Original Article

Cognitive Flexibility in Juvenile Anorexia Nervosain Relation to Comorbid Symptoms of Depression, Obsessive Compulsive Symptoms and Duration of Illness

Anne Rößner[1], Izabela Juniak[1], Betteke Maria van Noort, Ernst Pfeiffer, Ulrike Lehmkuhl, and Viola Kappel

Charité-Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy

[1] These authors contributed equally to this manuscript.

Abstract: *Objective:* Whereas the evidence in adolescents is inconsistent, anorexia nervosa (AN) in adults is characterized by weak cognitive flexibility. This study investigates cognitive flexibility in adolescents with AN and its potential associations with symptoms of depression, obsessive compulsive disorder (OCD), and duration of illness. *Methods:* 69 patients and 63 age-matched healthy controls (HC) from 9 till 19 years of age were assessed using the Trail-Making Test (TMT) and self-report questionnaires. *Results:* In hierarchical regression analyses, set-shifting ability did not differ between AN and HC, whereas AN patients reported significantly higher rates of depression symptoms and OCD symptoms. Age significantly predicted set-shifting in the total sample. Only among AN patients aged 14 years and older did set-shifting decline with increasing age. *Discussion:* The presence of AN with depression or OCD symptoms or the duration of illness do not influence cognitive flexibility in children and adolescents. Early interventions may be helpful to prevent a decline in cognitive flexibility in adolescent AN with increasing age.

Keywords: anorexia nervosa, adolescents, cognitive flexibility, set-shifting, comorbidity

Kognitive Flexibilität bei Jugendlichen mit Anorexia Nervosa in Verbindung mit Depressivität, Zwanghaftigkeit und Erkrankungsdauer

Zusammenfassung: *Fragestellung:* Während sich bei Erwachsenen mit Anorexia Nervosa (AN) Einschränkungen der kognitiven Flexibilität zeigen, sind die Befunde bei Jugendlichen uneinheitlich. Ziel dieser Studie war eine Untersuchung der kognitiven Flexibilität bei Jugendlichen mit AN und der möglichen Zusammenhänge mit Symptomen von Depression und Zwanghaftigkeit sowie der Dauer der Erkrankung. *Methodik:* Insgesamt wurden 69 Patientinnen mit AN und 63 gesunde Kontrollprobandinnen im Alter von 9 bis 19 Jahren mittels des Trail-Making-Tests (TMT) und Selbstbeurteilungsfragebögen untersucht. *Ergebnisse:* In hierarchischen Regressionsanalysen ergaben sich keine Unterschiede in der kognitiven Flexibilität zwischen Patientinnen und Kontrollprobandinnen, wobei Erstere deutlich höhere Ausprägungen der Depressivität und Zwanghaftigkeit angaben. Das Alter war in der Gesamtgruppe ein signifikanter Prädiktor der kognitiven Flexibilität; bei Patientinnen ab 14 Jahren zeigte sich hingegen bei steigendem Alter eine sinkende kognitive Flexibilität. *Schlussfolgerungen:* Das Vorliegen einer AN mit Symptomen von Depressivität oder Zwanghaftigkeit sowie die Dauer der Erkrankung zeigen keinen Einfluss auf die kognitive Flexibilität. Um bei jugendlichen Patientinnen mit AN einer negativen Entwicklung der kognitiven Flexibilität vorzubeugen, sind möglicherweise frühe Interventionen hilfreich.

Schlüsselwörter: Anorexia Nervosa, Jugendliche, kognitive Flexibilität, Set Shifting, Komorbidität

Anorexia nervosa (AN) is characterized by severe, self-induced weight loss and a tenacious refusal to maintain an age-specific minimum weight, driven by a significant body image distortion and an overwhelming fear of weight gain irrespective of significant underweight (American Psychiatric Association, 2003). AN is associated with high mortality rates and a chronic course of illness (Arcelus, Mitchell, Wales, & Nielsen, 2011; Steinhausen, 2009); current treatment approaches are often ineffective (Treasure, Claudino, & Zucker, 2010). In addition, AN is often accompanied by several comorbid disorders, most commonly depression and OCD (Salbach-Andrae et al., 2008; Swinbourne & Touyz, 2007; Wittchen & Hoyer, 2006). Furthermore, independent of a clinical diagnosis, patients with AN show

heightened levels of depression and OCD symptomatology when compared to healthy controls (HC; Andres-Perpina et al., 2011; Hatch et al., 2010; McAnarney et al., 2011).

A hallmark feature of patients with AN is behavioral and cognitive rigidity that often compromises the effectiveness of therapeutic interventions (Agrawal, 2009; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013). On a neuropsychological level, adults with acute as well as recovered AN show weak cognitive flexibility (Danner et al., 2012; Friederich & Herzog, 2011; Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Wu, Brockmeyer, Hartmann, Skunde, Herzog, & Friederich, 2014). Similar weaknesses were found in healthy sisters (Holliday et al., 2005) and twins (Kanakam, Raoult, Collier, & Treasure, 2013) of adolescents and adults with AN. Therefore, it is suggested that weak cognitive flexibility may be a cognitive endophenotype of AN, increasing the risk of development and maintenance of AN (Hay & Sachdev, 2011; Tenconi et al., 2010; van Autreve, Baene, Baeken, van Heeringen, & Vervaet, 2013). The biological correlates of cognitive flexibility in AN are considered in this context. For example, cognitive flexibility may be modulated by the level of agouti-related protein (Sarrar et al., 2011), whereas serum glutamine and cortisol level do not seem to be associated with neuropsychological functioning (Bühren et al., 2011; Nakazato et al., 2010). The previous findings are still too rudimentary to define biological markers of cognitive inflexibility in AN.

Cognitive flexibility is often operationalized as "set-shifting", i.e., the ability to quickly and accurately shift "back and forth between multiple tasks, operations, or mental sets" (Miyake et al., 2000). Weak cognitive flexibility may contribute to the perseverance of maladaptive thinking styles, behavioral patterns, and to rigid problem-solving approaches (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Stedal, Rose, Frampton, Landrø, & Lask, 2012). In patients with AN, this may contribute to a pathological fixation of topics like weight loss, calorie-counting, and extensive exercise routines, which lead to marked negative outcomes for the patient (Friederich, Wu, Simon, & Herzog, 2013). However, studies in juvenile AN reveal heterogeneous results demonstrating either weak set-shifting (Stedal et al., 2012) or no difficulties in performance when compared to HC (Bühren et al., 2012; Shott et al., 2012). To date, it remains unclear whether weak cognitive flexibility is present in juvenile AN.

Interestingly, cognitive flexibility was found to be impaired also in adults with either depression or OCD (see Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; McClintock, Husain, Greer, & Cullum, 2010 for an overview), while results in adolescents are inconsistent (Baune, Czira, Smith, Mitchell & Sinnamon, 2012; Klimkeit, Tonge, Bradshaw, Melvin, & Gould, 2011). Because of the connection between depression or OCD and cognitive flexibility, the question arises whether depression and/or OCD symptoms moderate cognitive flexibility in patients with AN.

Few studies have analyzed this question in adult populations, and most of these studies did not find a connection between cognitive flexibility and depression or OCD symptoms (Danner et al., 2012; Holliday et al., 2005; Roberts, Tchanturia, & Treasure, 2010; Tchanturia et al., 2004). However, some studies did show a slight connection between symptoms of depression and cognitive flexibility in adults with AN. Depression symptoms accounted for the difference in the performance on the Wisconsin Card Sorting Test (WCST) between AN and HC, but not in the performance on the Trail-Making Test Version B (TMT-B; Abbate-Daga et al., 2011). Another study suggested that symptoms of depression are connected to set-shifting (Kim, Kim, & Kim, 2010). However, set-shifting in AN and HC still differed after controlling for depression, so that depression symptoms may only partly account for set-shifting impairments. In contrast, adults with AN who were free of comorbid Axis-I-disorders did not show difficulties in set-shifting (Fassino et al., 2002; Giel et al., 2012; Murphy, Nutzinger, Paul, & Leplow, 2004), suggesting that impaired cognitive flexibility may partly result from comorbid disorders. This contradicts a study dividing patients with AN posthoc into groups with and without set-shifting impairments (Roberts et al., 2010): The groups differed neither in symptoms nor in the number of clinical diagnoses of depression or OCD.

To date, no studies have systematically analyzed the association between depression symptoms or OCD symptoms and cognitive flexibility in children and adolescents with AN. Similar to the adult literature, few studies with adolescents with AN controlled for depression while analyzing cognitive flexibility. Most of these studies found no correlation between depression and cognitive flexibility (Bühren et al., 2012; Hatch et al., 2010; Sarrar et al., 2011). Interestingly, OCD symptoms highly correlate with perfectionism, which was associated with lower set-shifting ability (Bühren et al., 2012). Adolescents with AN are free of comorbid disorders did not differ from HC with respect to cognitive flexibility measured by the TMT-B and/or WCST (Andres-Perpina et al., 2011; Castro-Fornieles et al., 2007), suggesting that comorbid disorders may influence cognitive flexibility in adolescents with AN.

The contrasting results of previous studies may partly be explained by methodological differences in terms of the use of different neuropsychological tasks and heterogeneous samples in regard to age, duration of illness, and comorbidities. The influence of symptoms of depression and OCD on cognitive flexibility was mostly analyzed as a covariate or in a correlation, without controlling for interaction effects and potential confounding variables. Some of the studies failed to include a healthy control group (Bay-

less et al., 2002) or are limited by a small sample size (Lauer, Gorzewski, Gerlinghoff, Backmund, & Zihl, 1999). Previous studies analyzed mixed samples consisting of currently ill and recovered patients (Danner et al., 2012) and/or patients with AN and bulimia nervosa together (Roberts et al., 2010), which may have distorted the results. No study systematically analyzed a wider age range or asked whether influence of depression symptoms of and OCD on cognitive flexibility differed in AN and HC. Furthermore, motor speed should be controlled for, seeing that this basic function may partly account for set-shifting impairments in AN and was found to be reduced in depression (Landrø, Stiles, & Sletvold, 2001) and OCD (Burdick, Robinson, Malhotra, & Szeszko, 2008). A connection between cognitive flexibility and clinical variables, for example, duration of illness or age of onset, was not found in most of the studies with adult AN populations (Castro et al., 2004; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996). One study analyzed the connection of duration of illness and cognitive flexibility in children and adolescents with AN and did not discover an influence of duration of illness (Shott et al., 2012). Moreover, a relationship was not consistently found between cognitive flexibility and body mass index (BMI = body weight/height^2) as a measure of starvation. Some studies found a positive connection (Dmitrzak-Weglarz, Slopien, Tyszkiewicz, Rybakowski, & Hauser, 2011; Mathias & Kent, 1998), whereas others did not (Bayless et al., 2002; Tchanturia et al., 2011; Bühren et al., 2012). Additionally, cognitive flexibility was still impaired after weight recovery and in long-term recovered patients (Danner et al., 2012; Tenconi et al., 2010). Hence, weaknesses in cognitive flexibility can only partly be explained by the level of starvation. In this context, inefficient cognitive flexibility in AN has been implicated as a stable trait-marker (Roberts et al., 2010; Tchanturia et al., 2011).

In sum, despite difficulties in cognitive flexibility in adults with AN, the results in adolescents remain inconsistent. The influence of comorbid depression or OCD on cognitive flexibility has rarely been studied in both adults and adolescents with AN. Therefore, we aim to investigate (1) whether children and adolescents with AN show impairments in cognitive flexibility, and (2) whether symptoms of depression and OCD influence cognitive flexibility. Additionally, we examine (3) the influence of the duration of illness and BMI-SDS on cognitive flexibility. To increase comparability with previous results, we additionally analyze set-shifting in two age groups: a subsample of adolescents aged 14 years and older and a subsample of children younger than 14 years of age. The division of the sample was in accordance with the concept of "early onset AN," which describes a disease onset before the age of 14 years (Fosson, Knibbs, Bryant-Waugh, & Lask, 1987).

Methods

Sample

The sample consisted of 69 female patients with AN (mean age = 14.3 years, *SD* = 2.1) and 63 female HC (mean age = 14.1 years, *SD* = 2.5). Participants ranging in age between 9.0 and 19.11 years were included. The diagnosis of AN was confirmed using a structured interview based on DSM-IV-TR criteria (SIAB-EX, Fichter & Quadflieg, 1999). Fifty-four patients fulfilled the criteria for restrictive AN, 8 patients fulfilled criteria for the binge-purge subtype. In 7 cases the SIAB-EX could not be conducted, so that the clinical diagnosis was used. The clinical sample was recruited in a German specialized treatment center for eating disorders and consisted of 8 outpatients and 61 inpatients. Data were collected within 4 weeks after the start of treatment. The recruitment of HC was achieved by distributing flyers and posters.

For all participants, body weight and height were objectively measured on the day of assessment. The BMI and BMI-SDS were calculated. Intelligence was measured via the Culture Fair Intelligence Test (CFT-20-R; Weiß, 2006), and only participants with an intelligence quotient (IQ) of more than 85 were included in the final sample. Additional exclusion criteria for HC were the presence or history of eating disorders (assessed with the SIAB-EX) or other psychiatric disorders, the presence of neurological or physical disorders, and long-term medication use, which were all systematically explored during the assessment. One patient was excluded from the sample because of an unusually long time taken to complete a task assessing motor speed, which was identified as an influential data point according to Cook's distance. Sample characteristics are presented in Table 1.

Ethical approval was obtained from the Research Ethics Board at the Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum in Germany. Written informed consent was given by the participants and their legal guardians before participation in the study.

Clinical Assessment

Depression Inventory for Children and Adolescents (DIKJ; Steinsmeier-Pelster, Schürmann, & Duda, 2000). The German version of the self-report questionnaire Children's Depression Inventory (CDI; Kovacs, 1985) was administered to assess the presence and severity of depression. Raw scores were used, since German norm data are not available for the age range of the current study.

Children's Obsessional Compulsive Inventory (ChOCI). The ChOCI (Shafran et al., 2003; German translation Kappel,

Table 1. Sample characteristics

Variable	AN (N = 69)	HC (N = 63)	t	df	p	d
	M ± SD	M ± SD				
Age (in years)	14.30 ± 2.09	14.08 ± 2.55	0.54	130	.59	0.09
BMI	15.27 ± 1.53	20.05 ± 2.78†	−12.00	92[d]	<.001	2.13
BMI-SDS	−2.07 ± 0.98	−0.14 ± 0.83†	13.91	128[d]	<.001	2.43
IQ (CFT-20-R)	107.12 ± 15.36	108.43 ± 12.37††	−0.53	127	.60	0.09
ED pathology [a]	2.93 ± 1.83º	0.40 ± 0.51ºº	10.98	78[d]	<.001	1.88
Depression (rs) [b]	18.09 ± 8.88º	5.94 ± 4.08†	10.17	96[d]	<.001	1.76
OCD symptoms (rs) [c]	13.67 ± 11.23+	5.46 ± 6.24	5.18	105[d]	<.001	0.09

Note. AN = anorexia nervosa; HC = healthy controls; IQ = intelligence; CFT-20-R = Culture Fair Test (Weiß, 2006); ED = eating disorder; rs = raw score; OCD = obsessive-compulsive disorder.
†n = 62; ††n = 60; ºn = 68; ººn = 61; +n = 67.
[a] Global score from the (Child) Eating Disorder Examination-Questionnaire (ChEDE-Q Hilbert, Hartmann & Czaja, 2008; EDE-Q Hilbert, Tuschen-Caffier, Karwautz, Niederhofer & Munsch, 2007).
[b] Depression inventory for children and adolescents (DIKJ; Stiensmeier-Pelster et al., 2000).
[c] Children's Obsessional Compulsive Inventory (ChOCI; Kappel et al. 2012; Shafran et al., 2003).
[d] Differences in degrees of freedom result from the usage of a Welch-Test for these variables.

Gries, & van Noort, 2012) is a self-report questionnaire assessing the content and severity of OCD symptoms in children and adolescents. In the present study, the total score of impairment associated with OCD symptoms was used as a measure of severity. Since there are no norm data available, raw scores were used.

Neuropsychological Assessment

Trail-Making Test (TMT). Two subtests of the TMT from the Delis-Kaplan Executive Functioning System (D-KEFS; Delis, Kaplan, & Kramer, 2001) were used. The TMT Condition 4 (TMT 4): *Number-Letter Switching*, which is comparable with the traditional TMT Version B (Lezak, 2004; Reitan & Wolfson, 1985), is a visual-motor sequencing task assessing set-shifting. This paper-and-pencil task requires the graphical connection between circles containing numbers and letters. Participants are instructed to switch back and forth between connecting numbers or letters and the time taken (in s) to complete is the measure of set-shifting ability. To control for motor speed as a key component necessary for performing the switching task (TMT 4), the TMT Condition 5 (TMT 5) was also administered. The time (in s) taken to connect all circles by drawing a line along a designated pathway is the measure of motor speed. Raw scores are used due to missing German norm data.

Statistical Analyses

IBM SPSS Statistics 22 was used for data analysis. Between-group differences in sample characteristics were examined using *t*-tests for independent samples. Hierarchical multiple regression analysis was performed to calculate the effect of age, motor speed, group, depression symptoms, and OCD symptoms as well as the interactions between these variables on set-shifting performance. In the AN group, duration of illness and BMI-SDS were included. Group membership was dummy-coded with HC as the reference group. All predictors were centered on their grand mean to reduce multicollinearity. The predictors were added gradually in the analysis with an order of steps derived from theoretical assumptions and previous research (Field, 2005). The models were compared using *F*-tests to examine whether the entry of a predictor contributed to a significant change in coefficient of determination R^2. By a nonsignificant increase in the explained variance, the predictor was excluded from the model and further analysis. In order to accurately compare results of the present study with previous studies, both analyses were conducted with and without motor speed as a predictor. The statistical assumptions for multiple regressions were met (normal distribution, reliable measurement of variables, independence of observations, no perfect multicollinearity, homoscedasticity, independent and normally distributed errors, a linear relationship between the independent

and dependent variables). Missing data were excluded listwise to allow for testing of change in R^2. In addition, two exploratory hierarchical multiple regression analyses were performed for (1) adolescents aged 14 years and older and (2) children younger than 14 years of age. The variables and procedure were the same as for the total sample.

Results

Compared to HC, AN patients showed significantly higher depression and OCD symptoms (see Table 1). With regard to motor speed, the AN group (M = 24.22, SD = 7.86) did not differ significantly from HC (M = 24.68, SD = 8.32; t (129) = −0.33, p = .75). Table 2 contains the coefficients of determination, their change after entering further predictors, and statistical significance. In the first step, age and motor speed were used to predict set-shifting. To test the first hypothesis, the group membership to AN or HC was included, which did not significantly change the coefficient of determination (step 2). Patients with AN did not differ significantly from HC in their set-shifting ability. The influence of age on set-shifting did not differ between AN and HC (step 3).

The following steps tested the hypothesis whether depression or OCD symptoms influence set-shifting (hypothesis 2). Depression symptoms accounted for 0.4 % of the variance in set-shifting and were no significant predictor (step 4a). The influence of depression symptoms on set-shifting did not differ between AN and HC (step 4b). This relationship was not moderated by age (step 5a), nor did age influence the relationship between depression symptoms and set-shifting differently in AN and HC (step 5b). Hypothesis 2a was rejected accordingly.

OCD symptoms accounted for 0.0 % of the variance and did not significantly predict set-shifting (step 6a). AN and HC did not differ in the influence of OCD symptoms on set-shifting (step 6b). Age was not a significant moderator of the relationship between OCD symptoms and set-shifting (step 7a). The moderating role of age on this relationship did not differ between AN and HC (step 7b). Hence, hypothesis 2b was rejected. The regression model did not change when motor speed was excluded from the prediction.

The coefficient of determination of the final model, which includes the variables age and motor speed, was R^2 = .302. This corresponds to a large effect size of f^2 = .43. The unstandardized regression coefficients can be found in the following Equation 1: set-shifting = 63.83** − 0.31 age** + 0.73 motor speed** (where **p < .001). The relationship between these variables is visualized in Figure 1.

To test the third hypothesis concerning the influence of duration of illness and BMI-SDS, an identical analysis was computed within the AN sample (N = 69). Results showed no influence of duration of illness (β = −0.06, p = .741) and BMI-SDS (β = 0.06, p = .830) on set-shifting ability. Furthermore, motor speed was not a significant predictor, resulting in a final model that solely includes age: Equation 2: set-shifting = 62.24** − 0.29 age* (where *p < .05, **p < .001) with R^2 = .13 and a small effect size of f^2 = .01.

Table 2. Explanation of variance by the hierarchical entry of variables predicting set-shifting (N = 132)

Step	Predictor	R^2	ΔR^2	ΔF (df_1, df_2)	p
1	Age + motor speed	.295	.302	26.852 (2, 124)	<.001
2	+ group (AN/HC)[a]	.310	.008	1.396 (1, 123)	.24
3	+ age x group[a]	.311	.009	1.544 (1, 123)	.22
4a	+ depression[a]	.306	.004	0.630 (1,123)	.43
4b	+ depression x group[a]	.311	.009	0.502 (3, 121)	.68
5a	+ depression x age[a]	.322	.020	1.793(2, 122)	.17
5b	+ depression x age x group[a]	.318	.016	0.943 (3, 121)	.43
6a	+ OCD symptoms[a]	.302	.000	0.003 (1, 123)	.96
6b	+ OCD symptoms x group[a]	.317	.015	0.898 (3, 121)	.45
7a	+ OCD symptoms x age[a]	.314	.012	1.049 (2, 122)	.36
7b	+ OCD symptoms x age x group[a]	.319	.017	1.001 (3, 121)	.40

Note. α = .05. AN = anorexia nervosa; HC = healthy controls; df_1 = degrees of freedom of numerator; df_2 = degrees of freedom of denominator.
[a] This predictor has been excluded from further analyses due to the nonsignificant change in R^2.

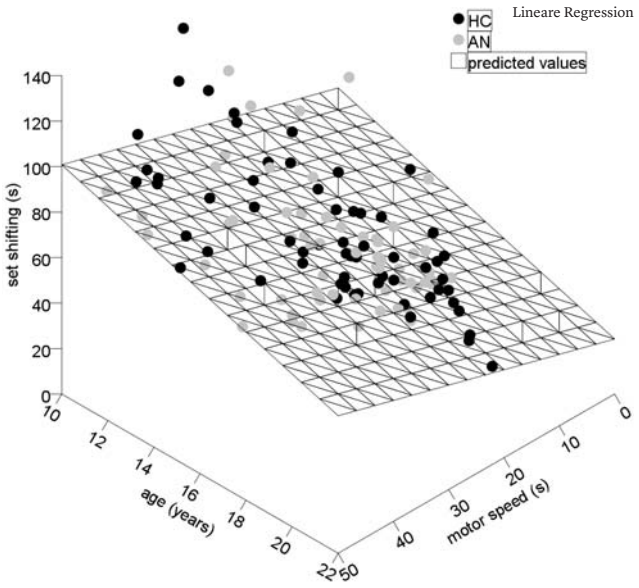

Figure 1. Relationship between the variables of the final regression model: age (in years), motor speed (in seconds), and set-shifting (in seconds) in AN and HC (since the variables do not differ between the groups, the predicted values are shown across the groups); s = seconds.

For an exploratory data analysis, the sample was divided into two age groups. The two groups of patients (adolescents ≥14 years, children <14 years) did not differ in BMI-SDS (adolescents: M = –1.05, SD = 1.52, children: M = –0.98, SD = 1.32; t (129) = –2.68, p = .789). The exploratory analysis was computed in the subsample of adolescents aged 14 years and older (n_{AN} = 41; n_{HC} =35). The results concerning hypotheses 1 and 2 were identical to the results of the whole sample. Interestingly, the influence of age on set-shifting was different: Age was not a significant predictor of set-shifting across AN and HC but differed significantly between both groups in this subsample. The unstandardized regression coefficients are shown in Table 3. The coefficient of determination was R^2 = .12 (medium effect size of f^2 = .14). In the HC group, the influence of age on set-shifting was not significant. Using an inverted dummy coding, the influence of age in the AN group (β = 0.43; p = .05) and the difference of the influence of age on set-shifting between AN and HC (β = –0.60; p = .03) were significant. In the adolescent HC subsample, age did not change set-shifting performance. In the adolescent AN subsample, older participants showed a slower set-shifting performance. This connection remained stable even after controlling for the duration of illness and BMI-SDS in the AN subsample.

The results of an identical analysis in the subsample of children younger than 14 years (N_{AN} = 28; N_{HC} = 28) showed that age was the only significant predictor (see Table 3) with no differences between AN and HC.

Discussion

In this study, cognitive flexibility and the potential influence of depression symptoms, OCD symptoms, duration of illness, and BMI-SDS on this ability were analyzed in a large sample of children and adolescents with AN compared to HC. Contradictory to our hypotheses, there were no differences in cognitive flexibility between juvenile patients with AN and HC. Moreover, depression symptoms, OCD symptoms, duration of illness, and BMI-SDS did not moderate set-shifting.

Our results are in accordance with previous studies, demonstrating no differences in cognitive flexibility in adolescents with AN and HC (Andres-Perpina et al., 2011; Dmitrzak-Weglarz et al., 2011; Fitzpatrick, Darcy, Colborn, Gudorf, & Lock, 2012; Hatch et al., 2010). However, other studies in juvenile AN did demonstrate subtle weak-

Table 3. Results of exploratory regression analyses examining set-shifting in a subsample of adolescents ≥ 14 years (n = 76) and a subsample of children < 14 years (n = 56)

	Adolescents ≥ 14 years				Children < 14 years			
Variable	b	SE	t (df = 74)	p	b	SE	t (df = 52)	p
Intercept	56.87	2.53	22.46	<.001*	76.49	4.40	17.38	<.001*
Age	–0.17	0.16	–1.07	.286	–0.86	0.29	–2.93	.005*
Motor speed	0.77	0.26	2.93	.005*	0.52	0.39	1.31	.196
Group	1.89	3.44	–0.55	.585	6.27	6.29	–0.55	.582
Age x group	0.60	0.27	2.26	.027*	0.37	0.37	1.84	.072

Note. Adolescents ≥ 14 years: R^2 = .17; children < 14 years: R^2 = .25; α = .05.

nesses in set-shifting compared with HC or norm data (Sarrar et al., 2011; Shott et al., 2012; Stedal et al., 2012). These inconsistencies may be explained by the suggestion that only a subgroup of patients shows impaired cognitive flexibility (Andres-Perpina et al., 2011; Lauer et al., 1999). A recent case series reported a high variability in neuropsychological profiles of children and adolescents with AN (Rose, Frampton, & Lask, 2012), indicating subgroups with and without distinct cognitive weaknesses. Our results contradict findings in adults with AN demonstrating weaknesses in cognitive flexibility (Danner et al., 2012; Friederich & Herzog, 2011; Holliday et al., 2005; Roberts et al., 2007; Tenconi et al., 2010). However, because of differences in brain maturation between young and adult patients with AN, only a limited comparability of studies in different age groups is given (Bühren, Holtkamp, Herpertz-Dahlmann, & Konrad, 2008).

In accordance with previous results, symptoms of depression and OCD did not moderate cognitive flexibility in juvenile AN after controlling for age and motor speed (Andres-Perpina et al., 2011; Hatch et al., 2010; Sarrar et al., 2011). Additionally, the influence of depression and OCD symptoms on cognitive flexibility did not differ between AN and HC. However, studies in adolescents (Andres-Perpina et al., 2011; Castro-Fornieles et al., 2007) and adults (Fassino et al., 2002; Giel et al., 2012; Storch et al., 2004) with AN indicate an influence of comorbid diagnosis rather than self-reported depression or OCD symptoms. For further differentiation, future studies should explore cognitive flexibility in different subgroups with AN with and without comorbidities as well as in patients with pure depression or OCD diagnosis.

Consistent with previous research, cognitive flexibility improved with increasing age in AN as well as in HC (Kalkut, Han, Lansing, Holdnack, & Delis, 2009). Interestingly, in the subgroup of patients aged 14 years and older, cognitive flexibility declined with increasing age, while in younger patients cognitive flexibility increased with age. Because of the cross-sectional nature of this study, one can only speculate whether the development of cognitive flexibility may be negatively affected by the illness.

In accordance with previous findings, duration of illness and BMI-SDS did not significantly predict set-shifting ability in AN (e.g., Bühren et al., 2012; Castro et al., 2004; Shott et al., 2012). Thus, set-shifting ability seems to be independent of these clinical variables, and the level of starvation may not alter cognitive flexibility in children and adolescents with AN. However, other findings suggest that set-shifting and BMI are associated, i.e., set-shifting ability is lower when weight decreases (Dmitrzak-Weglarz et al., 2011). It seems that at this point it is not possible to arrive at a definite conclusion regarding this association. Longitudinal studies are needed to examine the development of cognitive flexibility in AN patients over the course of their illness at different bodyweight-levels.

Particular strengths of the current study are the rather large sample size and the focus on children and adolescents, since there are very few studies focusing on this age group. Furthermore, age and motor speed as possible confounding variables were controlled for. Structured interviews to validate the clinical diagnosis of AN were used.

Some limitations reduce the generalizability of the results. First of all, self- report measures were used to assess symptoms of depression and OCD. Additionally, no norm data were available for some of the measures, and raw scores were used in the analyses. The norm data of the depression inventory DIKJ were limited to the age range 8 to 16 years. Nevertheless, to achieve comparability, we used the DIKJ also in participants aged 17 to 19 years. Second, future studies should consider structured interviews to achieve greater objectivity of the severity of comorbid clinical symptoms. Third, because of scheduling difficulties, the measurements took place at different points during the treatment. This may have influenced certain variables, particularly the severity of depression and BMI. Fourth, only one measure for set-shifting was used for cost-effectiveness. Despite the frequent use of the TMT, it provides a one-directional approach to cognitive flexibility. Another frequently used measure is the WCST. The TMT may not be sensitive enough to detect potential subtle weaknesses in cognitive flexibility in adolescents as opposed to the more severe weaknesses in adult AN. Therefore, future examinations of cognitive flexibility in juvenile AN may consider a more sensitive measure, e.g., the WCST. Finally, neuropsychological tests may pose a problem to accurately assessing clinically observed behavioral and cognitive inflexibility in adolescents with AN. Self-report as well as parent ratings of cognitive flexibility in adolescents partly deviate from neuropsychological results (McAnarney et al., 2011). The question arises whether neuropsychological tests, in general, allow an ecologically valid measurement of cognitive inflexibility observed in everyday life (Fassino et al., 2002) and whether they are associated with rigid thinking and behavioral patterns (Stedal et al., 2012).

Conclusion

While previous studies demonstrated weak cognitive flexibility in adults with AN, cognitive flexibility does not seem to be compromised in juvenile AN. This challenges the hypothesis of cognitive flexibility as a possible endophenotype of AN. Although juvenile AN patients are characterized by obsessionality, rigidity, and perfection-

ism (Halmi et al., 2012; Herpertz-Dahlmann, Seitz, & Konrad, 2011), these features do not seem to be associated with a reduced cognitive flexibility measured with neuropsychological tests. Moreover, comorbid symptoms of depression and OCD do not moderate cognitive flexibility in children and adolescents with AN. These findings help us to refine neuropathological models of AN and aid in the develop of new treatment approaches. Our findings suggest a decline in set-shifting with increasing age in adolescents with AN. Therefore, early trainings of cognitive flexibility, such as cognitive remediation therapy (Tchanturia, 2015), may be helpful in strengthening cognitive flexibility and preventing later impairments (as found in adults with AN by Danner et al., 2012; Friederich & Herzog, 2011; Holliday, Tchanturia, Landau, Collier, & Treasure, 2005). A first case report of a young girl with AN receiving cognitive remediation therapy describes its successful implementation followed by a positive disease course (van Noort, Pfeiffer, Lehmkuhl, & Kappel, 2015).

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Dr. phil. Dipl.-Psych. Viola Kappel
Charité-Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy
Augustenburger Platz 1
13353 Berlin
Germany

viola.kappel@charite.de

