Cognitive improvement following weight gain in patients with anorexia nervosa
A systematic review
Hemmingsen, Simone Daugaard; Wesselhoeft, Rikke; Lichtenstein, Mia Beck; Sjögren, Jan Magnus; Støving, René Klinkby

Published in:
European Eating Disorders Review

DOI:
10.1002/erv.2796

Publication date:
2021

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying this open access version.

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 15. Sep. 2023
Title page

Title: Cognitive improvement following weight gain in patients with anorexia nervosa: A systematic review

Short running title: Cognitive improvement following weight gain in anorexia nervosa

Authors: Simone Daugaard Hemmingsen1,5*, Rikke Wesselhoeft6,7, Mia Beck Lichtenstein8,9, Jan Magnus Sjögren10,11 and René Klinkby Støving1-5

1 Centre for Eating Disorder, Odense University Hospital, Denmark
2 Research Unit for Medical Endocrinology, Odense University Hospital, Denmark
3 Research Unit, Child and Adolescent Psychiatry, Mental Health Services in the Region of Southern Denmark
4 Department of Clinical Research, University of Southern Denmark
5 Open Patient data Explorative Network (OPEN), Denmark
6 Clinical Pharmacology and Pharmacy, Institute of Public Health, University of Southern Denmark
7 Child and Adolescent Mental Health Aabenraa, Mental Health Services in the Region of Southern Denmark
8 Centre for Telepsychiatry, Mental Health Services in the Region of Southern Denmark
9 Department of Clinical Research, University of Southern Denmark
10 Eating Disorder Unit, Mental Health Centre Ballerup, Mental Health Services in the Capital Region of Denmark
11 Department of Clinical Medicine, University of Copenhagen, Denmark

*Corresponding author: Simone Daugaard Hemmingsen1-5, MSc Psych, PhD student

e-mail: shemmingsen@health.sdu.dk, phone +45 28595305

Address: J.B. Winsløws Vej 28B, 5000 Odense C, Denmark

https://orcid.org/0000-0001-6789-7105

Acknowledgements

The authors would like to thank Laura Al-Dakhiel Winkler, MD, PhD, at the Research Unit, Child and Adolescent Psychiatry, Mental Health Services, Odense, for being part of our research group and participating in the screening of reports. We would also like to thank the statistician Pia Veldt Larsen for statistical assistance during preparation of the protocol and the manuscript. We want to thank Jesper Mogensen, Professor of Neuroscience, and Nicolaj Daugaard, Cand.Psych., at the Unit for Cognitive Neuroscience, University of Copenhagen, for fruitful discussions of interpretations of results. We would also like to thank Claire Gudex, MD, PhD, Associate Professor at the Department of Clinical Research, University of Southern Denmark, for editing the manuscript.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/erv.2796.

This article is protected by copyright. All rights reserved.
systematic review was supported by government funding from the Psychiatric Research Fund of Southern Denmark and the University of Southern Denmark. The funding sources had no role in preparation, execution, interpretation, analysis or publication of the review.

Conflict of interest
The authors declare no conflict of interest. None of the authors have received financial support or benefits from commercial sources for the systematic review.
Title page

Title: Cognitive improvement following weight gain in patients with anorexia nervosa: A systematic review

Short running title: Cognitive improvement following weight gain in anorexia nervosa

Authors: Simone Daugaard Hemmingsen1-5*, Rikke Wesselhoeft6,7, Mia Beck Lichtenstein8,9, Jan Magnus Sjögren10,11 and René Klinkby Støving1-5

1 Centre for Eating Disorder, Odense University Hospital, Denmark
2 Research Unit for Medical Endocrinology, Odense University Hospital, Denmark
3 Research Unit, Child and Adolescent Psychiatry, Mental Health Services in the Region of Southern Denmark
4 Department of Clinical Research, University of Southern Denmark
5 Open Patient data Explorative Network (OPEN), Denmark
6 Clinical Pharmacology and Pharmacy, Institute of Public Health, University of Southern Denmark
7 Child and Adolescent Mental Health Aabenraa, Mental Health Services in the Region of Southern Denmark
8 Centre for Telepsychiatry, Mental Health Services in the Region of Southern Denmark
9 Department of Clinical Research, University of Southern Denmark
10 Eating Disorder Unit, Mental Health Centre Ballerup, Mental Health Services in the Capital Region of Denmark
11 Department of Clinical Medicine, University of Copenhagen, Denmark

*Corresponding author: Simone Daugaard Hemmingsen1-5, MSc Psych, PhD student
e-mail: shemmingsen@health.sdu.dk, phone +45 28595305
Address: J.B. Winsløws Vej 28B, 5000 Odense C, Denmark
https://orcid.org/0000-0001-6789-7105

Acknowledgements

The authors would like to thank Laura Al-Dakhiel Winkler, MD, PhD, at the Research Unit, Child and Adolescent Psychiatry, Mental Health Services, Odense, for being part of our research group and participating in the screening of reports. We would also like to thank the statistician Pia Veldt Larsen for statistical assistance during preparation of the protocol and the manuscript. We want to thank Jesper Mogensen, Professor of Neuroscience, and Nicolaj Daugaard, Cand.Psych., at the Unit for Cognitive Neuroscience, University of Copenhagen, for fruitful discussions of interpretations of results. We would also like to thank Claire Gudex, MD, PhD, Associate Professor at the Department of Clinical Research, University of Southern Denmark, for editing the manuscript. The systematic review was supported by government funding from the Psychiatric Research Fund of
Southern Denmark and the University of Southern Denmark. The funding sources had no role in preparation, execution, interpretation, analysis or publication of the review.

Conflict of interest
The authors declare no conflict of interest. None of the authors have received financial support or benefits from commercial sources for the systematic review.

Manuscript word count:
4993 (incl references in text)
Abstract

Objective: Anorexia nervosa has been associated with cognitive impairment. While re-nutrition is one of the main treatment targets, the effect on cognitive impairments is unclear. The aim of this review was to examine whether cognitive functions improve after weight gain in patients with anorexia nervosa.

Method: A systematic review was performed following PRISMA guidelines (PROSPERO CRD42019081993). Literature searches were conducted May 20th, 2019 in PubMed, EMBASE, PsychINFO and Cochrane Library. Pairs of reviewers screened reports independently based on titles/abstracts (N=6539) and full texts (N=378). Furthermore, they assessed the quality of reports, including whether practice effects were accounted for.

Results: Twenty-four longitudinal reports were included featuring 757 patients and 419 healthy controls. Six studies examined children and adolescents. Four out of four studies found processing speed to improve above and beyond what could be assigned to practice effects and three out of four studies found that cognitive flexibility was unaffected after weight gain in children and adolescents. Results from studies of adults were inconclusive.

Discussion: The literature on cognitive change in patients with anorexia nervosa following weight gain is sparse. Preliminary conclusions can be made only for children and adolescents, where weight gain appeared to be associated with improved processing speed.

Keywords Anorexia nervosa, eating disorder, neuropsychology, executive function, malnutrition
Introduction

Anorexia nervosa (AN) is a serious illness with the highest mortality rate of all psychiatric disorders (Arcelus, Mitchell, Wales, & Nielsen, 2011). Less than half of patients with AN recover fully and approximately 20% remain chronically ill (Amianto, Spalatro, Ottone, Abbate Daga, & Fassino, 2017).

It has been suggested that cognitive functions play a role in the perpetuation of the disorder (Treasure & Schmidt, 2013). A number of studies have found that AN is associated with cognitive impairments relating to executive functions such as cognitive flexibility (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Tchanturia et al., 2012), central coherence (Abbate-Daga et al., 2015), and decision-making (Wu et al., 2016) but also relating to other cognitive functions such as attention (Seed, Dixon, McCluskey, & Young, 2000; Seed, McCue, Wesnes, Dahabra, & Young, 2002) and memory (Seed et al., 2000; Seed et al., 2002). Executive functions in particular seem to be impaired in adults with AN (Hirst et al., 2017; Kanakam & Treasure, 2013; Smith, Mason, Johnson, Lavender, & Wonderlich, 2018), and impairment of cognitive flexibility is well documented in the literature (Westwood, Stahl, Mandy, & Tchanturia, 2016). Women who had recovered from AN had impaired executive functions even after recovery (Danner et al., 2012; Lindner, Fichter, & Quadflieg, 2014; Tchanturia et al., 2012), suggesting that impaired executive function could be a premorbid trait of AN (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Tchanturia et al., 2011) and perhaps even passed on in families (Holliday et al., 2005; Lang, Treasure, & Tchanturia, 2016). Impaired cognitive performance in patients with AN may also be a result of undernutrition, however.
Studies examining cognitive functions in children and adults with AN show differences between these age groups (Westwood et al., 2016). Several studies comparing children and adolescents with AN to healthy control participants find no difference in cognitive flexibility performance (Andres-Perpina et al., 2011; Bentz et al., 2017; Dmitrzak-Weglarz et al., 2011), in contrast to findings for adults. Similarly, children and adolescents with AN do not present impairment in central coherence (Castro-Fornieles et al., 2009), attention (Calderoni et al., 2013), or memory (Andres-Perpina et al., 2011; Bentz et al., 2017). This gives rise to speculations as to whether cognitive impairment is a consequence of AN and/or long-term undernutrition (Bodell et al., 2014) rather than a premorbid trait (Holliday et al., 2005).

Low body weight due to restrictive eating is a main diagnostic criterion for AN (American Psychiatric Association, 2013). Malnourishment in patients with AN causes endocrinological and biological changes such as amenorrhea (Baskaran, Misra, & Klibanski, 2017) and hypercortisolemia (Miller, 2013). However, the effects of undernutrition on cognitive functions in patients with AN are less clear. Some studies report that the lower the body weight in patients with AN, the lower the cognitive performance (Abbate-Daga et al., 2011; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996; Mathias & Kent, 1998), whereas others find no significant association (Bayless et al., 2002; Calderoni et al., 2013).

Weight gain in the early stage of AN is believed to be important for long-term recovery (Bargiacchi, Clarke, Paulsen, & Leger, 2019). Re-nutrition is thus a main target in the treatment of AN (Bargiacchi et al., 2019), but its potential effect on cognitive performance is unclear. Longitudinal studies that examine cognitive performance before and after weight gain in individuals...
with AN can provide important information about the impact of weight gain on cognitive functions and potential cognitive sequelae of undernutrition.

Existing systematic literature reviews of cognitive performance in patients with AN have focused on cross-sectional studies (Bora & Kose, 2016; Ferraro, Kramer, & Weigel, 2018; Hirst et al., 2017; Lloyd & Steinglass, 2018; Ralph-Nearman, Achee, Lapidus, Stewart, & Filik, 2019; Smith et al., 2018; Westwood et al., 2016). We aimed to systematically review the literature for longitudinal studies investigating cognitive performance before and after weight gain in patients with AN. The objective was to examine whether cognitive functions improve following weight gain in patients with AN. The cognitive functions included were intelligence (IQ), general cognitive functioning, cognitive flexibility, decision-making, central coherence, memory, processing speed, psychomotor speed, learning, attention, information processing, language, mathematical abilities, sequence planning, and haptic perception.
Methods

A protocol describing search strategy, eligibility criteria, and intended outcome measurements was
developed in advance and registered with PROSPERO (registered 20 May 2019, published 20
August 2019; ID number: CRD42019081993; Available
from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019081993). The
reporting of the systematic review followed the Preferred Reporting Items for Systematic Reviews
and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

Search strategy

Literature searches were performed in the databases PubMed (NLM), EMBASE (Ovid),
PsychINFO (Ovid), and Cochrane library (Wiley) on May 20th, 2019. The block-building strategy
based on PIO (Population: anorexia nervosa; Intervention: weight gain; and Outcome: cognitive
performance) was used by combining single concept searches from each block. Search strategies
combined controlled vocabulary thesaurus terms (MeSH, Emtree, and Psychological Index Terms)
with keywords in each search block. We did not use search filters in order to include as many
studies as possible (Leeflang, Scholten, Rutjes, Reitsma, & Bossuyt, 2006). The search words,
including key words and thesaurus terms for each database, are provided in supplementary material.
The PubMed search was published a priori on PROSPERO. Supplementary manual searches were
performed on references listed in the included studies.

Study selection

The review process consisted of three phases (Figure 1): 1) A screening phase based on titles and
abstracts, 2) a screening phase based on full-text articles, and 3) a data extraction phase. EndNote
X9 was used for the handling of references. The online management tool for systematic reviews
Covidence (Veritas Health Innovation Ltd, 2020) was used for the systematic screening. In the first screening phase based on titles and abstracts, we divided reports into ‘no’ (reports clearly failing to fulfill at least one inclusion criteria (see below)), ‘yes’ (inclusion criteria clearly met), or ‘maybe’ (fulfillment of inclusion criteria unclear, reports then sent to the second screening phase). Pairs of reviewers from the research group (SH and RS, ML, or LW) independently reviewed all reports. Any disagreements between the reviewers were discussed for each report via Covidence (Veritas Health Innovation Ltd, 2020) in the first screening phase. In the second screening phase based on full-text articles, two reviewers (SH and RS) reviewed all full-text articles independently. All authors discussed any disagreements at consensus meetings and discussed final inclusion of reports. Only reports meeting all inclusion criteria were included in the literature review. During the data extraction phase, pairs of authors (SH and RS, ML, LW, RW, or JS) extracted data from the studies included at the second screening phase. The complete group of authors discussed any disagreements at consensus meetings.

**Eligibility criteria**

**Inclusion criteria (IC)**

IC1: Patients with an AN diagnosis according to DSM-IV (American Psychiatric Association, 1994), DSM-IV-TR (American Psychiatric Association, 2000), DSM-5 (American Psychiatric Association, 2013), or ICD-10 (World Health Organization, 2016). If studies examined other eating disorders, results had to be reported separately for AN.

IC2: Measurements of cognitive performance (this was changed from the original inclusion criterion stating that only studies using validated measurements of cognitive performance were to be included). The cognitive functions included are listed in Table 1.

IC3: Studies with at least one follow-up measurement.
IC4: English language research articles published in international peer-reviewed journals.

**Exclusion criteria (EC)**

EC1: Studies only reporting body weight at baseline.

EC2: Studies not reporting on cognitive change.

EC3: Studies published before 1994, i.e. before the publication of DSM-IV (American Psychiatric Association, 1994).

EC4: Case reports, registered protocols, and ongoing trials.

EC5: Studies investigating Cognitive Remediation Therapy (CRT) as CRT specifically targets cognitive improvement (Tchanturia, Giombini, Leppanen, & Kinnaird, 2017) and could bias results on the relationship between weight gain and cognitive performance. This exclusion criterion was not stated in the protocol.

**Data extraction and methodological quality assessment**

During the data extraction phase, we extracted descriptive information from the studies included (Table 1) and results on change in cognitive performance from baseline to follow-up.

The data extraction phase also included a methodological quality assessment based on elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist for cohort studies (von Elm et al., 2007), which was adapted to the aim of the current review. Study quality was reported as yes/no/not reported/not applicable in relation to specific issues (e.g. “Did the authors take relevant potential effect modifiers into account?”). Prior to the data extraction phase (but after the review protocol was published on PROSPERO), we decided to include the reporting of practice effect (see below) in the quality assessment. The data...
extraction sheet was adapted accordingly, specifying whether results were reported in relation to practice effects or not. The final version of the quality assessment checklist is included in the Appendix (Table 4).

The practice effect

Participants are likely to perform better at retest if neuropsychological performance is examined using the same test twice, and test-retest reliability is thus reported in technical manuals. The practice (or retest) effect is based on an increase in scores due to factors like memory for specific test items or acquired strategies (Calamia, Markon, & Tranel, 2012). The recommendation is to account for practice effect when interpreting changes in neuropsychological performance over time (Calamia et al., 2012). Some neuropsychological tests have a parallel version of the test that can be used for the second assessment to minimize practice effect. This does not entirely exclude the possibility of a practice effect, however, and the parallel version may differ in item difficulty, which could also affect retest scores (Calamia et al., 2012).

Studies were defined as reporting results in relation to the practice effect if; 1) they performed the cognitive tests on a control group at baseline and at follow-up and reported results for the patients with AN in relation to results from the control group, or 2) they referenced test-retest reliability from test statistics of the cognitive tests and reported results for the patients with AN in relation to test-retest reliability coefficients.

Data synthesis

It was not possible to perform a meta-analysis due to the variation in study samples, aims, interventions and outcome variables. Therefore, a quantitative synthesis is provided.
Results

Study inclusion

The 24 reports included in the review (see Table 1) represented 21 different studies as the reports by Pieters et al. (Pieters et al., 2006; Pieters et al., 2005; Pieters et al., 2004) were based on the same study sample, as were the two reports by Bühren et al. (Buehren et al., 2011; Buhren et al., 2012).

[Figure 1 about here]

Study characteristics

The 21 studies included 13 samples from Europe, five from the US, two from Australia, and one from Japan (Table 1). Publication years spanned from 2000 to 2017. Nine studies (equivalent to ten reports) included children and adolescents (Buehren et al., 2011; Buhren et al., 2012; Firk et al., 2015; Grunwald et al., 2001; Hatch et al., 2010; Lozano-Serra, Andrés-Perpiña, Lázaro-García, & Castro-Fornieles, 2014; Neumarker, Bzufka, Dudeck, Hein, & Neumarker, 2000; Sarrar et al., 2011; Telleus et al., 2016; Zwipp et al., 2014). Five studies included adolescents and adults (Ball, Mitchell, Touyz, Griffiths, & Beumont, 2004; Decker, Figner, & Steinglass, 2015; Epstein et al., 2001; Moser et al., 2003; Pieters et al., 2006; Pieters et al., 2005; Pieters et al., 2004). One study included children, adolescents, and young adults (Ritschel et al., 2015), while six studies did not report age range or target population (Bodell et al., 2014; Cavedini et al., 2006; Foerde & Steinglass, 2017; Koyama et al., 2012; Steward et al., 2016; Tchanturia et al., 2004). In total, 757 patients with AN and 419 healthy control participants featured in the studies. Follow-up assessments were conducted on 555 patients with AN. Mean duration between baseline and follow-
up ranged between one month (Epstein et al., 2001; Moser et al., 2003) and twelve months (Ball et al., 2004; Steward et al., 2016; Telleus et al., 2016). Baseline mean body mass index (BMI) varied from 12.8 (Koyama et al., 2012) to 16.8 (Foerde & Steinglass, 2017), indicating that mean illness severity ranged from moderate to extreme AN according to the DSM-5 (American Psychiatric Association, 2013). Follow-up mean BMI varied from 14.9 (Cavedini et al., 2006) to 20.6 (Bodell et al., 2014), indicating that some patients were still severely underweight at follow-up whereas other patients reached weight recovery.

A total of 41 different cognitive tests were used, including both experimental cognitive tasks and neuropsychological tests and test batteries. There was considerable variation in the cognitive tests used. Seven cognitive tests were used in more than one report (listed in Table 1) but sometimes only at baseline.

The studies varied in terms of the population characteristics (baseline BMI, age group, illness duration, and outpatient/inpatient setting), design (follow-up period and weight gain), and assessment of cognitive functions as well as the treatment for AN (Table 1).

[Table 1 about here]
**Data synthesis**

A total of 24 reports investigated whether cognitive functions improved from baseline to follow-up subsequent to weight gain.

*Figure 2 about here*

**Cognitive impairment at baseline**

Of the 14 reports that considered practice effect and included a control group, 11 found that patients with AN performed poorer at baseline than healthy control participants on at least one cognitive function (Buehren et al., 2011; Buhren et al., 2012; Cavedini et al., 2006; Decker et al., 2015; Firk et al., 2015; Foerde & Steinglass, 2017; Hatch et al., 2010; Lozano-Serra et al., 2014; Pieters et al., 2005; Sarrar et al., 2011; Telleus et al., 2016, reported in Telleus et al., 2015).

**Improvement in cognitive function following weight gain**

Out of the 24 reports included, 15 (representing 12 studies) presented results in relation to practice effects either by examining the change in performance on a control group measured twice (n = 14) or with reference to test-retest reliability of the cognitive test used (n = 1; Moser et al., 2003) (Figure 2). Of these 15 reports, 11 detected practice effects in the cognitive tests used (Buehren et al., 2011; Buhren et al., 2012; Decker et al., 2015; Foerde & Steinglass, 2017; Lozano-Serra et al., 2014; Moser et al., 2003; Pieters et al., 2006; Pieters et al., 2005; Pieters et al., 2004; Sarrar et al., 2011; Telleus et al., 2016), where three of them used alternative measurements at follow-up in a parallel design (Buehren et al., 2011; Lozano-Serra et al., 2014; Moser et al., 2003). The four studies that did not detect any practice effect used alternative measurements at follow-up (Cavedini et al., 2006; Epstein et al., 2001; Firk et al., 2015; Hatch et al., 2010).
Ten out of twelve studies that accounted for practice effect involved inpatients although two studies by Telléus et al. (Telleus et al., 2016) and Bühren et al. (Buehren et al., 2011; Buhren et al., 2012) included both outpatients and inpatients. Two studies (Firk et al., 2015; Sarrar et al., 2011) did not provide information about the patient population.

Cognitive change in children and adolescents: studies that account for practice effect

Table 2 gives an overview of cognitive functions that either did (+) or did not (-) improve more than attributable to practice effects following weight gain in children and adolescents with AN. Memory functions (disparate) improved at follow-up in two out of three studies, while processing speed improved in four out of four studies. Cognitive flexibility improved in one out of four studies. One study (two reports) of children and adolescents found no change in performance (verbal memory and cognitive flexibility) from baseline to follow-up.

[Table 2 about here]

Two tests were used in more than one study of children and adolescents that considered practice effect at both baseline and follow-up, making these studies directly comparable. Using the Rey Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995), which measures central coherence, Lozano-Serra et al. (2014) found improvement after weight gain in patients with AN, whereas Telléus et al. (2016) did not. Using the Trail Making Test (TMT) A (Reitan & Wolfson, 1985), which measures processing speed, Sarrar et al. (2011) and Telléus et al. (2016) found improvement for patients with AN after weight gain while Hatch et al. (2010) also noted improvement on a similar test of processing speed, the Switching of Attention Part I (Paul et al.,
Telléus et al. (2016) found that patients with AN did not improve after weight gain on the TMT B, which measures cognitive flexibility, and Hatch et al. (2010) found no improvement on a similar test, the Switching of Attention part II. Lozano-Serra et al. (2014) did not report on the specific improvement for TMT A or B, but reported that patients with AN did not differ from healthy participants on baseline scores.

**Cognitive change in adolescents and adults: studies that account for practice effect**

Table 3 gives an overview of cognitive functions that either did (+) or did not (-) improve more than attributable to practice effects following weight gain in adolescents and adults. Only general cognitive performance and decision-making were investigated in more than one study, and the results were conflicting. Moser et al. (2003) found that general cognitive performance improved after weight gain (N=28), whereas Epstein et al. (2001) did not (N=20). Decker et al. (2015) found that decision-making improved after weight gain (N=43), whereas Cavedini et al. (2006) did not (N=38). Patients were still severely underweight at follow-up in the study by Cavedini et al. (2006). The study was included here even though their aim was to examine whether cognitive impairment could predict clinical outcome (the opposite of our aim), and there is a risk of reverse causation. Four studies (six reports) found no cognitive improvement following weight gain (Table 3).

**Table 3 about here**

**Cognitive change in studies not accounting for practice effect**

Nine studies examined change in cognitive performance from baseline to follow-up without accounting for practice effect (Figure 2). Six of these studies found cognitive improvement in
patients with AN on one or more measurements following weight gain (Ball et al., 2004; Koyama et al., 2012; Neumarker et al., 2000; Steward et al., 2016; Tchanturia et al., 2004; Zwipp et al., 2014). The other three studies found no change in cognitive performance following weight gain (Bodell et al., 2014; Grunwald et al., 2001; Ritschel et al., 2015).

**Methodological quality assessment**

Overall, the included reports clearly described the setting (24 reports), cognitive variables (24 reports) and BMI inclusion criteria (23 studies; Appendix; Table 4). Some quality items were only addressed in a few studies, such as the representativeness of the sample (7 reports) and descriptions of re-nutrition intervention (5 reports).

The assessment of risk of bias (Appendix, Table 4) showed that 15 reports were evaluated to have low risk of bias because they reported practice effects (e.g. test-retest reliability coefficient) and reported results for patients with AN in relation to this. Six studies were evaluated to have low risk of bias because they statistically addressed dropouts at follow-up, and only two studies were evaluated to have low risk of bias due to blind assessment. However, 22 of the 24 reports had low risk of reporting bias as they reported the results for all defined outcome variables.

Two reports commented on a possible ceiling effect (Epstein et al., 2001; Moser et al., 2003). This was not evaluated in the risk of bias assessment but is a known potential risk of bias in longitudinal research of cognitive performance. If the test is easily performed, for example, the ceiling effect might mask differences between assessments if participants reach maximum scores (Epstein et al., 2001).
Only three studies specifically examined the relationship between amount of weight gained and improvement in a range of cognitive functions (Hatch et al., 2010; Moser et al., 2003; Telleus et al., 2016). All these studies considered practice effect regarding improvement of cognitive functions, and none found significant correlations.

None of the studies adjusted for baseline values of cognitive performance. This is recommended, because a patient with a high baseline value is more likely to have a high follow-up value than a patient with a low baseline value (Vickers & Altman, 2001). In addition, adjusting for baseline values of the outcome may increase the statistical power of the analyses, thus requiring smaller sample sizes (Vickers & Altman, 2001).

**Discussion**

This is the first systematic review examining whether cognitive functions improve in patients with AN who gain weight. The review included 21 longitudinal studies with considerable variation in age of study participants and outcome variables. While adults were not sufficiently comparable, preliminary conclusions can be made for children and adolescents with AN regarding processing speed and cognitive flexibility.

**Processing speed**

Processing speed was the cognitive function most often investigated and it was examined in four comparable studies of children and adolescents (Hatch et al., 2010; Lozano-Serra et al., 2014; Sarrar et al., 2011; Telleus et al., 2016). All four studies indicated that processing speed improved in young patients with AN after weight gain. This is an important finding because the speed of processing information may affect higher order cognitive processes such as executive functions.
(Nigg et al., 2017). Unlike cognitive inflexibility that has been linked to AN and suggested to be a premorbid trait (Holliday et al., 2005), processing speed is not suspected to be related to the development of AN. Processing speed impairment might therefore be a result of undernutrition, which is supported by the findings in this review where processing speed showed improvement following weight gain in children and adolescents.

In contrast, the literature did not indicate that psychomotor speed improved after weight gain in patients with AN. This was examined in only two studies (four reports), however, and they included different age groups (Pieters et al., 2006; Pieters et al., 2005; Pieters et al., 2004; Sarrar et al., 2011). This finding could imply a difference in the cognitive functions controlling processing speed and psychomotor speed. One possible explanation of the difference could be that processing speed can be divided into a simpler motor-based factor (psychomotor speed) and an executive-weighted factor (cognitive speed; (Cepeda, Blackwell, & Munakata, 2013). Psychomotor speed may thus be a contributing element to processing speed. It is possible that children and adolescents with AN have impaired cognitive speed (the executive function) but no impairment of psychomotor speed (the motor function). Opposing this hypothesis, the exact opposite findings were reported by Pieters et al. (2004) who investigated motor and cognitive aspects of a psychomotor speed task in adolescents and young adults with AN. However, their baseline assessment was performed approximately one month after admission, when patients had already gained weight, and the cognitive improvement might have occurred before the baseline assessment.

**Cognitive flexibility**

Cognitive flexibility did not appear to improve after weight gain in directly comparable studies of children and adolescents with AN (Buhren et al., 2012; Hatch et al., 2010; Telleus et al., 2016).
This could partly be explained by normal performance at the baseline low-weight state in young people with AN in most of the studies that examined cognitive flexibility (Hatch et al., 2010; Lozano-Serra et al., 2014; Telleus et al., 2016). The report by Bühren et al. (Buhren et al., 2012) even found that AN patients committed fewer errors than healthy participants in a cognitive flexibility task. However, they found longer reaction times for patients with AN and therefore reported a difference, with patients adopting a more perfectionistic cognitive style. Sarrar et al. (2011) used the probabilistic Object Reversal Task (Reischies, 1999) as a measurement of cognitive flexibility and concluded that children and adolescents with AN displayed slightly impaired cognitive flexibility. This was the only study that found improvement in cognitive flexibility following weight gain, although it did not reach the performance of healthy participants at follow-up.

Our findings from these longitudinal studies are supported by two previous reviews of case-control studies of cognitive flexibility in children and adolescents with AN. The systematic review by Lang et al. (2014) found that children and adolescents with AN did not have impaired cognitive flexibility (Lang, Stahl, Espie, Treasure, & Tchanturia, 2014). Furthermore, the systematic review by Westwood et al. (2016) found no significant difference between children with AN and healthy participants but a significant difference between adults with AN and healthy participants (Westwood et al., 2016).

Executive functions are still developing during adolescence (Blakemore & Choudhury, 2006; Crone, 2009). Our review suggests that impairment of executive functions in patients with AN may not arise until late adolescence or young adulthood. This is supported by findings from the previous systematic reviews of cognitive flexibility described above and from studies showing that plastic
maturation processes especially of the prefrontal cortex (which is associated with executive functions) are not completed until 25 years of age (Arain et al., 2013). Nutritional status also impacts maturation of the adolescent brain (Arain et al., 2013), and undernutrition during adolescence and young adulthood could be responsible for impaired executive functions in adults with AN.

This review does not allow conclusions regarding changes in cognitive flexibility after weight gain in adults with AN. It is possible that cognitive flexibility improves in this age group, but none of the studies that accounted for practice effect examined cognitive flexibility exclusively in adults. However, previous research indicates that cognitive flexibility impairment persists following recovery from AN (Danner et al., 2012).

Other cognitive functions
Decision-making was investigated in four studies, two of which accounted for practice effects (Cavedini et al., 2006; Decker et al., 2015). Decker et al. (2015) found improvement after weight gain, but Cavedini et al. (2006) did not. Interestingly, the two studies not accounting for practice effects found no improvement after weight gain (Bodell et al., 2014; Ritschel et al., 2015). Decision-making may thus not improve following weight gain. The literature regarding other cognitive functions and studies including both adolescents and adults was conflicting and inconclusive. It remains unclear whether the extent of weight gain affects the level of cognitive improvement, and whether cognitive improvement can be obtained without weight gain.

Strengths and limitations of the reports reviewed

This article is protected by copyright. All rights reserved.
Fifteen out of the 24 longitudinal reports accounted for practice effect. The other nine studies were not necessarily of lower quality but given the literature, we considered practice effects to be the most relevant risk of bias.

Follow-up was generally performed on small samples. Although high dropout is a well-recognized problem in studies and interventions addressing patients with AN (Guarda, 2008), eight studies did not report the number of patients who dropped out, and only six reports statistically addressed dropout at follow-up (Appendix, Table 4). This constitutes a serious risk of bias because it affects the representativeness of the sample, which was only described in seven of the reports. Furthermore, the duration of data collection was reported in only five reports (Table 1).

Only three studies examined whether there was an association between extent of weight gain and the level of improved cognitive performance (Hatch et al., 2010; Moser et al., 2003; Telleus et al., 2016). These studies did not adjust for baseline values of cognitive performance, possibly reducing their statistical power.

**Strengths and limitations of the present systematic review**

The systematic review was conducted in accordance with the PRISMA statement (Moher et al., 2009), which aims to maximize transparency and stringency in relation to objectives, methods, data extraction, and reporting of results. To reduce risk of bias, we assigned pairs of reviewers to each report for screening and data extraction, and all the review authors were engaged in the final selection of reports and data extraction. Furthermore, we made an extraction template for the quality assessment, based on the STROBE statement. This template was specifically designed to
assess the quality and the risk of bias for longitudinal studies on cognitive performance in patients with AN.

Some limitations need to be addressed, however. Even though our search strategy included many keywords and controlled vocabulary thesaurus terms, we may have omitted relevant words. The search strategy also required words related to weight and cognitive performance, and reports that did not mention these in the abstract could have been missed. The initial screening phase was based on titles and abstracts, which may have missed studies that reported on cognitive performance but did not provide this information in the abstract. However, all studies related to cognitive performance and AN were forwarded to the second screening phase, and only one additional report was included after the screening phases.

Reports were included regardless of psychotherapeutic treatment because we expected that re-nutrition would be a part of the intervention in all studies on patients with AN in accordance with international guidelines. Patients were treated in a variety of ways, and some received medication. There might thus be a therapeutic effect on cognitive performance, which we could not address.

Conclusion

This is the first systematic review to examine whether cognitive performance improves after weight gain in patients with AN. The literature in this field is remarkably scarce, and only 24 longitudinal reports were included. The heterogeneity of the studies prevented firm conclusions, and in adults with AN, it remains unclear whether cognitive functions improve following weight gain. For children and adolescents with AN, however, processing speed appeared to improve following weight gain. In contrast, cognitive flexibility appeared unaffected at follow up and equivalent to a
normal or slightly impaired level in children and adolescents. This is in line with findings from previous reviews of cross-sectional studies and suggests that cognitive flexibility impairment may not appear before adulthood.

**Recommendations**

We recommend that future longitudinal studies of cognitive performance in patients with AN make clear distinctions between children, adolescents, and adults. There is a lack of longitudinal studies of cognitive performance accounting for practice effect in exclusively adult samples with AN. Future studies should investigate whether cognitive improvement is associated with level of weight gain, when adjusted for baseline cognitive performance. This review indicates that children and adolescents with AN have the largest potential for recovery of cognitive functions. Weight gain seems to improve particularly processing speed performance in this age group. Performance on other cognitive functions could improve as well. Future studies should aim to determine the feasibility of treatment interventions.

**References**


Hatch, A., Madden, S., Kohn, M. R., Clarke, S., Touyz, S., Gordon, E., & Williams, L. M. (2010). In first presentation adolescent anorexia nervosa, do cognitive markers of underweight

This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.


**Figure legends**

**Figure 1.** PRISMA flow diagram of the literature search process;
Full text studies excluded: IC 1 not fulfilled (No DSM-IV, DSM-5 or ICD-10 diagnosis or no results for AN diagnosis separately): n=7; IC 2 not fulfilled (No measurement of cognitive performance): n=0; IC 3 not fulfilled (One measurement: Follow-up studies: n=3, Only cognitive tests at one test time: n=3, Case-control studies: n=190, Other study designs such as cross-sectional studies: n = 48); IC 4 not fulfilled (Studies not in English): n = 22. Exclusion criteria fulfilled (Study not reporting on cognitive improvement: n=1, Study not reporting weight: n=1, Case reports: n =5, RCTs and longitudinal studies on CRT: n =6, Ongoing trials and protocols: n=12); More than one exclusion reason (IC 1 + IC 3 not fulfilled: n=19, IC 2 + IC 3 not fulfilled: n=4, IC 3 not fulfilled + exclusion criteria (CRT) fulfilled: n=1, Exclusion criteria fulfilled (CRT + feasibility study): n =1); Exclusion due to other reasons (Duplicates overlooked: n=16, Dissertation abstracts: n=11, Commentaries: n=3, Validation study: n=1, Prevalence study: n=1); IC=Inclusion criteria; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; RCT = randomized controlled trials; CRT = Cognitive Remediation Therapy.

**Figure 2.** Overall results for the 24 reports included regarding improvement of cognitive functions after weight-gain.
**Table 1.** Characteristics of 24 longitudinal reports included in the systematic review of cognitive performance in patients with anorexia nervosa

<p>| Table 1. Characteristics of 24 longitudinal reports included in the systematic review of cognitive performance in patients with anorexia nervosa |
|---------------------------------|-----------------|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| <strong>Author</strong> and <strong>Year</strong> | <strong>Country</strong> | <strong>Population</strong> | <strong>Sample size</strong> | <strong>Sex %</strong> | <strong>Age T1 (Mean ±SD)</strong> | <strong>Range</strong> | <strong>Illness duration (Mean ±SD)</strong> | <strong>Sample size T1, T2</strong> | <strong>BMI Mean (±SD) T1-T2</strong> | <strong>Assessment at T1 before/after admission</strong> | <strong>Duration of data-collection</strong> | <strong>Classification</strong> | <strong>Treatment</strong> | <strong>Type of cognitive functions</strong> | <strong>Neuropsychological tests</strong> |
| Ball (2004) | Australia | Inpatients - Outpatients/ day hospital - Mixed | 100 | - | - 18.7 (3.0) - 13-24 | - 18 months | - NR -25 | - - 12 months | - 15.6 (1.2) - 19.96 (1.50) | NR | NR | - DSM-IV | - Cognitive Behavioral Therapy - Family Based Therapy | - Information processing - Modified Stroop |
| Bodell (2014) | USA | Inpatients - | 100 | - | - 25.58 (5.83) - NR | - 14.68 (2.19) years | - 22 -14 | - - NR | - 15.78 (2.25) - 20.60 (0.86) | 6-10 days after admission | NR | - DSM-IV-TR | - Decision-making - IGT |
| Buehren (2011) | Germany | Inpatients - | 100 | - | - 15.4 (1.3) - 12-17 | - 32 - 10 | - NR | - 122 (33) days - 57-193 days | - 15.3 (1.2) - 18.4 (1.8) | 7 days after admission | NR | - DSM-IV | - Weight-rehabilitation program - Verbal memory - LGT 2.5 (German paper-pencil test) |
| Buehren (2012) | Germany | Mixed: Inpatients and day hospital | 100 | - | - 15.6 (1.5) - 12-17 | - 12.2 (7.4) months | - 32 | - 122 (33) days - 57-193 days | - 15.4 (1.2) - 18.2 (1.9) | 7 days after admission | 9 months | - DSM-IV | - Weight-rehabilitation program - Cognitive flexibility - Visual set shifting task - Amsterdam neuropsychological tasks program |
| Cavedini (2006) | Italy | Inpatients - | 100 | - | - 24.5 (5.2) - NR | - 13.1 (3.2) years | - 42 | - 127.6 (44.1) days - 142 (1.7) AN-R: 14.9 (1.8) AN-BP: 16.8 (1.9) | - 14.2 (1.7) - AN-R: 14.9 (1.8) AN-BP: 16.8 (1.9) | 7 days after admission | 10 months | - ICD-10 - DSM-IV | - Cognitive Behavioral Therapy - Drug treatment program - Decision-making - IGT - Weigl’s sorting test - object alternation test |
| Decker (2015) | USA | Inpatients - | 96.6 | - | - 25 (7.5) - 16-45 | - 14.1 (2.1) years | - 54 | - 52.6 (15.6) days - 16.6 (1.5) - 20.4 (0.7) | - 1.5 week after admission | NR | NR | - DSM-5 | - Desicion-making (delay discounting) - Wechsler Test of Adult Reading - Money choice |</p>
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Country</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Mean Age/Range</th>
<th>Mean Follow-up</th>
<th>Time After Admission</th>
<th>Measurement</th>
<th>Treatment Approach</th>
<th>Task(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein (2001)</td>
<td>USA</td>
<td>Inpatients</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>7 days after admission</td>
<td>-</td>
<td>General cognitive impairment</td>
<td>MMSE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>31.3 (19.09) days</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>15.63 (2.43) days</td>
<td>18.32 (1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firk (2015)</td>
<td>Germany</td>
<td>Inpatients</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>3 weeks after admission</td>
<td>-</td>
<td>Multi-modal treatment approach</td>
<td>SRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>15.3 (1.5) days</td>
<td>17.9 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foerde (2017)</td>
<td>USA</td>
<td>Inpatients</td>
<td>97.2</td>
<td>8.1 (7.4) years</td>
<td>36</td>
<td>1 week after admission</td>
<td>-</td>
<td>Intensive weight-restoration treatment</td>
<td>Feedback learning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>16.8 (1.3) days</td>
<td>20.3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grunwald (2001)</td>
<td>Germany</td>
<td>Inpatients</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>7 days after admission</td>
<td>-</td>
<td>Haptic perception</td>
<td>Haptic task</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>16.43 (1.30) months</td>
<td>8-26 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatch (2010)</td>
<td>Australia</td>
<td>Inpatients</td>
<td>100</td>
<td>10.31 (1.69) months</td>
<td>37</td>
<td>3-10 days after admission</td>
<td>-</td>
<td>Nutritional rehabilitation</td>
<td>IntegNeuro (computerized battery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>17.4 (6.55) months</td>
<td>8-26 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>15.16 (1.45) months</td>
<td>16.79 (1.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koyama (2012)</td>
<td>Japan</td>
<td>Inpatients</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>3-10 days after admission</td>
<td>-</td>
<td>Intelligence (IQ)</td>
<td>WAIS-III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>12.84 (0.41; n=14) weeks</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>13.18 (0.46; n=8)</td>
<td>18.31 (1.00; n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lozano-Serra (2014)</td>
<td>Spain</td>
<td>Inpatients (T1)</td>
<td>100</td>
<td>12.26 (8.1) months</td>
<td>25</td>
<td>7 days after admission</td>
<td>-</td>
<td>Biological management</td>
<td>WISC-R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>15.4 (1.6) months</td>
<td>19.0 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>16.10 (0.93) months</td>
<td>18.08 (0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed (T2): Outpatients</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>1 week after admission</td>
<td>4 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>12.25 (7.28) weeks</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>12.84 (0.41; n=14) weeks</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Age (Mean, SD)</td>
<td>Gender Distribution</td>
<td>Length of Stay (Mean, SD)</td>
<td>Program Focus</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>---------</td>
<td>-------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Moser (2003)</td>
<td>USA</td>
<td>Inpatients</td>
<td>100</td>
<td>26.43 (8.70)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cognitive Behavioral Therapy - Nutritional rehabilitation</td>
<td></td>
</tr>
<tr>
<td>Neumärker (2000)</td>
<td>Germany</td>
<td>Inpatients</td>
<td>NR</td>
<td>14.5 (1.59)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Memory - Attention - Language</td>
<td></td>
</tr>
<tr>
<td>Pieters (2004)</td>
<td>NR</td>
<td>Inpatients</td>
<td>NR</td>
<td>18.17 (2.15)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treatment program with nutritional rehabilitation - Psychomotor/processing speed - DST from WAIS</td>
<td></td>
</tr>
<tr>
<td>Pieters (2005)</td>
<td>NR</td>
<td>Inpatients</td>
<td>100</td>
<td>17.75 (2.35)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treatment program with nutritional rehabilitation - Psychomotor/processing speed - Drawing task - 3 copying tasks</td>
<td></td>
</tr>
<tr>
<td>Pieters (2006)</td>
<td>Belgium</td>
<td>Inpatients</td>
<td>100</td>
<td>17.72 (2.56)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treatment program with nutritional rehabilitation - Psychomotor/processing speed - Sequence planning task (reaction time, movement time, pen-up time)</td>
<td></td>
</tr>
<tr>
<td>Ritschel (2015)</td>
<td>Germany</td>
<td>Inpatients</td>
<td>100</td>
<td>15-29 (2.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Behaviorally oriented nutritional rehabilitation program - Decision-making (delay discounting) - Intertemporal choice task</td>
<td></td>
</tr>
<tr>
<td>Sarrar (2011)</td>
<td>Germany</td>
<td>NR</td>
<td>100</td>
<td>16.2 (1.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cognitive flexibility - Psychomotor/processing speed - pORT - TMT A - DST - CFT-20-R</td>
<td></td>
</tr>
<tr>
<td>Steward (2016)</td>
<td>Spain</td>
<td>Day hospital</td>
<td>100</td>
<td>28.8 (9.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cognitive Behavioral Therapy - targets nutritional and dietary needs - Decision-making - IGT</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Sample</td>
<td>Sex</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Baseline Assessment</td>
<td>Follow-up Assessment</td>
<td>Cognitive Domain</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
<td>-----</td>
<td>-----</td>
<td>-----------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Tchanturia</td>
<td>2004</td>
<td>UK - Inpatients</td>
<td>100</td>
<td>-</td>
<td>27.2 (8.3)</td>
<td>NR</td>
<td>NR</td>
<td>-34</td>
<td>22</td>
</tr>
<tr>
<td>Telléus</td>
<td>2016</td>
<td>Denmark - Mixed</td>
<td>91.6</td>
<td>7%</td>
<td>14.7 - 10-17 years</td>
<td>NR</td>
<td>1.2 (1.2) years</td>
<td>94</td>
<td>60</td>
</tr>
<tr>
<td>Zwipp</td>
<td>2014</td>
<td>Germany - Inpatients</td>
<td>100</td>
<td>-</td>
<td>15.9 (2.6)</td>
<td>NR</td>
<td>2.2 (1.9) and 2.8 (2.3) years</td>
<td>72</td>
<td>14</td>
</tr>
</tbody>
</table>

Note. T1 = Baseline assessment; T2 = Follow-up assessment; BMI = Body mass index; ICD = International Classification of Diseases; DSM = Diagnostic and Statistical Manual of Mental Disorders; NR = Not reported; Stroop = Stroop Color and Word Test; IGT = Iowa Gambling Task; LGT = Lern- und Gedächtnistest 3; MMSE = MINI Mental State Examination; SRT = Serial Reaction Time; WTAR = Wechsler Test of Adult Reading; TMT = Trail Making Test; LNS = Letter Number Sequencing; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children, WMS = Wechsler Memory Scale; RCFT = Rey Osterrieth Complex Figure Test; WCST = Wisconsin Card Sorting Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CFT-20 = Culture Fair Intelligence Test; DST = Digit Symbol Task; pORT = Probabilistic Object Reversal Task; Brixton = Brixton Spatial Anticipation Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; TOMAL-2 = Test of Memory and Learning-2.
Table 2. Improvement of cognitive functions following weight-gain in children and adolescents in studies accounting for practice effect

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>General cognitive performance/Q</th>
<th>Memory, overall</th>
<th>Visual memory</th>
<th>Verbal memory</th>
<th>Working memory</th>
<th>Implicit learning</th>
<th>Cognitive flexibility</th>
<th>Central coherence</th>
<th>Attention</th>
<th>Processing speed</th>
<th>Psychomotor speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buehren/ Bühren (2011; 2012)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Firk (2015)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hatch (2010)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lozano-Serra (2014)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sarrar (2011)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Telléus (2016)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. + improvement of cognitive performance; - no improvement of cognitive performance.

Table 3. Improvement of cognitive functions following weight-gain in adolescents and adults in studies accounting for practice effect

This article is protected by copyright. All rights reserved.
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>General cognitive performance</th>
<th>Immediate memory</th>
<th>Delayed memory</th>
<th>Feedback learning</th>
<th>Decision-making</th>
<th>Central coherence</th>
<th>Language</th>
<th>Attention</th>
<th>Psychomotor speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavedini (2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decker (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein (2001)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foerde (2017)</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moser (2003)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* + improvement of cognitive performance; - no improvement of cognitive performance.

Cavedini (2006) and Foerde (2017) did not report age range. In Cavedini (2006), patients were still severely underweight at follow-up.
### Table 4. Quality assessment including risk of bias of the 24 reports included in the systematic review

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; author (year)</th>
<th>Setting</th>
<th>Participants</th>
<th>Variables</th>
<th>Bias</th>
<th>Study size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball (2004)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NR</td>
</tr>
<tr>
<td>Bodell (2014)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NR</td>
</tr>
<tr>
<td>Buehren (2011)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Bühren (2012)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cavedini (2006)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Decker (2015)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Epstein (2001)</td>
<td>Y</td>
<td>NR</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Firk (2015)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Foeber (2017)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Grunwald (2001)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Study</td>
<td>Setting clearly described?</td>
<td>Minimum treatment duration (or BMI increase) before follow-up stated?</td>
<td>Sample description</td>
<td>Inclusion criteria for BMI reported?</td>
<td>Cognition variable(s) well described?</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------</td>
<td>--------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Hatch (2010)</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Koyoma (2012)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Lozano-Serra (2014)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Moser (2003)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
</tr>
<tr>
<td>Neumärker (2000)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
</tr>
<tr>
<td>Pieters (2004)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Pieters (2005)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Pieters (2006)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Ritschel (2015)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
</tr>
<tr>
<td>Sarrar (2011)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
</tr>
<tr>
<td>Steward (2016)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NR</td>
</tr>
<tr>
<td>Tchanturia (2004)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Telléus (2016)</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Zwipp (2014)</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>N</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Note.** Y = Yes; N = No; NR = Not reported; NA = Not applicable; Green = Low risk of bias; Red = High risk of bias

Questions: 1. Was the setting clearly described?; 2. Was the minimum treatment duration (or BMI increase) before follow-up stated?; 3. Was the sample described (one of the following)?: a) Representativeness, b) Whole sample, c) Random sample, d) Consecutive sample, e) Convenience sample; 4. Was the inclusion criteria for BMI reported?; 5. Was the cognition variable(s) well described?; 6. Was the re-nutrition intervention described?; 7. Were the instruments used to measure cognition reported to be validated?; 8. Was weight measured objectively?; 9. Was height measured objectively?; 10. Was weight-gain clearly defined?; 11. Did the authors take relevant potential effect modifiers into account (e.g. socio-economic factors, age, education, co-morbid psychosis or schizophrenia, depression and anxiety comorbidity, energy intake vs. no energy intake)?; 12. Were the predictor and outcome variables assessed independently?; 13. Did they report the retest/practice effect? Either as a) reference of test-retest reliability or b) own study of test retest effect (on control group); 14. Was cognitive improvement defined as more than the retest improvement according to the test – retest reliability (either reference or own study)?; 15. Were all defined outcome variables reported in results? (reporting bias); 16. Was loss to follow-up addressed statistically?; 17. Did the authors perform a power calculation?; 18. If yes: Did the number of participants match the power calculation?
Figure 1. PRISMA Flow Diagram

Note. Full text studies excluded: IC 1 not fulfilled (No DSM-IV, DSM-5 or ICD-10 diagnosis or no results for AN diagnosis separately): n=7; IC 2 not fulfilled (No measurement of cognitive performance): n=0; IC 3 not fulfilled (One measurement: Follow-up studies: n=3, Only cognitive tests at one test time: n=3, Case-control studies: n=190, Other study designs such as cross-sectional studies: n = 48); IC 4 not fulfilled (Studies not in English): n = 22. Exclusion criteria fulfilled (Study not reporting on cognitive improvement: n=1, Study not reporting weight: n=1, Case reports: n =5, RCTs and longitudinal studies on CRT: n =6, Ongoing trials and protocols: n=12); More than one exclusion reason (IC 1 + IC 3 not fulfilled: n=19, IC 2 + IC 3 not fulfilled: n=4, IC 3 not fulfilled + exclusion criteria (CRT) fulfilled: n=1, Exclusion criteria fulfilled (CRT + feasibility study): n =1); Exclusion due to other reasons (Duplicates overlooked: n=16, Dissertation abstracts: n=11, Commentaries: n=3, Validation study: n=1, Prevalence study: n=1)
Figure 2. Overall results for the 24 reports included regarding improvement of cognitive functions after weight-gain.
Abbreviations

AN = anorexia nervosa
IQ = intelligence
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses statement
PIO = population, intervention, and outcome
IC = inclusion criteria
DSM = Diagnostic and Statistical Manual of Mental Disorders
ICD = International Classification of Diseases
EC = exclusion criteria
CRT = Cognitive Remediation Therapy
STROBE = Strengthening the Reporting of Observational Studies in Epidemiology statement
BMI = body mass index
RCFT = Rey Osterrieth Complex Figure Test
TMT = Trail Making Test

Highlights

Weight gain appears to be associated with improved processing speed in children and adolescents with anorexia nervosa. It remains unclear whether cognitive functions can improve after weight gain in adults with anorexia nervosa. We recommend clear distinction between children, adolescents, and adults in future longitudinal studies of cognitive performance in patients with anorexia nervosa.