Journal of Psychiatric Research 112 (2019) 71–76

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Set-shifting in adolescents with weight-restored anorexia nervosa and their unaffected family members

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ARTICLE INFO

Keywords:
Anorexia nervosa
Adolescents
Executive functions
Set-shifting
Inhibition

ABSTRACT

Set-shifting difficulties have been suggested to underlie rigid and inflexible thinking in patients with anorexia nervosa (AN). Studies reported set-shifting deficiencies in adults with AN and also in their unaffected family members, suggesting that set-shifting deficits are heritable in AN. Surprisingly, studies failed to show set-shifting difficulties in adolescents with AN. If set-shifting difficulties are heritable, it is not clear why they are absent in adolescents with AN. The current study aimed to elucidate this discrepancy by assessing several components of set-shifting in adolescents with weight-restored AN (WR-AN) and their unaffected parents and siblings. Twenty-one families that include an adolescent who was diagnosed with AN prior to weight restoration (N = 19), an unaffected parent (N = 18), and an unaffected sibling (N = 20) were recruited. Additionally, 28 healthy control families were recruited and included an age-matched adolescent (N = 27), a parent (N = 26), and a sibling (N = 17). Visual-motor set-shifting, verbal set-shifting, and set-shifting clean of inhibition were assessed using the Delis-Kaplan Executive Function System. The results revealed intact set-shifting in parents and siblings of adolescents with WR-AN. Surprisingly, the results revealed superior visual-motor and verbal set-shifting in adolescents with WR-AN compared to age-matched controls. However, when controlling for inhibition abilities, poorer set-shifting was revealed in adolescents with WR-AN. The results suggest that superior inhibition abilities in adolescents with WR-AN may compensate for their set-shifting deficiencies. The study emphasizes the importance of controlling for inhibition abilities when assessing neurocognitive functioning in adolescents with AN. Furthermore, the study does not support the notion that set-shifting deficits are heritable in adolescent AN.

1. Introduction

Anorexia nervosa (AN) is a severe eating disorder characterized by significant weight loss as a result of restricted eating, intense fear of gaining weight and body image disturbance (American Psychiatric Association, 2013). AN commonly onsets during adolescence and its prevalence among these young individuals has increased over the years (Smink et al., 2012). Current evidence-based treatments for adults with AN have limited success and relapse after treatment is common (Kass et al., 2013; Khalsa et al., 2017). Some clinical phenotypes that are associated with AN may hinder successful treatment. For example, rigid and inflexible thinking style is often observed in patients with AN and may interfere with the patients' ability to consider behavioral and cognitive change during therapy (Treasure and Schmidt, 2013).

During the past decade, multiple studies have suggested that difficulties in set-shifting (i.e., the neurocognitive ability that permits shifting back and forth between multiple tasks, operations, or mental sets; Miyake et al., 2000) underlie inflexible thinking style in patients with AN (for reviews see Hirst et al., 2017; Smith et al., 2018; Wu et al., 2014). These studies reported poor set-shifting abilities in adults with AN compared to healthy controls. Several studies also demonstrated set-shifting difficulties in sisters and mothers of adult patients with AN, suggesting that poor set-shifting may be heritable in AN and independent of malnourishment or illness severity (Galimberti et al., 2013; Holliday et al., 2005; Kanakam et al., 2013; Lang et al., 2016; Roberts et al., 2010; Tenconi et al., 2010).

Nevertheless, the literature regarding set-shifting difficulties among adolescents with AN is characterized by many contradictory findings and inconsistencies. In fact, a meta-analysis from 2014 on set-shifting among children and adolescents with AN, reported weak evidence for set shifting difficulties in these younger patients (Lang et al., 2014). The absence of set-shifting difficulties in adolescents with AN was also

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https://doi.org/10.1016/j.jpsychires.2019.02.022
Received 5 December 2018; Received in revised form 20 February 2019; Accepted 25 February 2019

reported in more recent studies (e.g., Herbrich et al. 2018; Kjaersdam Telléus et al., 2015; van Noort et al., 2016). Some of these studies suggested that poor set-shifting could be a result of enduring illness and long-term starvation (e.g., van Noort et al., 2016). However, this notion does not fit with the evidence demonstrating set-shifting difficulties in unaffected family members of patients with AN. Thus, it is unclear why recent meta analyses show only weak evidence for set shifting difficulties in adolescents with AN (e.g., Lang et al., 2014; Smith et al., 2018).

A potential explanation is that set-shifting difficulties exist in adolescents with AN, but compensatory mechanisms mask these difficulties. Particularly, it has been previously reported that set-shifting tasks involve an inhibition component (Koch et al., 2010). For example, in the popular Wisconsin Card Sorting Test (WCST), participants need to switch between sorting principles (capturing set-shifting abilities) but also to inhibit inappropriate responses (requiring inhibitory control resources; Miyake et al., 2000). Notably, superior inhibitory control abilities in AN are assumed to play a role in these patients' ability to severely restrict eating (Hill et al., 2016; Kaye et al., 2009). Some evidence supports this assumption. A neuroimaging study that assessed the ability of adolescents with AN to inhibit prepotent responses showed reduced inhibition-related brain activity when inhibition demands increased. This suggests that adolescents with AN require less inhibitory resources to maintain behavioral performance as inhibitory load increases (Wierenga et al., 2014). In addition, Weinbach et al. (2017) recently showed that adolescents with AN have superior ability to inhibit attention to irrelevant information while focusing on a given task compared to healthy adolescents. Theoretically, in a set-shifting task that relies on both inhibition and set-shifting abilities, improved inhibition could compensate for poor set-shifting abilities and lead to null effects. Thus, controlling for inhibition abilities when assessing set-shifting in adolescents with AN is potentially important in order to uncover set-shifting difficulties in these patients.

The goal of the current study was to shed light on set-shifting abilities in adolescents with AN, their siblings and parents and comparing performance to healthy adolescents and their siblings and parents. The study included adolescents with AN who were weight-restored (WR-AN) during their participation to ensure that a current state of starvation does not impact cognitive functioning.

In order to conduct a comprehensive assessment of set-shifting abilities, three components of set-shifting were assessed using the Delis-Kaplan Executive Function System (DKEFS; Delis et al., 2001): a) visual-motor set-shifting, b) verbal set-shifting, and c) set-shifting clean of inhibition. Visual-motor set-shifting reflects the participant's ability to efficiently scan visual information and carry out motor responses while shifting between different task rules. Verbal set-shifting represents the ability to retrieve semantic knowledge and respond verbally while shifting between semantic categories. Lastly, a measure of set-shifting clean of inhibition was assessed. This measure isolates verbal inhibition abilities from task-switching abilities thus providing a pure measure of set-shifting clean of inhibition (Delis et al., 2001).

It was hypothesized that, in accordance with previous literature, poorer set-shifting abilities will be observed in parents and siblings of adolescents with WR-AN compared to parents and siblings of aged-matched healthy controls (HC) in all set-shifting measures. In addition, it was expected that poorer set-shifting abilities in adolescents with WR-AN will be found compared to HC only when controlling for their inhibition abilities.

2. Methods

2.1. Participants

A total of 21 families that include an adolescent with WR-AN and 28 HC families participated in the study. Due to some missing data, the final dataset included 19 female adolescents diagnosed with AN prior to weight restoration, 18 of their parents (3 fathers and 15 mothers) and 20 of their siblings (all females). HC families included 27 female adolescents, 26 of their parents (all mothers) and 17 siblings (9 males). All patients and their unaffected relatives were recruited from the Eating Disorder Outpatient Clinic at Stanford School of Medicine. HC and their relatives were recruited via advertisements in the local community. Inclusion criteria for the AN group were: a) Diagnosis of AN based on the Diagnostic and Statistical Manual of Mental Disorders IV, text revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria before weight gain. b) Age between 12 and 19. c) Weight restored defined by percentage of ideal body weight (%IBW) greater than 85% of median body weight, defined as the weight associated with the 50th percentile body-mass index (BMI) for the age, sex, and height. d) Weight restoration was not due to binge eating episodes. e) Having a sibling within 5 years' age difference and a parent without an eating disorder willing to participate. f) Absence of any neurological illness, brain injury or trauma that could interfere with neurocognitive functioning. Inclusion criteria for the age-matched HC were: a) Absence of current or history of an eating disorder. b) Age between 12 and 19. c) % IBW > 85%. d) Having a sibling within 5 years' age difference and a parent without an eating disorder willing to participate. e) Absence of any neurological illness, brain injury or trauma that could interfere with neurocognitive functioning.

Among the adolescents with WR-AN, 15 were diagnosed with a restrictive subtype and 4 with a binge eating/purging subtype of AN prior to weight restoration. 1 patient was diagnosed with comorbid post-traumatic stress disorder, 6 with comorbid depressive disorders, 2 with comorbid OCD, and 1 with comorbid general anxiety disorder. Among parents of patients with AN, 1 was diagnosed with a depressive disorder and 1 with an anxiety disorder. Among siblings of patients with AN, 1 was diagnosed with a depressive disorder, 1 with an anxiety disorder, and 1 with OCD. Among HC, 1 was diagnosed with a specific phobia. Among parents of HC, 3 were diagnosed with a depressive disorder and 2 with an anxiety disorder. None of the siblings of HC were diagnosed with any psychiatric disorder. Demographic and clinical data of all the participants is presented in Table 1.

2.2. Measures

2.2.1. Clinical assessments

All participants under the age of 18 were diagnosed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997). Participants who were 18 and above were diagnosed using the Structured Clinical Interview for DSM-IV-TR, Axis I Disorders (SCID-I; First et al., 2002). In addition, all participants completed the Eating Disorder Examination (v16) interview (Fairburn et al., 2008) in order to assess eating disorders symptoms and severity. Height and weight were measured on the day of the assessment.

2.2.2. Intelligence assessment

All participants completed the Wechsler Abbreviated Scale of Intelligence, second edition (WASI-II), which is suitable for individuals above the age of 6. The WASI-II includes four sub-tests: Matrix Reasoning, Block Design, Vocabulary and Similarities and provides intelligence estimates in verbal and perceptual reasoning as well as full-scale IQ.

2.2.3. Set-shifting assessment

The DKEFS (Delis et al., 2001) was used to obtain three components of set-shifting abilities; visual-motor set shifting, verbal set-shifting, and set-shifting minus inhibition.

2.2.3.1. Visual-motor set-shifting. Visual-motor set-shifting is measured in the DKEFS using the Trail-Making Test. The test includes a condition in which participants need to switch between connecting numbers and letters in a sequential order on a worksheet (Number-Letter Switching

Table 1
Means and standard deviation (in parenthesis) of all participants' clinical and demographic measures.

	AN Families (N = 21)			HC Families (N = 28)		
	WR-AN (N = 19)	AN-Parents (N = 18)	AN-Siblings (N = 20)	HC (N = 27)	HC -Parents (N = 26)	HC-Siblings (N = 17)
Age[a]	15.5 (1.9)	48 (5.9)	15 (2.9)	15.2 (1.6)	47.7 (4.8)	14.9 (3.6)
BMI[b]	19.5 (1.7)	25.5 (3.3)	21 (4)	20.7 (2.1)	26.7 (5.1)	19.8 (2.4)
%IBW	97 (8.4)	N/A	110.4 (24.9)	104.3 (10.9)	N/A	101.8 (12.3)
WASI Full Scale[c]	117.3 (11.2)	113.3 (10.3)	113.6 (11.3)	111.9 (9)	114.9 (9.8)	112 (10.8)
WASI Verbal	119.1 (12.8)	109.2 (10.1)	114.5 (12.1)	115.3 (10.5)	112.1 (8.9)	114.6 (14.3)
WASI Performance	111.6 (9.2)	114.4 (11.2)	109.8 (11.5)	105.7 (8.1)	112.4 (13.2)	106.8 (10)
EDE-Global	1.8 (1.5)	0.8 (0.4)	0.4 (0.5)	0.3 (0.4)	0.9 (0.7)	0.3 (0.3)
EDE-Restraint	1.6 (1.6)	0.5 (0.6)	0.3 (0.7)	0.1 (0.5)	0.7 (0.8)	0.1 (0.3)
EDE-Shape concerns	2.4 (1.9)	1.2 (0.7)	0.7 (1)	0.4 (0.5)	1.4 (1.2)	0.5 (0.6)
EDE-Weight concerns	2 (1.7)	1.3 (0.8)	0.5 (0.7)	0.5 (0.6)	1.5 (1.2)	0.3 (0.4)
EDE-Eating concerns	1 (1.1)	0.1 (0.2)	0.2 (0.2)	0.09 (0.2)	0.2 (0.3)	0.1 (0.2)

Note. WR-AN: weight-restored anorexia nervosa; HC: healthy controls; BMI: Body-Mass Index; %IBW: Percentage of Ideal Body Weight; WASI: Wechsler Abbreviated Scale of Intelligence; EDE: Eating Disorder Examination.
[a] Details regarding age is missing from 1 parent of a patient with WR-AN.
[b] Due to technical issues, weight and height data was lost for 2 patients with WR-AN, 1 parent of a patient with WR-AN, 3 parents of HC and 1 sibling of HC.
[c] WASI scores are missing for 1 sibling of a patient with WR-AN.

condition). The time required to complete the task is a measure of visual-motor set-shifting abilities.

2.2.3.2. Verbal set-shifting. The verbal fluency test in the DKEFS requires participants to generate as many words as they can that belong to a certain category (e.g., animals) in 60 s. In a Category Switching condition, participants alternate between different categories (e.g., fruit and furniture). The total correct responses in this condition represents a measure of verbal set-shifting.

2.2.3.3. Set-shifting minus inhibition. The Color-Word Interference Test in the DKEFS is a variant of the Stroop task (Stroop, 1935) in which color words are presented to the participant in different ink colors. In an Inhibition condition, participants are required to name the ink color of the printed word and ignore it's meaning (e.g., say 'red' when the word 'blue' is printed in a red color). Overcoming the automatic tendency to read the word requires inhibition resources. In an Inhibition/Switching condition, participants switch between naming the color and the word, that is, switching back and forth between two competing tasks. Subtracting the Inhibition condition response time from the Inhibition/Switching condition response time provides a purer measure of set-shifting without inhibition.

2.3. Procedure

After providing informed consent and assent, participants completed a diagnostic evaluation using the K-SADS or SCID-I. Then participants completed the EDE interview. Following that, they completed the DKEFS. The current study is part of a more comprehensive research project that included other neuropsychological tests and magnetic resonance imaging (MRI) scanning that are not the focus of the current study. The study was approved by the department institutional review board.

2.4. Data analysis

Demographic and clinical measures were assessed between the groups using independent *t*-test. To reduce the potential for a type 1 error and considering correlations between the three main dependent measures (Number-Letter Switching, Category Switching, Inhibition, Inhibition/Switching, and Inhibition/Switching minus Inhibition), three Multivariate Analyses of Variance (MANOVAs) were conducted in order to compare performance between family members (targets, parents, and siblings) in the different groups (AN families vs. HC families). If the MANOVA was significant, we carried out independent t-tests of assess the differences on each measure separately.

Because family members are considered dependent data standard methods for group comparison that assume that observations are independent (e.g., ANOVA) could not be carried out and a series of paired t-tests were conducted in order to assess differences between family members within each family category on the set-shifting measures. Analyses on all measures in the DKEFS were conducted using scaled scores to ensure that they are corrected for age. Cohen's d is reported with 0.2, 0.5, and 0.8 representing small, medium and large effect sizes, respectively.

3. Results

3.1. Clinical and demographic measures

Table 1 presents clinical and demographic measures of the participants. Adolescents with WR-AN and HC did not differ in age ($t(44) = 0.57$, $p = .56$, $d = 0.17$, 95% CI [-0.41, 0.75]) or in the WASI full scale IQ score ($t(44) = 1.77$, $p = .08$, $d = 0.51$, 95% CI [-0.07, 1.12]). Adolescents with WR-AN had lower %IBW ($t(42) = 2.35$, $p = .02$, $d = 0.74$, 95% CI [0.09, 1.34]) and higher EDE-Global scores compared to HC ($t(44) = 4.89$, $p < .001$, $d = 1.35$, 95% CI [0.79, 2.11]). Parents of adolescents with WR-AN did not differ from HC parents in age ($t(41) = 0.07$, $p = .93$, $d = 0.01$, 95% CI [-0.58, 0.63]), BMI ($t(38) = 0.67$, $p = .50$, $d = 0.22$, 95% CI [-0.41, 0.84]), WASI full scale IQ score ($t(42) = 0.49$, $p = .62$, $d = 0.15$, 95% CI [-0.45, 0.75]), or EDE-Global score ($t(42) = 0.7$, $p = .48$, $d = 0.24$, 95% CI [-0.38, 0.81]). Siblings of adolescents with WR-AN and siblings of HC were not significantly different in age ($t(35) = 0.99$, $p = .32$, $d = 0.33$, 95% CI [-0.32, 0.97]), %IBW ($t(33) = 0.26$, $p = .26$, $d = 0.08$, 95% CI [-0.57, 0.74]), WASI full scale IQ ($t(34) = 0.42$, $p = .67$, $d = 0.14$, 95% CI [-0.51, 0.79]), or EDE-Global score ($t(35) = 0.93$, $p = .35$, $d = 0.38$, 95% CI [-0.34, 0.95]).

3.2. Set-shifting measures

Table 2 presents scaled scores of all participants in the measures of interest. The MANOVA assessing differences between adolescents with WR-AN and HC in the set-shifting measures was significant, $F(3, 42) = 3.84$, $p = .01$; Wilks' $\lambda = 0.78$, Partial $\eta 2 = .21$.

Contrary to the hypothesis, adolescents with WR-AN scored better than HC in visual-motor set-shifting (i.e., Number-Letter Switching; $t(44) = 2.06$, $p = .04$, $d = 0.61$, 95% CI [0.01, 1.21]) and in the verbal

Table 2
Scaled scores and standard deviations (in parenthesis) of the DKEFS's variables of interest.

	AN Families (N = 21)			HC Families (N = 28)		
	WR-AN (N = 19)	AN- Parents (N = 18)	AN-Siblings (N = 20)	HC (N = 27)	HC-parents (N = 26)	HC-Siblings (N = 17)
Trail Making Test						
Number-Letter Switching	11.5 (2)	10.8 (2.7)	10.4 (3)	10.2 (2.2)	11.2 (2.1)	9.6 (1.7)
Verbal Fluency Test						
Category Switching	14.3 (2.6)	12.5 (3.6)	12.1 (3.5)	12.2 (2.8)	12.5 (3.7)	10.6 (3.6)
Color-Word Interference Test						
Inhibition	12.2 (1.6)	10.7 (3.4)	10.9 (3)	10 (2.9)	10.6 (3.6)	9.3 (3.2)
Inhibition/Switching	11.9 (1.7)	11 (2.7)	11 (2.8)	10.7 (2.3)	11.9 (2.1)	9.7 (3.2)
Inhibition/Switching vs. Inhibition	9.6 (1.4)	10.3 (2.5)	10 (1.8)	10.7 (1.7)	11.4 (2.7)	9.7 (2.7)

Note. WR-AN: weight-restored-anorexia nervosa; HC: Healthy controls.

set-shifting measure (i.e., Category Switching; t(44) = 2.59, p = .01, d = 0.77, 95% CI [0.16, 1.38]). Adolescents with WR-AN also had better scores on the Switching/Inhibition measure, although this comparison was not significant (t(44) = 1.86, p = .06, d = 0.59, 95% CI [-0.04, 1.15]). In accordance with the hypothesis, adolescents with WR-AN showed superior performance compared to HC in the Inhibition measure (t(44) = 2.97, p = .005, d = 0.93, 95% CI [0.26, 1.5]). Critically, after subtracting the Inhibition score from the Switching/Inhibition score in order to obtain a measure of pure set-shifting and thereby accounting for WR-AN superior inhibition, poorer set-shifting of adolescents with WR-AN compared to HC was uncovered (t(44) = 2.28, p = .02, d = 0.7, 95% CI [0.07, 1.28]).

The MANOVA assessing differences between set-shifting measures amongst parents in the two groups was not significant, $F(3, 40) = 1.04$, p = .38; Wilks' λ = 0.92, Partial $\eta 2$ = .07 nor was the MAVONA for the siblings analyses, $F(3, 33) = 0.58$, p = .62; Wilks' λ = 0.94, Partial $\eta 2$ = .05.

Within group analyses in AN families showed that adolescents with WR-AN were not different from their parents on any of the variables of interest (all $p > .10$). In addition, adolescents with WR-AN performance did no significantly differ from that of their siblings on any measure (all $p > .10$) except for Category Switching in which adolescents with WR-AN showed superior performance compared to their siblings, t(17) = 2.25, p = .03, d = 0.54, 95% CI [0.01, 1.11].

4. Discussion

The goal of the current study was to assess several facets of set-shifting abilities in adolescents with WR-AN and their unaffected family members. Contrary to the hypothesis, the results did not reveal set-shifting difficulties in parents and siblings of adolescents with WR-AN compared to parents and siblings of healthy adolescents. In addition, and contrary to the hypothesis, adolescents with WR-AN showed superior visual-motor and verbal set-shifting abilities compared to healthy adolescents. However, when pure set-shifting abilities were examined by controlling for inhibition abilities, poorer set-shifting performance was observed in adolescents with WR-AN compared to HC.

To the best of our knowledge, this is the first study to assess set-shifting in adolescents with WR-AN, their unaffected siblings and parents and compare performance to age-matched healthy adolescents and their siblings and parents in a single study. The results of the current study did not show evidence for set-shifting difficulties in unaffected family members of adolescents with WR-AN on any of the set-shifting measures examined (i.e., visual-motor set-shifting, verbal set-shifting, and set-shifting clean of inhibition). These results suggest that set-shifting difficulties are not necessarily heritable in adolescent AN. However, it should be noted that several previous studies did report poor set-shifting abilities in unaffected sisters and mothers of individuals with AN (e.g., Lang et al., 2016; Roberts et al., 2010; Tenconi et al., 2010). A possible explanation for this discrepancy is methodological differences between these studies and the current study. Specifically, most previous studies used the WCST to assess set-shifting abilities while the current study used the DKEFS in the attempt to assess multiple facets of set-shifting using a single test. It could be that set-shifting abilities as assessed in the WCST tap different set-shifting components compared to those tested in the DKEFS. For example, the WCST requires set-shifting under conditions of uncertainty regarding the ongoing task's rules while in the DKEFS decisions are made using rules known in advance. A study assessing set-shifting in unaffected family members using multiple set-shifting tasks would be able to assess this possibility. Another possible explanation for the lack of set-shifting difficulties present in family members in the current study could be that set-shifting deficits are more salient in relatives of patients with acute and enduring AN. Specifically, previous studies used samples of adult patients with acute AN while the current study is the first to assess set-shifting in relatives of adolescents with AN. Moreover, adolescents in the current study were weight restored, thus their AN may be less likely to persist or recur in adulthood, leaving the possibility that set-shifting deficits are more heritable in AN that persists into adulthood. Heterogeneity in the unaffected relatives' performance could also explain why no differences were found between the patients and their relatives. A longitudinal study that attempts to predict the development of acute and enduring AN via the set-shifting profile of the patients' family members could shed light on this issue.

The results of the current study also demonstrated that adolescents with WR-AN had superior performance compared to HC in visual-motor and verbal set-shifting. This is surprising because the literature on adults with AN consistently reported poor set-shifting in adults with AN (Smith et al., 2018) and the literature on adolescents with AN mostly showed no set-shifting difficulties (Lang et al., 2014). However, we suggested that superior inhibition abilities in adolescents with AN may compensate for their poor set-shifting abilities, because a) set-shifting tasks often include inhibition components as indicated by studies finding correlations between set-shifting and inhibition abilities (Karr et al., 2018; Koch et al., 2010; Miyake et al., 2000) and b) studies reported superior inhibition abilities in adolescents with AN (Weinbach et al., 2017; Wierenga et al., 2014). If superior inhibition abilities compensate for poor set-shifting in adolescents with AN, then controlling for inhibition abilities while assessing set-shifting might reveal set-shifting difficulties in these patients. This possibility was examined in the current study and the results showed that in the framework of the color-word Stroop task, adolescents with WR-AN showed superior inhibition abilities compared to controls. Importantly, in a measure that removes the inhibition component from the task's set-shifting/inhibition measure, greater set-shifting difficulties were observed in adolescents with AN compared to controls. This is a key finding of the current study because it may explain why the vast majority of studies on set-shifting in adolescents with AN do not find set-shifting difficulties in these patients. The current study emphasizes the need to control for inhibition abilities when assessing set-shifting in adolescents with AN.

A follow-up question that should be addressed is why superior inhibition abilities do not compensate for poor set-shifting abilities in

adults with AN, a population in which poor set-shifting is more evident. Although this study does not provide empirical evidence to answer this question, it is possible that inhibition abilities in AN deteriorate as the illness progresses, thus, making set-shifting difficulties more salient (i.e., because the inhibition component no longer compensates). Several studies show that unlike adolescents, adults with AN have deficiencies in their inhibitory control (Collantoni et al., 2016; Galimberti et al., 2012; Kullmann et al., 2014). Deterioration of inhibition abilities could partially explain diagnostic crossover from restrictive AN to binge eating/purging AN subtype over time (Eddy et al., 2008). That is, when inhibition abilities deteriorate overtime, the patients are more susceptible for impulsive binge eating and/or purging episodes. A longitudinal study that follows inhibitory control abilities over time in adolescents with AN might clarify this issue. Additionally, better understanding the developmental trajectories of cognitive abilities in healthy populations and those with psychopathologies will help assess the points at which abnormalities in neurocognitive mechanisms may develop.

Several limitations of the current study should be acknowledged. It could be that some of the absent effects in the unaffected-relatives' analyses can be explained by the small sample size. However, it should be noted that the effect sizes in the unaffected relatives' comparisons were small. Furthermore, previous studies that did show differences between mother and sisters of adults with AN and controls had similar or smaller samples than the current study (e.g., Galimberti et al., 2013; Lang et al., 2016). In addition, the study's sample was not large enough to assess potential differences between the restrictive and the binge eating/purging subtypes of AN or the contribution of comorbidities to set-shifting abilities. This is important because the neurocognitive profile of the two subtypes is likely different and executive functions impairments are linked with various psychopathologies. Lastly, the current study focused on patients with AN who were weight-restored. While the advantage of studying this population is that the results are not affected by current state of starvation, the disadvantage is that they cannot be generalized to patients with AN who are underweight.

Taken together, the results of the current study could not confirm the presence of set-shifting difficulties in unaffected parents and siblings of adolescents with AN. Future studies should attempt to use multiple assessment measures of set-shifting in larger samples of unaffected family members in order to better characterize set-shifting abilities in this population. The key finding of the current study is that superior inhibition abilities may compensate for set-shifting difficulties in adolescents with WR-AN. Thus, the study provides a potential explanation for previous studies failure to show set-shifting difficulties in adolescents with AN and highlights the importance of disentangling various neurocognitive functions that may interact when assessing neurocognitive mechanisms in psychopathology.

The results of the current study could have practical clinical implications. Cognitive remediation therapy (CRT) has become an increasingly popular adjacent treatment for adults and adolescents with AN (Tchanturia et al., 2017, 2014). CRT aims to improve neurocognitive abilities via instructed training in hopes to impact clinical symptoms of AN. Parts of CRT include inhibition and set-shifting training procedures. Considering the current study results suggesting that superior inhibition abilities may compensate for poor set-shifting in adolescents with WR-AN, CRT could increase its efficiency by focusing more on improving set-shifting abilities rather than inhibition abilities that are already overactive in adolescents with AN. It has also been suggested that overactive inhibitory control may contribute to restricted eating in AN (Hill et al., 2016; Kaye et al., 2009). Thus, training patients with AN to improve their inhibition abilities may not be ideal.

Declarations of interest

None.

Acknowledgment

This study was supported by the National Institute of Mental Health (grant K24 MH074467 to JL). NW was supported by the Israel Science Foundation (grant 52/16, Post-Doctoral Fellowship) and by the Fulbright Foundation. CB was supported by the National Institute of Mental Health (grant K23 MH106794).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.022.

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