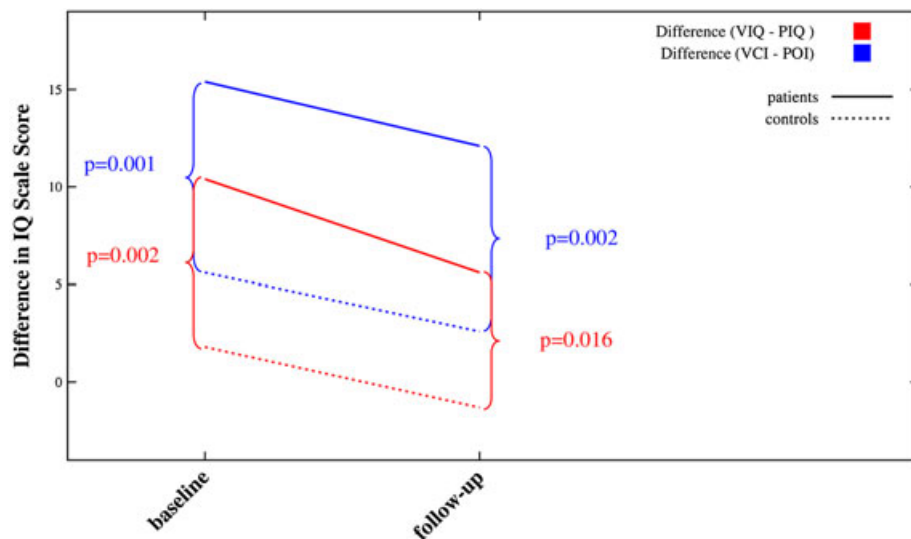

Figure 2. Difference in IQ scores between VIQ/PIQ and VCI/POI in patients with AN and HC at, respectively baseline and follow-up

time. POI is the component of intelligence that manifests in the performance of tasks requiring little or no acquired knowledge; it includes the ability to analyse information and solve problems by using visual reasoning (Flanagan & Kaufman, 2009). Fluid intelligence (Cattell, 1971) is a central component of POI (Kaplan & Saccuzzo, 2005). Fluid intelligence allows one to work in complex situations and underwrites the capacity to think logically and to analyse and solve problems in new situations without the use of previously acquired knowledge (Cattell, 1971).

The uneven cognitive profile highlighted by the significant difference between verbal and nonverbal intelligence functions, that is the significant difference between VIQ and PIQ as well as VCI and POI in the patients with AN and the HCs, is also consistent with the finding by McCormick et al. (2008), who found that patients with AN had a higher verbal intelligence than nonverbal

intelligence function. Thus, in the study by McCormick et al. (2008), a Wechsler Adult Intelligence Scale-Revised (WAIS-R) VIQ of 100.9 and a PIQ of 91.6 were found in patients with AN. An uneven cognitive profile highlighted by the significant difference in verbal and nonverbal intelligence functions in the patients with AN compared with that of the HCs was found both in the baseline study (Kjaersdam Telleus et al., 2015) and at follow-up. Thus, the uneven cognitive profile in patients with AN is a stable trait and does not appear to be illness dependent. Therefore, it may be suggested that this inefficiency could be pre morbid and thereby may be a predisposing factor, among other predisposing factors such as psychological, genetic, biological and sociocultural factors, which contribute to illness progression (Bruch, 1973; Woodside et al., 2001). Another possibility could be that the uneven cognitive profile might be a sequelae of having/having had AN.

Table 2 Logistic analysis of baseline cognition and recovery of BMI

	OR	CI (95%)		*p* value	N
Age	0.57	0.35	0.94	0.0276	55
Gender	0.18	0.01	2.70	0.2119	55
WISC-III/WAIS-III					
Full-scale IQ (FSIQ)	0.99	0.94	1.05	0.7982	54
Verbal IQ (VIQ)	0.98	0.93	1.03	0.4275	54
Performance (PIQ)	1.01	0.96	1.07	0.6317	54
Difference (VIQ - PIQ)	0.96	0.90	1.02	0.1840	54
Verbal comprehension index (VCI)	0.98	0.93	1.03	0.3985	54
Working memory index (WMI)	1.00	0.95	1.06	0.9158	54
Perceptual organization index (POI)	0.99	0.94	1.05	0.8078	54
Processing speed index (PSI)	1.02	0.98	1.07	0.3653	54
Difference (VCI - POI)	0.98	0.94	1.03	0.5288	54
Rey Osterreith Complex Figure Test (RCFT)					
Copy	0.96	0.73	1.28	0.7982	54
Time to copy	1.00	0.99	1.01	0.9898	50
Immediate recall	0.96	0.85	1.08	0.4722	55
Delayed recall	0.96	0.85	1.07	0.4491	55
Trail Making Tests (TMT)					
A	0.98	0.92	1.03	0.3939	55
B	1.01	0.98	1.05	0.4482	55
Difference (B - A)	1.04	0.98	1.11	0.1495	55
TOMAL-2					
Memory for stories	0.92	0.84	1.02	0.1150	46
Memory for stories—delayed recall	0.93	0.85	1.02	0.1202	46
Word-selective Reminding	1.01	0.94	1.10	0.7356	47
Word-selective reminding—delayed recall	0.77	0.40	1.51	0.4509	47
Cambridge Neuropsychological Test Automated Battery (CANTAB)					
Intra-Extra Dimensional Set Shift (IED)	1.12	0.77	1.62	0.5664	53
Intra-Extra Dimensional Set Shift (IED) total errors adjusted	1.00	0.98	1.01	0.5429	53
Intra-Extra Dimensional Set Shift (IED) EDS errors	0.97	0.89	1.06	0.4903	53
Recognition Memory (PRM) number correct	0.98	0.66	1.44	0.9008	52
Spatial Recognition Memory (SRM) number correct	0.99	0.64	1.52	0.9631	52
Simple and Choice Reaction Time (RTI) five-choice movement time	1.04	0.92	1.18	0.5137	46
Simple and Choice Reaction Time (RTI) five-choice reaction time	1.00	0.99	1.02	0.7762	46
Simple and Choice Reaction Time (RTI) simple movement time	1.06	0.94	1.19	0.3424	46
Simple and Choice Reaction Time (RTI) simple reaction time	1.00	0.99	1.01	0.7810	46
Information Processing (RVP) A (×10)	0.76	0.13	4.62	0.7665	52
Stockings of Cambridge (SOC) problems solved in minimum moves	0.89	0.59	1.35	0.5736	51
Stockings of Cambridge (SOC) mean initial thinking time 5	1.00	1.00	1.00	0.7207	51
Stockings of Cambridge (SOC) mean moves 5	0.88	0.59	1.32	0.5329	51
Stockings of Cambridge (SOC) mean subsequent thinking time 5	1.00	1.00	1.00	0.2148	51
Spatial Span (SSP) span length	0.68	0.38	1.23	0.2054	51
Spatial Working Memory (SWM) strategy	1.09	0.91	1.31	0.3448	51
Spatial Working Memory (SWM) total errors	0.97	0.93	1.01	0.1244	51

However, the occurrences of an uneven intelligence profile in children and adolescents with AN should be interpreted cautiously as the differences between VIQ and PIQ are relatively common in the general population. For example, 37.3% of Danish children in the standardisation group for the Wechsler Intelligence Scale for Children, third edition (WISC-III) achieved a difference of 15 IQ points or more between VIQ and PIQ, and 10.0% demonstrated a difference of 26 IQ points or more (Wechsler, 2009).

In general, no significant differences in the change in cognitive functions were found between the patients with AN and the HCs. However, motor speed was one exception, with a greater improvement in change found in the patients with AN than in the HCs. TMT-A is a measure of visual attention and motor speed while RTI (five-choice movement time and simple movement time form CANTAB) is a measure of response latency and motor speed. Thus, both TMT-A and RTI have motor speed as a common component. This study's findings suggest that motor speed may normalise over time, and these results are consistent with the findings of other longitudinal studies. Similar findings by Hatch et al. (2010) also suggest that patients with AN who were underweight performed worse than HCs on motor speed, but these inefficiencies appeared to normalise when the patients' weight was restored (Hatch et al.,

Table 3 Association between BMI and change in cognition

	BMI > WHO 15th percentile at follow-up (N = 46)		BMI ≤ WHO 15th percentile at follow-up (N = 9)			
	Change	SD	Change	SD	Diff	*p* value
WISC-III/WAIS-III						
Full-scale IQ (FSIQ)	4.7	13.3	5.9	12.6	-1.2	0.644
Verbal IQ (VIQ)	1.5	12.7	5.9	9.4	-4.4	0.222
Performance (PIQ)	6.8	13.4	4.1	13.7	2.7	0.687
Difference (VIQ - PIQ)	*−5.3*	*13.1*	*1.8*	*8.2*	*−7.0*	*0.129*
Verbal comprehension index (VCI)	4.2	13.7	6.2	10.4	-2.1	0.610
Working memory index (WMI)	-0.2	11.2	-5.3	32.5	5.1	0.545
Perceptual organization index (POI)	7.3	14.8	2.7	14.9	4.7	0.368
Processing speed index (PSI)	4.5	16.4	4.1	8.7	0.4	0.775
Difference (VCI - POI)	*−3.2*	*14.0*	*3.6*	*10.5*	*−6.7*	*0.213*
Rey Osterreith Complex Figure Test (RCFT)						
Copy	-0.8	3.2	-0.3	2.5	-0.5	0.855
Time to copy	-56.8	82.5	-32.3	44.0	-24.5	0.597
Immediate recall	1.7	5.6	2.2	4.9	-0.5	0.850
Delayed recall	1.3	5.7	0.6	6.6	0.7	0.803
Trail Making Tests (TMT)						
A	-5.6	9.8	-14.1	15.9	8.5	0.182
B	-3.3	41.7	-4.9	18.6	1.6	0.887
Difference (B - A)	*2.1*	*38.5*	*9.2*	*16.1*	*−7.2*	*0.155*
TOMAL-2						
Memory for stories	2.4	7.6	-1.3	7.1	3.7	0.274
Memory for stories—delayed recall	2.2	8.9	-0.3	7.1	2.5	0.462
Word-selective reminding	2.0	10.8	5.5	4.0	-3.5	0.129
Word-selective reminding—delayed recall	0.4	2.6	0.7	0.8	-0.3	0.419
Cambridge Neuropsychological Test Automated Battery (CANTAB)						
Intra-Extra Dimensional Set Shift (IED) stages completed	0.1579	1.6850	1.1250	2.4749	-0.9671	0.160
Intra-Extra Dimensional Set Shift (IED) total errors adjusted	-6.4474	39.8319	-25.2500	49.6783	18.8026	0.252
Intra-Extra Dimensional Set Shift (IED) EDS errors	-0.3684	9.4766	0.2500	14.0484	-0.6184	0.977
Recognition Memory (PRM) number correct	0.3514	2.6270	-0.1250	1.7269	0.4764	0.940
Spatial Recognition Memory (SRM) number correct	0.3243	2.1992	-0.8750	1.8851	1.1993	0.126
Simple and Choice Reaction Time (RTI) five-choice movement time	-39.27	95.67	-1.95	34.22	-37.32	0.392
Simple and Choice Reaction Time (RTI) five-choice reaction time	-44.12	213.19	-23.72	35.76	-20.40	0.499
Simple and Choice Reaction Time (RTI) simple movement time	-52.40	152.18	56.05	90.64	-108.45	0.079
Simple and Choice Reaction Time (RTI) simple reaction time	-30.45	118.98	-17.18	22.13	-13.27	0.589
Information Processing (RVP) A	0.0246	0.0379	0.0263	0.0602	-0.0017	0.411
Stockings of Cambridge (SOC) problems solved in minimum moves	1.6389	2.4860	1.0000	1.1952	0.6389	0.612
Stockings of Cambridge (SOC) mean initial thinking time 5	2480.68	5379.49	5705.64	16 868.13	-3224.96	0.390
Stockings of Cambridge (SOC) mean moves 5	-1.0833	2.0930	-0.8750	0.9258	-0.2083	0.801
Stockings of Cambridge (SOC) mean subsequent thinking time 5	29.84	1177.58	-1005.06	2581.12	1034.90	0.417
Spatial Span (SSP) span length	0.5000	1.3326	-0.1250	1.5526	0.6250	0.415
Spatial Working Memory (SWM) strategy	-1.0833	5.9203	-3.0000	5.9040	1.9167	0.512
Spatial Working Memory (SWM) total errors	-5.8056	16.9163	-6.6250	10.7695	0.8194	0.493

Four patients had missing BMI at follow-up, one patient is excluded owing to having a BMI > 18.5 at baseline.

2010). Likewise the study results comply with the findings by Zwipp *et al.* (2014), which included that motor speed was found to increase with weight gain in patients with AN.

A significant difference in VIQ between the patients with AN and the HCs was found at baseline but not at follow-up. However, as this difference was not found in the large baseline cohort (Kjaersdam Telleus *et al.*, 2015), this finding may be the result of reduced strength due to a smaller sample size in the follow-up study.

The other hypotheses of the study were that changes in the cognitive functions of patients who recovered weight would be significantly different from those of patients who did not recover normal body weight at 1 year follow-up and that baseline cognition would be a predictor of weight recovery.

No association between weight recovery, that is normalisation of BMI, and baseline cognition was found, indicating that cognitive functions and the odds of having a healthy BMI at 1 year follow-up and at baseline are not associated. This finding is supported by the findings of Tchanturia *et al.* (2011), who also found no association between set shifting and BMI in adult patients with AN (Tchanturia *et al.*, 2011).

These study findings suggest that cognition does not predict whether patients with AN will recover from their eating disorder. As most of the patients with AN showed a normalisation of BMI and only nine did not, there was not enough statistical power in the data of this small group to rule out that a relationship exists. However, the lack of association between BMI and change in cognitive functions, coupled with the observed uniform development of cognitive functions, indicates that weight recovery cannot be predicted from cognitive measures, at least not in a short time frame of 1 year as was the case in this study.

However, the correlation between age and normalisation of BMI suggests that older patients with AN have lower odds of normalising their weight and BMI and that younger patients have higher odds of recovering weight. This correlation further implies that the age of patients with AN is associated with the odds of overcoming the illness. This finding is consistent with the findings of other studies that found that early age at first hospitalisation was associated with clinical weight recovery and better outcomes (Errichiello, Iodice, Bruzzese, Gherghi, & Senatore, 2015; Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). As the illness duration in the group of patients with AN in this study was short, with an average duration of 1.2 years and with only one patient with a illness duration of more than 3 years, the results indicate that the age of the patient rather than illness duration is the decisive factor. This finding might be vital, as it suggests the importance of early detection and treatment.

The significant difference in age between the dropout group and the follow-up group, with patients in the follow-up group being significantly younger than the dropout group, should probably be explained by the parents' higher level of involvement and parental authority, keeping the patients in treatment and participation in the research project. Likewise, a group difference was found between the dropout group and the follow-up group with respect to VIQ. This difference represents a trend towards lower VIQ in the group of patients who dropped out of the study. A possible explanation is that patients in the follow-up group who had significantly higher VIQ compared with patients who did not participate at follow-up might have a better understanding of the importance of participating in research.

To summarise, the similar cognitive development in the patients with AN and HCs may suggest that cognitive development in patients with AN was not affected by the illness, as the development of cognition was similar to that of healthy children and adolescents. Although some cognitive inefficiencies were stable, including nonverbal intelligence functions, another cognitive function, motor speed, appears to be illness dependent and normalises over time. Although this cognitive function appears to be reversible and illness dependent, most cognitive functions appear to be illness independent and may be seen as predisposing factors for the illness rather than being triggered by the illness itself. Cognitive functions do not seem to be potential predictors of weight recovery. Likewise, there does not seem to be an association between BMI and cognitive inefficiencies in patients with AN.

Strengths and limitations

This follow-up study of cognitive functions conducted in children and adolescents with AN consisted of a large number of participants. This is one of only a few longitudinal studies of cognitive functions in children and adolescents with AN, and the study includes extensive data. A development component is included in the study, and the study results are controlled through a robust comparison group.

However, there are some limitations that should be mentioned. The main limitation is the reduced participant sample at follow-up. Although 120 participants, 60 matched pairs, still constitute a considerable participant sample, the smaller sample size, compared with baseline, nonetheless weakens the strength of the study. Similarly, the lack of data, such as weight, in some patients with AN, further reduces the strength of the regression analyses.

This study includes a comprehensive neuropsychological test battery. RCFT is used to assess visual memory according to Meyer and Meyer's manual. In recent years RCFT has been used as a measure of central coherences in some AN studies. In this study the RCFT results cannot be used for this purpose. Likewise, the Wisconsin Card Sorting test (WCST) is often used in eating disorder research. A decision was made to include Intra–Extra Dimensional Set Shift (IED) from CANTAB, which is a computerised analogue of WCST. This introduces a limitation in regard to comparing this study's longitudinal data with data in some existing literature on AN.

The findings of this study suggest that, with the exception of motor speed, AN does not influence cognitive development in children and adolescents over a period of 1 year. However, it is possible that the relatively brief follow-up period is too short a period to detect such differences and that a long-term follow-up might produce other results. Investigating this issue could be a highly relevant objective for future research.

Conclusions

As the study design included a 1-year follow-up, this study was able to investigate potential changes in cognitive functions over time. One of the hypotheses of the study was that the development of cognitive functions in children and adolescents with AN would be significantly reduced compared with that of matched HCs. However, the difference in the development of cognitive functions observed in the patients with AN, as well as in the HC participants, was nonsignificant, with the exception of motor speed. A significantly greater improvement was detected in motor speed, relative to a smaller improvement in the HC participants, resulting in a normalisation of performance in the patients with AN.

Based on the significant difference in POI in the patients with AN when compared with the HC participants, and a stable significantly uneven intelligence profile with a significantly larger difference between verbal and nonverbal intelligence abilities in the patients with AN than in the HC participants, suggests that the nonverbal intelligence inefficiencies could be pre morbid and thereby indicate a predisposition to the development of the illness.

Another hypothesis of the study was that the change in intelligence and specific cognitive functions of patients who recovered weight would be significantly different from that of patients who did not recover normal body weight at follow-up. There does not seem to be an association between BMI and changes in cognitive functions in patients with AN. Thus, the study results display a similar cognitive performance change between groups over time, indicating that cognitive functions were not significantly affected by the illness.

A further hypothesis of the study was that the baseline cognitive profile would be a predictor of weight recovery. The cognitive profile does not appear to be associated with patients' weight recovery from the eating disorder. Age, however, may be associated with the odds of obtaining a healthy BMI. Thus, the younger the patients, the higher the odds that they will recover weight.

The study contributes useful new information on the development of cognitive functions in children and adolescents with AN over time. First of all, motor speed seems associated with recovery and may be related to AN and low body weight. Increased knowledge regarding the uneven intelligence profile and the inefficiencies in the nonverbal intelligence functions in children and adolescents with AN may have an impact on clinical practice. Any inefficiency in cognitive functions in these young patients may have an impact in relation to therapeutic work. Similarly, increased knowledge regarding the cognitive profile of children and adolescents with AN may be important for the organisation of cognitive training for patients (Tchanturia et al, 2014). Training of specific cognitive functions in children and adolescents with AN should be based on knowledge of this patient group rather than knowledge based on the adult patient group.

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