



Increased cognitive flexibility mediates the improvement of eating disorders symptoms, depressive symptoms and level of daily life functioning in patients with anorexia nervosa treated in specialised centres

Philibert Duriez, Héline Kaya Lefèvre, Laura Di Lodovico, Odile Viltart,
Philip Gorwood

► To cite this version:

Philibert Duriez, Héline Kaya Lefèvre, Laura Di Lodovico, Odile Viltart, Philip Gorwood. Increased cognitive flexibility mediates the improvement of eating disorders symptoms, depressive symptoms and level of daily life functioning in patients with anorexia nervosa treated in specialised centres. *European Eating Disorders Review*, 2021, 29 (4), pp.600-610. 10.1002/erv.2829 . inserm-03203038v2

HAL Id: inserm-03203038

<https://inserm.hal.science/inserm-03203038v2>

Submitted on 5 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Title: Increased cognitive flexibility mediates the improvement of eating disorders symptoms, depressive symptoms and level of daily life functioning in patients with anorexia nervosa treated in specialized centers

Running title: cognitive flexibility in anorexia nervosa

Philibert Duriez^{1,2}, Héline Kaya Lefèvre^{1,3}, Laura Di Lodovico^{1,2}, Odile Viltart^{2,4}, Philip

Gorwood^{1,2}

Affiliations:

¹GHU Paris Psychiatrie et Neurosciences, Hôpital Sainte-Anne, CMME, F-75014 Paris, France

²Université de Paris, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, F-75014 Paris, France

³Université de Paris, LPPS, F-92100 Boulogne-Billancourt, France

⁴Cité scientifique, SN4, Université de Lille, 59491 Villeneuve d'Ascq, France

For correspondance : Héline Kaya Lefèvre, PhD. Hôpital Sainte-Anne (Clinique des Maladies Mentales et de l'Encéphale), 100 rue de la Santé. 75674 PARIS Cedex 14. FRANCE

e-mail: h.kaya_lefevre@ghu-paris.fr

The study protocol was approved by *Comité de Protection des Personnes Ile de France III* (EUDRACT N°: 2008-A008 17-48; CPP N°Am5355-2-2592).

Data availability statement: the data generated and analyzed during the current study are available from the corresponding author on request.

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgment: none

Conflict of interest: Philip Gorwood received during the last 5 years fees for presentations at congresses or participation in scientific boards from Alcediag-Alcen, Angelini, GSK, Janssen, Lundbeck, Otsuka, SAGE and Servier. Philibert Duriez, Héline Kaya Lefèvre, Laura Di Lodovico and Odile Viltart declare that they have no conflict of interest.

ABSTRACT

Objective: poor cognitive flexibility has been highlighted in patients with anorexia nervosa (AN), contributing to the development and maintenance of symptoms. The aim of the present study is to investigate how enhanced cognitive flexibility is involved in treatment outcomes in patients with AN. **Method:** one-hundred and thirty female out-patients treated for AN have been assessed at baseline and after four months of treatment. Path analyses were used to investigate the mediating role of cognitive flexibility, measured through the Brixton test, on a wide range of outcomes: body mass index, eating disorder symptoms, daily life functioning, anxiety, depression, emotions, self-rated silhouette. **Results:** cognitive flexibility was improved during treatment, and enhanced cognitive flexibility explains a significant part of level of the improvement in daily life functioning (26%), reduction of eating disorder symptoms (18%) and reduction of depressive symptoms (17%). Others outcomes were also improved, but these improvements were not mediated by cognitive flexibility. **Conclusions:** results suggest that enhancing cognitive flexibility could help reduce rigid cognitive and behavioural patterns involved in AN, thus improving everyday functioning and clinical severity. Further studies combining different types of cognitive flexibility evaluation as well as neuroimaging may be necessary to better establish which of its aspects are involved in patients' improvement.

Keywords: anorexia nervosa; cognitive flexibility; eating disorders; depressive symptoms; treatment efficacy

HIGHLIGHTS

- Cognitive flexibility is improved with 4 months of usual treatment for anorexia nervosa and increased cognitive flexibility explains a significant part of clinical improvement
- Enhancing cognitive flexibility may help to improve daily-life functioning, depressive symptoms and anorexia nervosa symptoms
- Results support the use of therapeutic strategies focused on cognitive remediation in patients with anorexia nervosa

INTRODUCTION AND AIMS

Anorexia nervosa (AN) is a mental disorder mainly characterized by severe and self-induced weight loss, refusal to maintain a minimum weight, body distortion, and excessive fear of gaining weight (American Psychiatric Association, 2003). It is currently the psychiatric disorder with the highest mortality rate (Arcelus et al., 2011; Franko et al., 2013). Patients with AN in specialized centers are treated by different therapeutic approaches, such as family interventions (Watson & Bulik, 2013), nutritional interventions, cognitive and behavioral therapy or interpersonal therapy (Brockmeyer, Friederich & Schmidt, 2017). Overall, treatment for AN has been mainly focused on eating and weight symptoms (Treasure & Schmidt, 2013).

However, relapses are frequent as, for example, treatment response may be influenced by premorbid vulnerabilities (Treasure & Russel, 2011; Treasure & Schmidt, 2013). Patients with AN are often characterized by behavioral rigidity, obsessional personality traits and ritualized behaviors (Cassin & van Ranson, 2005; Herpertz-Dahlmann et al., 2008; Friederich & Herzog, 2011). Stereotypes and rigid behaviors mostly concern control of weight, eating and body shape, but patients with AN have also been shown to demonstrate symmetry obsessions and order compulsions (Friederich & Herzog, 2011). It has been suggested that neurocognitive inefficiencies may underlie these behaviors (Friederich & Herzog, 2011).

Cognitive inefficiencies such as poor cognitive flexibility exist in patients with anorexia nervosa (for recent meta-analysis, see Keegan, Tchanturia & Wade, 2020), and appear to play an important role in the development and maintenance of the disorder (Fassino et al., 2002; Pendleton-Jones et al., 1991; Tchanturia et al., 2001, 2002, 2004). Cognitive flexibility refers to the ability to shift between multiple tasks, operations, or mental sets (Miyake et al., 2000) and can be measured through different types of tasks such as the Trail Making Task (TMT,

Reitan, 1958), the Wisconsin Card Sorting Test (WCST, Berg, 1948), or the Brixton Test (Burgess & Shallice, 1997).

Cognitive dysfunctions can be a consequence of starvation (Keys et al., 1950; Katzman et al., 2001; Roberts et al., 2007), malnutrition leading to functional and structural changes in the brain (Leppanen, Adamson & Tchanturia, 2018; Fonville et al., 2014); but impaired cognitive flexibility is also considered a risk factor for anorexia nervosa (Steinglass, Walsh & Stern, 2006). Poor cognitive flexibility remains in recovered patients with AN (Wu et al., 2014; Friederich & Herzog, 2011; Danner et al., 2012; Tchanturia et al., 2012) and is shared by healthy relatives (Friederich & Herzog, 2011; Holliday et al., 2005; Kanakam et al., 2013), which suggest that it may constitute an endophenotype of the disorder increasing the risk of development and maintenance of AN. These findings imply that impaired cognitive flexibility can be considered a trait characteristic rather than a temporary state due to starvation (Sato et al., 2013). However, recovered patients with past AN have better performance than currently ill patients, suggesting that cognitive flexibility can be improved in therapy (Tchanturia et al., 2012).

Poor cognitive flexibility can be involved in the perseverance of maladaptive and rigid cognitive and behavioral patterns (Roberts et al., 2007; Stedal et al., 2012). It can contribute to the maintenance of clinical symptoms in AN (Sato et al., 2013; Steinglass, Walsh & Starn, 2006) such as fixation on weight loss, weight control and calories counting, excessive exercise routines (Rößner et al., 2017), or even body distortion image. The latter might be of particular interest as reducing body image flexibility is a predictor of eating disorders (Pellizer, Waller & Wade, 2018). According to the cognitive-interpersonal maintenance model, inflexibility and rigid habits are reinforced by successfully leading to the goal of weight loss, thereby creating a vicious circle which maintains the disorder (Treasure and Schmidt, 2013). Therefore, one

could imagine that cognitive flexibility may be involved in AN severity and course of illness. Indeed, inefficiencies in cognitive flexibility are associated with treatment resistance (Sato et al., 2013; Treasure & Schmidt, 2013), but several studies found no correlation with body weight (Fassino et al., 2002; Roberts, Tchanturia & Treasure, 2010; Holliday et al., 2005).

Poor cognitive flexibility in anorexia nervosa has been clearly established. However, we do not know to what extent the clinical improvement of AN can be mediated by enhanced cognitive flexibility; despite previous literature suggesting that cognitive flexibility may play a significant role in treatment outcomes. Such question could be analyzed in a cohort study and by using pathway analysis, where mediators are being distinguished from risk factors. We therefore used in this present study a protocol (Gorwood et al., 2019) allowing such distinction.

This study aims to explore the mediating role of enhanced cognitive flexibility on treatment outcomes in patients with AN treated in specialized centers. We chose to rely on a variety of outcomes used in studies investigating treatment efficacy in AN: Body Mass Index (BMI) and level of severity of AN symptoms are among the most frequent, but some studies rather focus on the tendency to correct how one assesses his/her own silhouette, how mood (positive and negative emotions) is improved (Bodell & Keel, 2010), or even on the improvement of functioning in daily life (Mitchison et al., 2013). Anxiety and depressive symptoms were also taken into account, previous studies suggesting that they are negatively impacted by altered cognitive flexibility (Johnco, Wuthrich & Rapee, 2014; Maramis, Mahajudin & Khotib, 2020). Considering that poor cognitive flexibility appears to be a risk factor of AN and could be involved in the maintenance of symptoms, we made the hypothesis

that enhanced cognitive flexibility was a significant mediator of positive outcomes in patients with AN.

METHOD

Participants and procedure

Two-hundred and ten (N=210) female out-patients with AN were initially recruited in 13 eating disorders specialized centers throughout France. All patients were assessed during a face-to-face interview with a psychiatrist with at least five years of experience in eating disorders, and were included when fulfilling the DSM 5 criteria for anorexia nervosa (American Psychiatric Association, 2013).

We excluded patients that were lost to follow-up, and others patients were excluded because there was mandatory data missing such as their initial BMI or their age. The final sample was therefore composed of 61% from the whole sample (N=130).

Participants who did not attend the follow-up visit had a center effect ($\chi^2=29.257$, $df=12$, $p=0.004$), and were characterized by a higher initial (16.128, $SD= 2.966$; $F=5.116$, $p=0.025$), minimum (13.919, $SD=2.159$; $F=8.397$, $p=0.004$), and highest (21.970, $SD=5.666$; $F=4.441$, $p=0.036$) BMI, and fewer positive (26.05, $SD=7.986$; $F=6.534$, $p=0.011$) and negative (26.04, $SD=6.641$; $F=55.982$, $p<0.001$) emotions according to the results of PANAS (Gorwood et al., 2019).

The care provided for patients can vary between centers, but consistently includes a multidisciplinary approach involving both a psychiatrist or a psychologist and a nutritionist or a dietician, and all patients are offered at least one recognized psychological approach to

eating disorders (family therapy, cognitive-behavioral therapy, interpersonal therapy...), as well as psychotropic drugs when needed (primarily anti-depressants).

Patients were assessed at admission and approximately four months later. In the end, the average time period between first and second evaluation was 121.47 days.

The study protocol was approved by *Comité de Protection des Personnes Ile de France III* (EUDRACT N°: 2008-A008 17–48; CPP N°Am5355-2-2592). All patients gave written informed consent prior to participation. All data was recorded anonymously. The study was conducted according to ethics recommendations from the Helsinki declaration (World Medical Association, 2013).

Instruments

Clinical assessments included questions regarding socio-demographic data (age, educational level, working activity, familial history of eating disorder), as well as clinical data such as age of onset and current, ideal and lifetime maximum and minimum Body Mass Index (BMI).

Eating disorder symptoms were assessed using the Eating Attitudes Test – 26 (EAT 26) (Garner & Garfinkel, 1979; Leichner et al., 1994), composed by three subdivisions: “bulimia”, “dieting”, and “oral control” (Garner & Garfinkel, 1979). Patients also undertook a body image perception test, where they were instructed to choose the silhouette that most closely represents their current body when viewing a diagram representing the progression of ten female silhouettes from 1 (underweight) to 10 (overweight), each corresponding to a specific BMI (Williamson et al., 1993). Body image distortion is therefore determined by the difference between the image chosen by the patient and the image corresponding to the patient’s present BMI.

Functioning in daily life was assessed using the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002), assessing the level of impairment in the ability to work, manage the home, engage in social and private activities, and maintain close relationships.

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), consisting of two 7-items scales, one for anxiety symptoms, and one for depressive symptoms. The emotional state was assessed using the Positive and Negative Affect Schedule (PANAS) which measures current mood state and consist of two 10-items scales, one for positive affects, and one for negative affects.

Finally, cognitive flexibility was assessed using the Brixton Test (Burgess & Shallice, 1997; Tchanturia et al., 2011). Participants were asked to predict the movements of a blue circle, which changes location after each response. A concept (rule) has to be inferred from its movements to make accurate predictions. Occasionally, the pattern of movement changes, and participants have to abandon the old concept in favor of a new one. Previous research suggests that there exists no practice effect for this test (Burke et al., 2014, van den Berg et al., 2009).

Statistical analysis

We performed analyses using the SPSS® statistical package for social sciences version 17.0 (IBM, Delaware, Chicago). Data distributions were checked for normality using Kolmogorov-Smirnov Test prior to analyses.

Differences between baseline and follow-up were compared using Student t-test for paired sample, and effect size was calculated using Cohen's d (Sawilowsky, 2009; Cohen, 1988).

Path analyses were conducted using the PROCESS macro for SPSS, in order to test for the mediating role of cognitive flexibility improvement in the impact of treatment on positive outcomes. Separate analyses were carried out for each outcome variable. Cognitive flexibility was entered as the mediator, treatment was the independent variable, and the treatment outcome was entered as the dependent variable.

RESULTS

Among the final sample of 130 patients, the mean age was 25.95 years old (SD=8.25), the mean age of onset was 17.24 years old (SD=4.86), and the average BMI at baseline was 15.52 (SD=1.75).

All variables were improved following treatment. The effect was the largest on decrease of eating disorder symptomatology ($d=0.48$), then, in descending order, higher BMI ($d=0.45$), less negative emotions assessed through the PANAS ($d=0.41$), lower level of depressive symptoms ($d=0.40$), lower level of anxiety ($d=0.37$), less silhouette distortions ($d=0.31$), lower level of dysfunctioning according to the WSAS ($d=0.28$), and more positive emotions ($d=0.20$) (**Table 1**).

Cognitive flexibility was also improved ($d=0.37$) (**Table 1 and Figure 1**) and had a direct significant effect on eating disorder symptoms ($\beta=-0.29$, $p<.001$), daily life functioning ($\beta=-0.16$, $p<.001$) and depressive symptoms ($\beta=-0.05$, $p=.012$) (**Figure 2 and Table 2**).

Mediation analysis showed that these three improved outcomes were partially explained by a collinear effect of the treatment on cognitive flexibility, explaining 26% of the improvement of daily life functioning, 18% of the reduction of eating disorder symptoms and 17% of lower depressive symptoms (**Figure 2 and Table 2**). The bootstrapping indirect effect

of treatment on daily life functioning (CI 95% [(-1.412) – (-0.295)]), eating disorder symptoms (CI 95% [(-2.404) – (-0.482)]) and depressive symptoms (CI 95% [(-0.477) – (-0.050)]) through enhanced cognitive flexibility was significant (confidence intervals not including 0).

There was no evidence suggesting that cognitive flexibility mediates the improvement of others outcomes, considering that Brixton scores were not associated with BMI ($p=0.448$), positive ($p=0.943$) and negative emotions ($p=0.234$), anxiety (0.058) or silhouette distortion ($p=0.079$). BMI was the least influenced by the improvement of cognitive flexibility (3%).

DISCUSSION

In this cohort of patients with anorexia nervosa treated for four months in specialized centers for eating disorders, a significative improvement of all clinical, physiological, functional and cognitive variables was observed.

Previous studies suggest that poor cognitive flexibility could be a stable marker of AN (Filoteo et al., 2014; Tchanturia et al., 2011). At first, our results might not fit such hypothesis, considering that cognitive flexibility appears to significantly improve during treatment. However, previous studies have shown that in spite of an improvement of cognitive flexibility in recovered patients with AN, their performance remains lower compared to controls participants (Roberts et al., 2007; Tchanturia et al., 2004).

In line with our hypothesis, the improvement of cognitive flexibility mediates the impact of treatment on some outcome variables, such as the level of functioning in daily life, the severity of eating disorders and the intensity of depressive symptoms.

These results are in line with previous literature showing that patients with poor clinical outcome performed worse at baseline on both TMT-B and the WCST suggesting that

cognitive flexibility may be a predictor of the immediate ability to recover (Harper et al., 2017). Another study showed that regional brain activation associated with set-shifting (using the Wisconsin Card Sort Test) predicted treatment response in 21 females with AN who were treated for 8 to 16 weeks (Garrett et al., 2014).

Fronto-striatal alterations during instrumental learning, particularly within the caudate body, offer therefore a nice interpretation of these different findings, where habit-driven are favored at the expense of reward seeking (Duriez et al., 2019). Excess of habit formation has been recently described as correlated to a lack of cognitive flexibility measured by TMT in restrictive-type AN and associated to dorsal striatum functioning in a mice model (Favier et al., 2020). Habits strength was also related to severity and longer course of AN (Davis et al., 2020). Together, these findings help understanding how cognitive flexibility and perseverative tendencies may be involved in a large range of high-order processes, contributing to the development and maintenance of anorexia nervosa. This is also in line with the idea that cognitive flexibility could constitute an intermediate factor which could be used for the improvement of anorexia nervosa. This hypothesis also nicely fits the observation of the high level of psychiatric comorbidity observed in patients with AN, such as Autistic Spectrum Disorders (ASD) (Westwood et al., 2016) and obsessive-compulsive disorder (OCD) (Halmi et al., 2005; Friederich & Herzog, 2011), those two disorders being also characterized by high cognitive rigidity and perseverative tendencies. A large correlation ($r=0.5$) has indeed been observed between the polygenic risk score of AN and OCD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

On the other hand, improved cognitive flexibility had a very limited role in the improvement of others parameters such as BMI. The lack of a significant role of cognitive

flexibility in the increase of BMI in patients treated for AN has already been shown (1) in a study also using the Brixton test (Tchanturia et al., 2011) when distinguishing controls, patients with acute AN and recovered patients, (2) in another one finding no correlation between BMI and the WCST (Fassino et al., 2002), and (3) in a third one conducted among adolescents treated by an integrated model of psychotherapy (Kucharska et al., 2019).

This study has several limitations. The main limitation of this study is the lack of a control group, preventing us from definitive conclusions regarding the impact of treatment. Several patients were also lost at post-treatment, although this attrition rate can be considered usual in such longitudinal protocols. Patients that were lost at follow-up displayed higher BMI and less negative and positive emotions, which limits the representativeness of the final sample. Regarding representativeness, it is also interesting to note that, using the WSAS, our sample had significantly lower level of daily-life functioning at baseline (mean=23.43) compared to other relatively similar sample which ranged between 16 to 20 (Bramford et al., 2015; Touyz et al., 2013).

Furthermore, only one instrument has been used to assess cognitive flexibility, the Brixton test which mainly focuses on reversal learning (i.e., the ability to switch between a previously learned rule to a new one). It would be interesting to try and reproduce these findings while combining the Brixton to other tasks, for example by focusing more on attentional set-shifting (using for example the TMT, i.e. switching attention between numbers and letters). Such investigations would be especially relevant considering that 1) tests assessing cognitive flexibility sometimes provide discrepant results (such as TMT and the WCST in Abbate-Daga et al., 2011) and 2) attentional set-shifting and reversal learning have distinct neural correlates (Wildes, Forbes & Marcus, 2014). Cognitive flexibility is in fact a

large, complex and multidimensional concept which is assessed through a variety of tasks (Wildes, Forbes & Marcus, 2014); and further studies are needed to better establish which of its aspects are involved in AN vulnerability and patients' response to treatment. Another aspect is that the Brixton had limited improvements over time when considering the small effect size ($d=0.37$). On the other hand, to reduce the attrition rate the length of the cohort was only 4 months, such a short interval probably precludes obtaining large improvements. The link between cognitive flexibility and functioning in daily life should therefore be tested on larger time intervals.

Finally, it is also important to note that the learning effect was not controlled, even though a practice effect for the Brixton test is unlikely (van den Berg et al., 2009, Burke et al., 2014). It is difficult to guess its impact as the repetition effect could be relatively homogeneous in all patients and more or less independent of the mediator analyses performed herein. However, it would be interesting to reproduce the results using the alternate forms of the TMT which display strong test-retest reliability (Wagner et al., 2011; Atkinson et al., 2007, 2009).

From a clinical perspective, results suggest that enhancing cognitive flexibility could help reduce rigid cognitive and behavioral patterns involved in AN and that the reduction of such inflexible thinking styles and behavioral rituals could also help improve everyday functioning and reduce depressive symptoms.

The mediating role of enhanced cognitive flexibility on both eating disorder (ED) symptoms and level of depression is particularly interesting, considering the high comorbidity between EDs and Major Depressive Disorder (MDD) (between 50% to 75%) (American psychiatric Association Workgroup on Eating Disorders, 2006). MDD comorbid with EDs has in

fact been associated with worse ED outcome (Berkman et al., 2007; Lowe et al., 2001), and higher rates of both suicide attempts and suicide mortality in EDs (Forcano et al., 2009; Bulik et al., 2008; Crow et al., 2009). Previous studies also found that depressive symptoms in AN patients were not improved with usual antidepressant treatment (Walsh et al., 2006; Attia et al., 1998). Our results suggest that improving cognitive flexibility may be an efficient therapeutic strategy for AN patients with a high level of depression. To confirm this hypothesis, further studies should investigate the benefits of improving cognitive flexibility in patients with AN and comorbid MDD.

Overall, our findings support previous literature showing the benefits of teaching cognitive skills in AN; for example by using Cognitive Remediation Therapy (CRT). Recent literature highlighted in fact the beneficial effect of CRT for patients with AN (Tchanturia et al., 2014; Tchanturia & Lock, 2011), and CRT has been shown to have a positive impact on neurocognitive processing (such as central coherence and set shifting abilities) and treatment retention in patients with EDs (Tchanturia et al., 2008; Leppanen, Adamson & Tchanturia, 2018; Hagan, Christensen & Forbush, 2020; Tchanturia et al., 2017). However, improving cognitive flexibility may not be sufficient to positively impact other important outcomes such as BMI, which underlines the necessity to maintain AN-specific treatments such as nutritional programs. As suggested by Keegan and his colleagues (2020), CRT may be more relevant as an adjunct therapy improving treatment efficacy. Further studies may investigate how targeting cognitive flexibility prior to other treatments (such as CBT) can increase positive outcomes and decrease relapsing rates.

REFERENCES

1. Abbate-Daga, G., Buzzichelli, S., Amianto, F., Rocca, G., Marzola, E., McClintock, S. M., & Fassino, S. (2011). Cognitive flexibility in verbal and nonverbal domains and decision making in anorexia nervosa patients: A pilot study. *BMC Psychiatry*, 11, 162.
2. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.
3. American Psychiatric Association Workgroup on Eating Disorders Practice (2006). Guideline for the treatment of patients with eating disorders (revision). *American Journal of Psychiatry*, 163, 1–39.
4. Atkinson, T.M. & Ryan, J.P. (2007). The use of variants of the Trail Making Test in serial assessment: a construct validity study. *Journal of Psychoeducational Assessment*, 26(1), 42-53.
5. Atkinson, T., Ryan, J., Lent, A.R., Wallis, A., Schachter, H. & Coder, R. Three trail making tests for use in neuropsychological assessments with brief intertest intervals. *Journal of Clinical and Experimental Neuropsychology*, 32(1), 15-8.
6. Attia, E., Haiman, C., Walsh, B. T. & Flater, S. R. (1998). Does fluoxetine augment the impatient treatment of anorexia nervosa? *American Journal of Psychiatry*, 155, 548–551.
7. Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S. (2011). Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Archives of General Psychiatry*, 68(7), 724-731.
8. Bamford, B., Barras, C., Sly, R., Stiles-Shields, C., Touyz, S., Le Grange, D., ... Lacey, H. (2014). Eating disorder symptoms and quality of life: Where should clinicians place

their focus in severe and enduring anorexia nervosa? *International Journal of Eating Disorders*, 48(1), 133–138.

9. Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology*, 39, 15-22.
10. Berkman, N. D., Lohr, K. N. & Bulik, C. M. (2007). Outcomes of eating disorders: a systematic review of the literature. *International Journal of Eating Disorders*, 40, 293–309.
11. Bienvenu, T., Lebrun, N., Clarke, J., Duriez, P., Gorwood, P., & Ramoz, N. (2019). De novo deleterious variants that may alter the dopaminergic reward pathway are associated with anorexia nervosa. *Eating and Weight Disorders: EWD*.
12. Bodell, L. P. & Keel, P. M. (2010). Current treatment for anorexia nervosa: efficacy, safety, and adherence. *Psychological Research and Behavior Management*, 3, 91-108.
13. Brockmeyer, T., Friederich, H.-C., & Schmidt, U. (2018). Advances in the treatment of anorexia nervosa : A review of established and emerging interventions. *Psychological Medicine*, 48(8), 1228-1256.
14. Burgess, P. & Shallice, T. (1997). *The Hayling and Brixton Tests. Test manual*.
15. Bulik, C. M., Thornton, L., Pinheiro, A. P., Plotnicov, K., Klump, K. L. et al. (2008) Suicide attempts in anorexia nervosa. *Psychosomatic Medicine*, 70, 378–383.
16. Burke, T., Wynne, B., O'Brien, C., Elamin, M., Bede, P., Hardiman, O., & Pender, N. (2014). Retrospective investigations of practice effects on repeated neuropsychological measures of executive functioning. *The Irish Journal of Psychology*, 35(4), 178-187.
17. Cassin, S. E., & von Ranson, K. M. (2005). Personality and eating disorders: A decade in review. *Clinical Psychology Review*, 25(7), 895-916.

18. Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd ed.)* (Lawrence Earlbaum Associates). NJ: Hillsdale.
19. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, & Cross-Disorder Group of the Psychiatric Genomics Consortium. (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*, 179(7), 1469-1482.e11.
20. Crow, S. J., Peterson, C. B., Swanson, S. A., Raymond, N. C., Specker, S., Eckert, E. D. & Mitchell, J. E. (2009). Increased mortality in bulimia nervosa and other eating disorders. *American Journal of Psychiatry*, 166, 1342–1346.
21. Danner, U. N., Sanders, N., Smeets, P. A. M., van Meer, F., Adan, R. A. H., Hoek, H. W., & van Elburg, A. A. (2012). Neuropsychological weaknesses in anorexia nervosa: Set-shifting, central coherence, and decision making in currently ill and recovered women. *The International Journal of Eating Disorders*, 45(5), 685-694.
22. Duriez, P., Ramoz, N., Gorwood, P., Viltart, O., & Tolle, V. (2019). A Metabolic Perspective on Reward Abnormalities in Anorexia Nervosa. *Trends in Endocrinology & Metabolism*, 30(12), 915-928.
23. Fassino, S., Pieró, A., Daga, G. A., Leombruni, P., Mortara, P., & Rovera, G. G. (2002). Attentional biases and frontal functioning in anorexia nervosa. *The International Journal of Eating Disorders*, 31(3), 274-283.
24. Filoteo, J. V., Paul, E. J., Ashby, F. G., Frank, G. K. W., Helie, S., Rockwell, R., Bischoff-Grethe, A., Wierenga, C., & Kaye, W. H. (2014). Simulating category learning and set shifting deficits in patients weight-restored from anorexia nervosa. *Neuropsychology*, 28(5), 741-751.
25. Fonville, L., Giampietro, V., Davies, H., Lounes, N., Simmons, A., Williams, S., &

- Tchanturia, K. (2014). Cognitive remediation, brain function and central coherence : An anorexia nervosa pilot study. *Annals of General Psychiatry*, 13(1), 25.
26. Forcano, L., Fernandez-Aranda, F., Alvarez-Moya, E., Bulik, C., Granero, R. et al. (2009). Suicide attempts in bulimia nervosa: personality and psychopathological correlates. *European Psychiatry*, 24, 91–97.
27. Franko, D. L., Keshaviah, A., Eddy, K. T., Krishna, M., Davis, M. C., Keel, P. K., & Herzog, D. B. (2013). A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *The American Journal of Psychiatry*, 170(8), 917-925.
28. Friederich, H.-C., & Herzog, W. (2011). Cognitive-behavioral flexibility in anorexia nervosa. *Current Topics in Behavioral Neurosciences*, 6, 111-123.
29. Garner, D. M., & Garfinkel, P. E. (1979). The Eating Attitudes Test: An index of the symptoms of anorexia nervosa. *Psychological Medicine*, 9(2), 273-279.
30. Garrett, A. S., Lock, J., Datta, N., Beenhaker, J., Kesler, S. R., & Reiss, A. L. (2014). Predicting clinical outcome using brain activation associated with set-shifting and central coherence skills in Anorexia Nervosa. *Journal of Psychiatric Research*, 57, 26-33.
31. Gorwood, P., Duriez, P., Lengvenyte, A., Guillaume, S., Criquillion, S., & FFAB network. (2019). Clinical insight in anorexia nervosa : Associated and predictive factors. *Psychiatry Research*, 281, 112561.
32. Hagan, K.E., Christensen, K.A., Forbush, K.T. (2020) A preliminary systematic review and meta-analysis of randomized-controlled trials of cognitive remediation therapy for anorexia nervosa. *Eating Behaviors*. Doi: 10.1016/j.eatbeh.2020.101391.
33. Halmi, K. A., Tozzi, F., Thornton, L. M., Crow, S., Fichter, M. M., Kaplan, A. S., Keel, P., Klump, K. L., Lilienfeld, L. R., Mitchell, J. E., Plotnicov, K. H., Pollice, C., Rotondo, A., Strober, M., Woodside, D. B., Berrettini, W. H., Kaye, W. H., & Bulik, C. M. (2005). The

- relation among perfectionism, obsessive-compulsive personality disorder and obsessive-compulsive disorder in individuals with eating disorders. *The International Journal of Eating Disorders*, 38(4), 371-374.
34. Harper, J. A., Brodrick, B., Van Enkevort, E., & McAdams, C. J. (2017). Neuropsychological and cognitive correlates of recovery in anorexia nervosa. *European eating disorders review : the journal of the Eating Disorders Association*, 25(6), 491-500.
 35. Herpertz-Dahlmann, B., & Salbach-Andrae, H. (2009). Overview of treatment modalities in adolescent anorexia nervosa. *Child and Adolescent Psychiatric Clinics of North America*, 18(1), 131-145.
 36. Holliday, J., Tchanturia, K., Landau, S., Collier, D., & Treasure, J. (2005). Is impaired set-shifting an endophenotype of anorexia nervosa? *The American Journal of Psychiatry*, 162(12), 2269-2275.
 37. Johnco, C., Wuthrich, V. M., & Rapee, R. M. (2014). The influence of cognitive flexibility on treatment outcome and cognitive restructuring skill acquisition during cognitive behavioural treatment for anxiety and depression in older adults: Results of a pilot study. *Behaviour Research and Therapy*, 57, 55–64.
 38. Jones, B. P., Duncan, C. C., Brouwers, P., & Mirsky, A. F. (1991). Cognition in eating disorders. *Journal of Clinical and Experimental Neuropsychology*, 13(5), 711-728.
 39. Kanakam, N., Raoult, C., Collier, D., & Treasure, J. (2013). Set shifting and central coherence as neurocognitive endophenotypes in eating disorders: A preliminary investigation in twins. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, 14(6), 464-475.
 40. Katzman, D. K., Christensen, B., Young, A. R., & Zipursky, R. B. (2001). Starving the

brain: Structural abnormalities and cognitive impairment in adolescents with anorexia nervosa. *Seminars in Clinical Neuropsychiatry*, 6(2), 146-152.

41. Keegan, E., Tchanturia, K., & Wade, T. D. (2020). Central coherence and set-shifting between nonunderweight eating disorders and anorexia nervosa: A systematic review and meta-analysis. *International Journal of Eating Disorders*. Doi: 10.1002/eat.23430.
42. Keys, A., Brozek, J., Henschel, A., Mickelsen, O. & Taylor, H. L. (1950) *The biology of human starvation, Vols. I–II*. University of Minnesota Press, Minneapolis, MN.
43. Lao-Kaim, N. P., Fonville, L., Giampietro, V. P., Williams, S. C. R., Simmons, A., & Tchanturia, K. (2015). Aberrant function of learning and cognitive control networks underlie inefficient cognitive flexibility in anorexia nervosa: A cross-sectional fMRI study. *PloS One*, 10(5), e0124027.
44. Leichner, P., Steiger, H., Puentes-Neuman, G., Perreault, M., & et al. (1994). Validation d'une échelle d'attitudes alimentaires auprès d'une population québécoise francophone. [Validation of the Eating Attitudes Test (EAT-26) in a French-speaking population of Quebec.]. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*, 39(1), 49-54.
45. Leppanen, J., Adamson, J., & Tchanturia, K. (2018). Impact of Cognitive Remediation Therapy on Neurocognitive Processing in Anorexia Nervosa. *Frontiers in Psychiatry*, 9.
46. Lowe, B., Zipfel, S., Bucholz, C., Dupont, Y., Reas, D. L. & Herzog, W. (2001). Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. *Psychological Medicine*, 31, 881–890.
47. Maramis, M.M., Mahajudin, M.S., Khotib, J. (2020) Impaired Cognitive Flexibility and Working Memory Precedes Depression: A Rat Model to Study Depression. *Neuropsychobiology*. Doi: 10.1159/000508682.

48. Michison, D., Hay, P., Engel, S., Crosby, S., Le grange, D. et al. (2013). Assessment of quality of life in people with severe and enduring anorexia nervosa: a comparison of generic and specific instruments. *BMC Psychiatry*, 13, 284.
49. Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex « Frontal Lobe » tasks: A latent variable analysis. *Cognitive Psychology*, 41(1), 49-100.
50. Pellizzer, M.L., Waller, G., Wade, T.D. (2018). Body image flexibility: A predictor and moderator of outcome in transdiagnostic outpatient eating disorder treatment. *International Journal of Eating Disorders*, 51(4), 368-372.
51. Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271-276.
52. Roberts, M. E., Tchanturia, K., Stahl, D., Southgate, L., & Treasure, J. (2007). A systematic review and meta-analysis of set-shifting ability in eating disorders. *Psychological Medicine*, 37(8), 1075-1084.
53. Rößner, A., Juniak, I., van Noort, B. M., Pfeiffer, E., Lehmkuhl, U., & Kappel, V. (2017). Cognitive Flexibility in Juvenile Anorexia Nervosa in Relation to Comorbid Symptoms of Depression, Obsessive Compulsive Symptoms and Duration of Illness. *Zeitschrift Fur Kinder- Und Jugendpsychiatrie Und Psychotherapie*, 45(5), 371-380.
54. Sato, Y., Saito, N., Utsumi, A., Aizawa, E., Shoji, T., Izumiyama, M., Mushiake, H., Hongo, M., & Fukudo, S. (2013). Neural Basis of Impaired Cognitive Flexibility in Patients with Anorexia Nervosa. *PLoS ONE*, 8(5).
55. Sawilowsky, S. (2009). New Effect Size Rules of Thumb. *Journal of Modern Applied Statistical Methods*, 8(2), 597-599

56. Stedal, K., Rose, M., Frampton, I., Landrø, N. I., & Lask, B. (2012). The neuropsychological profile of children, adolescents, and young adults with anorexia nervosa. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, 27(3), 329-337.
57. Steinglass, J. E., Walsh, B. T., & Stern, Y. (2006). Set shifting deficit in anorexia nervosa. *Journal of the International Neuropsychological Society: JINS*, 12(3), 431-435.
58. Tchanturia, K., Davies, H., Roberts, M., Harrison, A., Nakazato, M., Schmidt, U., ... Morris, R. (2012). Poor Cognitive Flexibility in Eating Disorders: Examining the Evidence using the Wisconsin Card Sorting Task. *PLoS ONE*, 7(1), e28331.
59. Tchanturia, K., Giombini, L., Leppanen, J., & Kinnaird, E. (2017). Evidence for cognitive remediation therapy in young people with anorexia nervosa: Systematic review and meta-analysis of the literature. *European Eating Disorders Review*, 25, 227–236.
60. Tchanturia, K., Morris, R. G., Anderluh, M. B., Collier, D. A., Nikolaou, V., & Treasure, J. (2004). Set shifting in anorexia nervosa: An examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits. *Journal of Psychiatric Research*, 38(5), 545-552.
61. Tchanturia, K., Morris, R. G., Surguladze, S., & Treasure, J. (2002). An examination of perceptual and cognitive set shifting tasks in acute anorexia nervosa and following recovery. *Eating and Weight Disorders: EWD*, 7(4), 312-315.
62. Tchanturia, K., Serpell, L., Troop, N., & Treasure, J. (2001). Perceptual illusions in eating disorders: Rigid and fluctuating styles. *Journal of Behavior Therapy and Experimental Psychiatry*, 32(3), 107-115.
63. Tchanturia, Kate, Anderluh, M. B., Morris, R. G., Rabe-Hesketh, S., Collier, D. A., Sanchez, P., & Treasure, J. L. (2004). Cognitive flexibility in anorexia nervosa and

- bulimia nervosa. *Journal of the International Neuropsychological Society: JINS*, 10(4), 513-520.
64. Tchanturia, Kate, Davies, H., Lopez, C., Schmidt, U., Treasure, J., & Wykes, T. (2008). Neuropsychological task performance before and after cognitive remediation in anorexia nervosa: A pilot case-series. *Psychological Medicine*, 38(9), 1371-1373.
 65. Tchanturia, Kate, Harrison, A., Davies, H., Roberts, M., Oldershaw, A., Nakazato, M., Stahl, D., Morris, R., Schmidt, U., & Treasure, J. (2011). Cognitive flexibility and clinical severity in eating disorders. *PloS One*, 6(6), e20462.
 66. Tchanturia, Kate, & Lock, J. (2011). Cognitive remediation therapy for eating disorders: Development, refinement and future directions. *Current Topics in Behavioral Neurosciences*, 6, 269-287.
 67. Touyz, S., Le Grange, D., Lacey, H., Hay, P., Smith, R., Maguire, S., ... Crosby, R. D. (2013). Treating severe and enduring anorexia nervosa: a randomized controlled trial. *Psychological Medicine*, 43(12), 2501–2511.
 68. Treasure, J., & Russell, G. (2011). The case for early intervention in anorexia nervosa: Theoretical exploration of maintaining factors. *The British Journal of Psychiatry: The Journal of Mental Science*, 199(1), 5-7.
 69. Treasure, J., & Schmidt, U. (2013). The cognitive-interpersonal maintenance model of anorexia nervosa revisited: A summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. *Journal of Eating Disorders*, 1(1), 13.
 70. van den Berg, E., Nys, G. M., Brands, A. M., Ruis, C., van Zandvoort, M.J., & Kessels, R. P. (2009). The Brixton Anticipation Test as a test for executive function: validity in patients groups and norms for older adults. *Journal of the International*

Neuropsychological Society, 15(5):695-703.

71. Wagner, S., Helmreich, I., Dahmen, N., Lieb, K. & Tadic, A. (2011). Reliability of three alternate forms of the Trail Making Tests a and B. *Archives of Clinical Neuropsychology*, 26(4), 314-321.
72. Walsh, B. T., Kaplan, A. S., Attia, E., Olmsted, M., Parides, M. et al. (2006). Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *Journal of the American Medical Association*, 295, 2605-2612.
73. Watson, H. J., & Bulik, C. M. (2013). Update on the treatment of anorexia nervosa: Review of clinical trials, practice guidelines and emerging interventions. *Psychological Medicine*, 43(12), 2477-2500.
74. Westwood, H., Stahl, D., Mandy, W., & Tchanturia, K. (2016). The set-shifting profiles of anorexia nervosa and autism spectrum disorder using the Wisconsin Card Sorting Test: a systematic review and meta-analysis. *Psychological Medicine*, 46(9), 1809–1827.
75. Wildes, J. E., Forbes, E. E., & Marcus, M. D. (2014). Advancing research on cognitive flexibility in eating disorders: The importance of distinguishing attentional set-shifting and reversal learning. *The International Journal of Eating Disorders*, 47(3), 227-230.
76. Williamson, D. A., Cubic, B. A., & Gleaves, D. H. (1993). Equivalence of body image disturbances in anorexia and bulimia nervosa. *Journal of Abnormal Psychology*, 102(1), 177-180.
77. World Medical Association (2013), World Medical Association Declaration of Helsinki. *Journal of the American Medical Association*, 310(20): 2191-2194.
78. Wu, M., Brockmeyer, T., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2014). Set-shifting ability across the spectrum of eating disorders and in overweight

and obesity: A systematic review and meta-analysis. *Psychological Medicine*, 44(16), 3365-3385.

Table 1. *Clinical characteristics of 130 patients with AN at baseline and four months after treatment*

	Baseline		Post-treatment		Baseline vs. Post-treatment	
	Mean	SD	Mean	SD	t (p)	d
BMI	15.52	1.75	16.50	2.55	<0.001	0.45
Brixton	33.35	10.70	37.22	10.43	<0.001	0.37
EAT Total	34.85	16.60	26.70	17.28	<0.001	0.48
EAT Dieting	18.52	10.42	14.35	10.26	<0.001	0.40
EAT Bulimia	7.76	4.55	6.16	4.96	<0.001	0.34
EAT Oral	8.57	4.90	6.19	4.73	<0.001	0.49
HADS Anxiety	13.29	4.13	11.67	4.67	<0.001	0.37
HADS Depression	9.05	3.74	7.48	4.02	<0.001	0.40
PANAS Positive	29.25	6.84	30.62	6.95	0.012	0.20
PANAS Negative	35.99	7.90	32.43	9.43	<0.001	0.41
Selt-rated silhouette	4.27	2.57	5.06	2.58	<0.001	0.31
WSAS	23.43	8.21	19.32	10.45	<0.001	0.28

BMI: Body Mass Index; NART: National Adult Reading Test; EAT: Eating Attitudes Test; HADS: Hospital Anxiety and Depression scale; PANAS: Positive and Negative Affect Schedule; WSAS: Work and Social Adjustment Scale

Table 2. Path analysis testing the role of cognitive flexibility (through the Brixton test) to explain the impact of 4 months treatment on clinical, emotional, physiological and functional outcomes

Tested variables	Statistics	Tested outcome variables							
		Eating disorder symptoms (EAT-26)	Negative emotions (PANAS -)	Positive emotions (PANAS+)	Functioning (WSAS)	BMI	Anxiety symptoms (HADS-A)	Depressive symptoms (HADS-D)	Silhouette (Mouchez)
Direct effect of treatment on outcome	Coefficient	-6.128	0.310	2.459	-2.285	2.136	-1.157	-1.143	0.754
	p	0.001	0.761	0.003	0.035	<0.001	0.020	0.012	0.014
	% of direct effect†	82.02%	Na	99.51%	74.38%	96.83%	85.70%	82.89%	87.27%
Direct effect of treatment on Brixton	Coefficient	4.680	4.780	4.780	4.790	4.004	4.780	4.790	4.780
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Brixton effect on outcome	Coefficient	-0.287	-0.052	0.002	-0.164	-0.759	-0.040	-0.050	-0.023
	p	<0.001	0.234	0.943	<0.001	0.448	0.058	0.012	0.079
Indirect effect of treatment on outcome through Brixton	Coefficient	-1.343	-0.249	0.012	-0.787	0.070	-0.193	-0.236	0.110
	[min;max]	[-2.404;-0.482]	[-0.682;0.189]	[-0.338;0.379]	[-1.412;-0.295]	[-0.301;0.129]	[-0.416;0.002]	[-0.477;-0.050]	[-0.265;0.007]
	% of total effect‡	17.98%	Na	0.49%	25.62%	3.17%	14.30%	17.11%	12.73%
Total effect		-7.471	1.010	2.471	-3.072	2.206	-1.35	-1.379	0.864
R ²		0.077	0.004	0.027	0.059	0.059	0.033	0.046	0.023

† the % of direct effect was computed by dividing the direct coefficient by the sum of the direct and indirect coefficients

‡ the % of total effect was computed by dividing the indirect coefficient by the sum of the direct and indirect coefficients

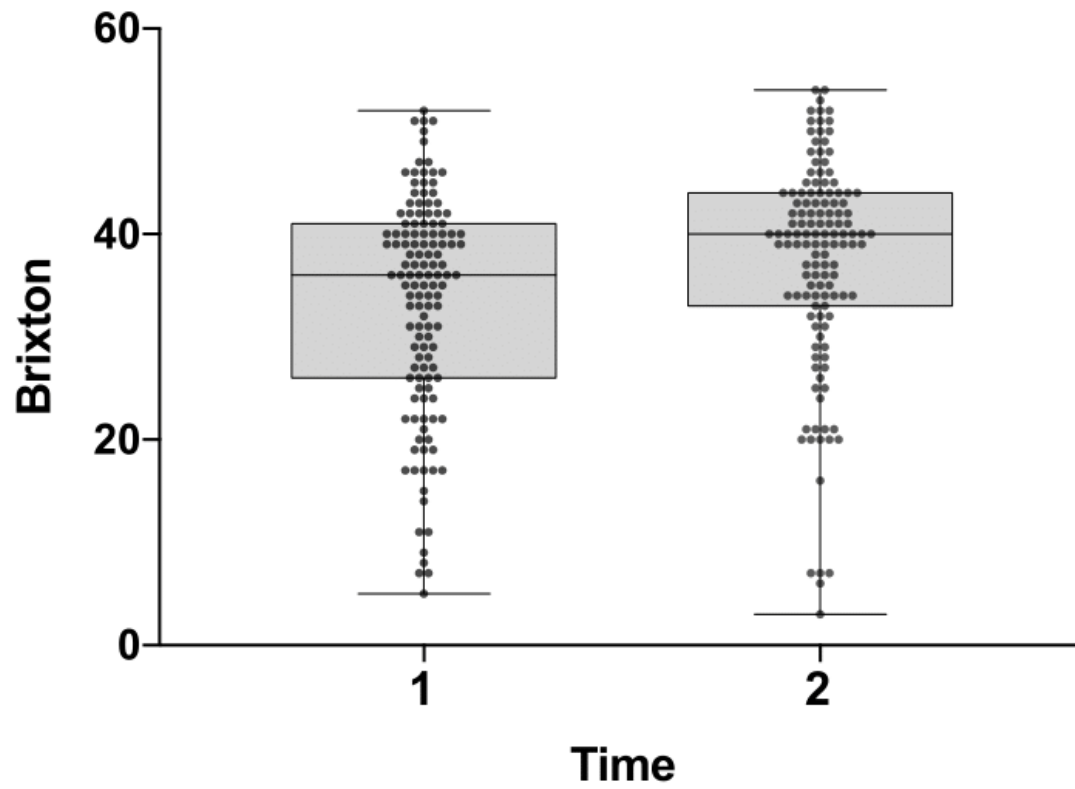
na= not applicable (with no significant effect, direct and indirect effects were not comparable)

Figure legends

Figure 1. *Cognitive flexibility (Brixton Test) before and after four months of treatment in patients with anorexia nervosa*

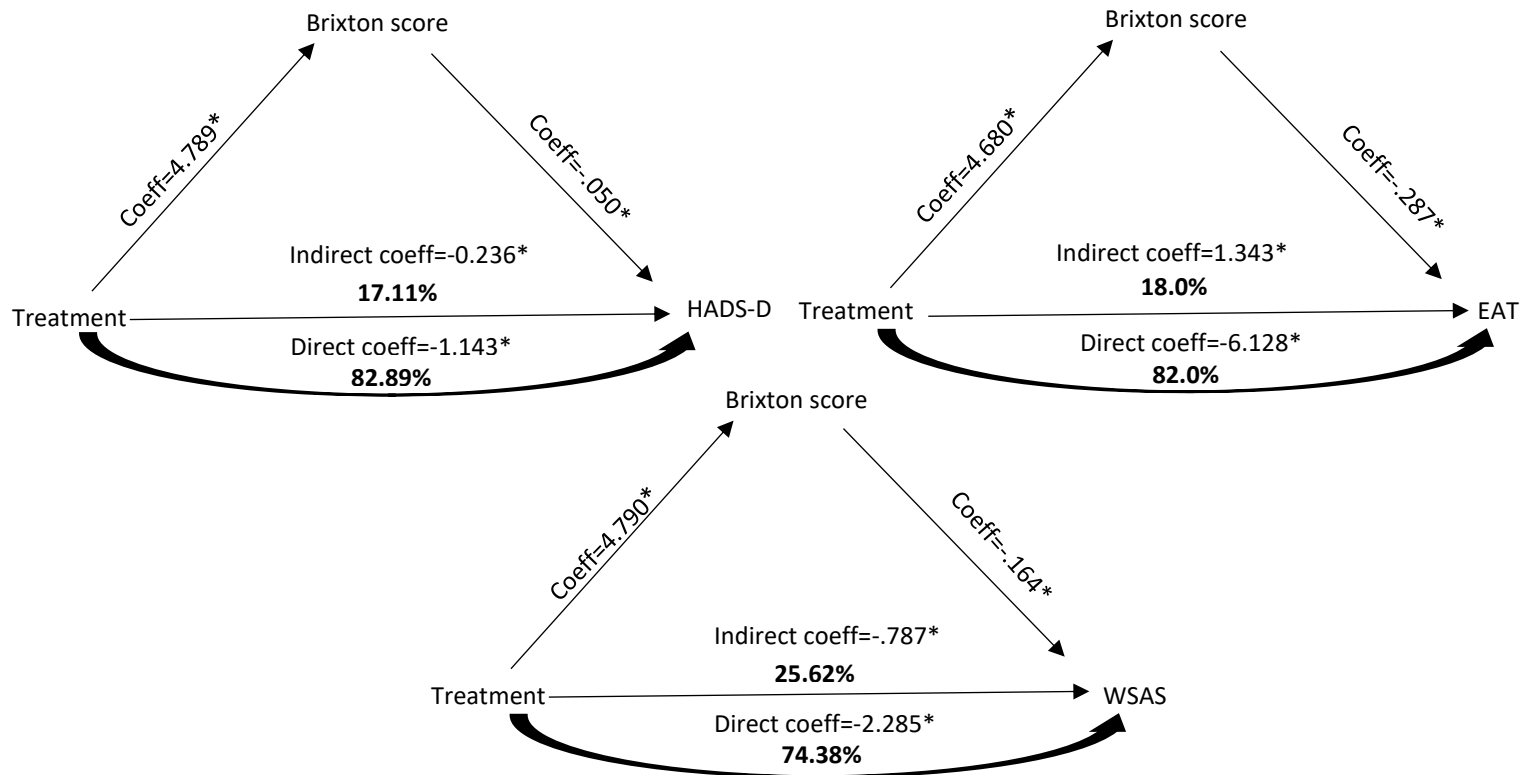
Figure 2. *Cognitive flexibility (Brixton Test) as a mediator of the improvement of depressive symptoms, functioning and symptom severity in treated patients with anorexia nervosa*

Figure 1. Cognitive flexibility (Brixton Test) before and after four mounths of treatment in patients with anorexia nervosa



1: before treatment ; 2: after treatment

Figure 2. Cognitive flexibility (Brixton Test) as a mediator of the improvement of depressive symptoms, functioning and symptom severity in treated patients with anorexia nervosa



HADS-D: Hospital Anxiety and Depression Scale, Depression score; WSAS: Working and Social Adjustment Scale; EAT: Eating Attitudes Test

Indirect coeff=indirect effect of treatment on outcome variable through mediator (Brixton score)

Direct coeff= direct effect of treatment on outcome variable