

BRIEF REPORT

Anxiety Impacts Cognitive Inhibition in Remitted Anorexia Nervosa

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Abstract

Objective: Eating disorders are complex psychiatric disorders, associated with alterations in neural and cognitive functioning. Research suggests inhibition and set-shifting deficits in anorexia nervosa (AN), but less is known about the persistence of these deficits after recovery, or their relationship to comorbid psychiatric symptoms.

Method: Women aged 19–45 remitted from AN (RAN, $N = 47$) and controls (CW, $N = 24$) completed the Delis–Kaplan Executive Function System Color-Word Interference Test. It was hypothesized that RAN, and those with higher anxiety or depression, would demonstrate worse Inhibition and Switching task performance than CW.

Results: Differences in performance between groups trended toward significance on Inhibition Ratio ($p = 0.08$) but were nonsignificant on Inhibition/Switching Ratio ($p = 0.93$). A model including State Anxiety and diagnosis revealed a significant independent effect of State Anxiety ($p = 0.026$), but not of diagnosis nor their interaction. Regressing State Anxiety on Color-Word Interference Test Inhibition among just the RAN group was significant [$\beta = 0.37$, $t(46) = 2.63$, $p = 0.012$] but among just CW was not ($p = 0.54$).

Discussion: Interference control for neutral stimuli is influenced by anxiety in women with a history of AN. Anxiety is linked with greater symptom severity among AN individuals, and state anxiety may account for larger deficits seen on tasks using disorder-specific stimuli. Future research is warranted to elucidate the nature of neuropsychological deficits in eating disorders. Copyright © 2016 John Wiley & Sons, Ltd and Eating Disorders Association

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Introduction

Anorexia nervosa (AN) is a severe psychiatric illness characterized by extreme restriction of food intake and dangerous weight loss. Considerable research has documented neuropsychological impairments in a number of domains in AN, including deficits in cognitive set-shifting (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005), central coherence (Lang, Lopez, Stahl, Tchanturia, & Treasure, 2014) and reversal learning (Filoteo et al., 2014).

Behavioural inhibition is a temperament construct characterized by elevated behavioural control and restricted thinking (Claes, Mitchell, & Vandereycken, 2012). Generally, AN is linked to high restraint and overconcern with consequences. Exaggerated cognitive inhibition and interference control may contribute to cognitive rigidity (Friederich & Herzog, 2011). Interference control (selective attention and cognitive inhibition) is evoked during the Stroop task (MacLeod, 1991), in which one must inhibit one behaviour (e.g. reading a word) in favour of another (e.g. naming the colour). Research in AN shows an interference effect, but

typically uses modified Stroop tasks using symptom-specific food or body shape words (Dobson & Dozois, 2004). It remains unclear whether this deficit is related to general neuropsychological impairment.

Set-shifting refers to the ability to switch between mental sets, or behavioural objectives (Miyake et al., 2000), and requires inhibition of previous behavioural response patterns in order to adhere to changing task parameters. Research has demonstrated impaired set-shifting in AN (Steinglass, Walsh, & Stern, 2006; Tchanturia et al., 2011; Tchanturia et al., 2012), suggesting cognitive flexibility difficulties in adapting to changing demands. Poor set-shifting may be a heritable trait in families of women with AN (Lang et al., 2014) and has been linked to severity of the disorder (Tchanturia et al., 2011).

These alterations in executive function may or may not be reversible with weight gain. Research in weight-restored and recovered AN (RAN) samples reveal significant differences compared with healthy controls on the Wisconsin Card Sorting Test (Tchanturia et al., 2012), as well as tests of planning (Lindner, Fitcher, & Quadflieg, 2012), and psychomotor ability

(Bosanac et al., 2007), and no significant differences compared with ill participants (Bosanac et al., 2007; Lindner et al., 2012) suggesting deficits may not resolve with symptom remittance. However, other studies of neuropsychological performance in AN suggest improvement following remission. Tchanturia and colleagues (Tchanturia et al., 2011; Tchanturia et al., 2012) have demonstrated that RAN participants performed significantly better than those with current AN diagnoses on measures of set-shifting. On a motor inhibition task, Oberndorfer and colleagues (Oberndorfer, Kaye, Simmons, Strigo, & Matthews, 2011) found that RAN performed on par with healthy participants, but failed to show increased activation in the medial prefrontal cortex with increasing difficulty. These discrepancies highlight the importance of measuring multiple facets of cognitive function within the same sample under the same conditions.

Anorexia nervosa is also linked with elevated anxiety evident prior to onset, persisting after recovery (Kaye et al., 2004), suggesting that it may be a temperamental trait for this population. High anxiety is associated with poor outcome in AN (Kaye et al., 2004), greater symptom severity and lower body mass index (BMI) during illness (Dellava et al., 2010). Despite evidence of elevated anxiety and neuropsychological deficits, there is limited research exploring the impact of anxiety on cognitive performance in AN. State anxiety, assessed by the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983), accounts for significant variance in performance on some measures of cognitive performance in AN (Billingsley-Marshall et al., 2013), while in other psychiatric populations, comorbid anxiety may exacerbate impairment in executive function (Lynche, Jonassen, Stiles, Ulleberg, & Landro, 2011; Wu et al., 2011).

Because many set-shifting tasks involve implicit learning and inhibition of previously learned rules that may influence task performance, this study aimed to identify deficits specific to inhibition or task-switching and the impact of anxiety on performance using the Color-Word Inhibition Test (CWIT) of the Delis–Kaplan Executive Function System (Delis, Kramer, Kaplan, & Holdnack, 2004). The CWIT has many advantages: (i) it avoids confounding symptom provocation from emotional words with inhibition by using only neutral stimuli; (ii) it assesses task-switching without additional demands of rule generation or problem solving; and (iii) ratio scores account for baseline reading and colour-naming speed. We hypothesized that higher anxiety in the RAN group would be linked to worse performance, as demonstrated by higher ratio scores on CWIT inhibition and switching tasks.

Methods

Recruitment

RAN women ($N=47$, of whom 19 also had a history of bulimia nervosa) and healthy control women (CW, $N=24$) were all included as a part of a larger study at the University of California, San Diego (UCSD). All participants were aged 19–45, and right-handed. RAN participants had a history of Diagnostic and Statistical Manual of Mental Disorders Fourth Edition diagnosis for AN, onset of illness greater than 4 years prior to participation, both maintenance of stable weight between 90% and 120% ideal body weight and regular menstrual cycles for the prior 12 months.

Participants were recruited through flyer and online advertisements on the UCSD campus and in the wider community.

Exclusion criteria were evaluated using structured interviews conducted by doctoral-level psychologists and for the RAN group included (i) eating disorder (ED)-related behaviours or cognitions for 12 months prior to study participation; (ii) alcohol or substance abuse/dependence within the previous 3 months; (iii) current severe diagnosis of a severe major affective disorder, anxiety disorder, or other psychopathology that may interfere with participation; (iv) use of psychoactive medication or antidepressants; and (v) presence of major neurological or medical disorders.

The CW group had no stigmata suggestive of an ED or any psychiatric, medical, or neurological illness. They had maintained an IBW between 90% and 120% since menarche. The study was conducted according to the institutional review board regulations of UCSD. Written informed consent was obtained from all participants.

Measures

Beck Depression Inventory II (Beck, Steer, Ball, & Ranieri, 1996)

The Beck Depression Inventory is a widely used measure of depression, with high reliability, adequate convergent validity, and strong internal consistency (Cronbach's $\alpha=0.86$ among psychiatric outpatients, 0.81 among a non-psychiatric sample) (Beck, Steer, & Carbin, 1988; Beck et al., 1996). Twenty-one items are scored 0–3; higher scores indicate more severe depression.

State-Trait Anxiety Inventory (Spielberger, 1983)

This self-report questionnaire is an internally consistent (Cronbach's $\alpha=0.86–0.95$), reliable, and valid measure of anxiety severity (Spielberger, 1983). Each of two subscales (State Anxiety and Trait Anxiety) contains 20 items on a 4-point rating scale, with higher scores indicating greater anxiety.

Delis–Kaplan Executive Function System (Delis et al., 2004)

The Delis–Kaplan Executive Function System is a non-computerized battery of standardized neuropsychological assessments of executive function that have been used in past studies of ED (Fitzpatrick, Darcy, Colborn, Gudorf, & Lock, 2012; Rose, Davis, Frampton, & Lask, 2011). This study focuses on the performance on the Color-Word Interference Test, a measure of verbal inhibition and task-switching. In Condition 1, participants identify colours, and in Condition 2, participants read colour words, providing baseline measures of colour naming and reading speed. Condition 3 (Inhibition) is an adapted Stroop paradigm, while Condition 4 (Inhibition/Switching) requires participants to switch between reading words and identifying the ink colour of those words. Increased scores indicate worse performance.

Statistical analyses

Baseline performance was calculated by taking average completion time of Conditions 1 and 2. Inhibition Ratio scores were calculated to control for baseline performance, and Inhibition-Switching Ratio scores were calculated to identify task-switching

performance, controlling for Inhibition. One-way ANOVAs were used to calculate differences in demographic and clinical variables and to compare performance on CWIT Ratio scores. Hierarchical linear regression analyses were employed to evaluate the impact of clinical variables on neuropsychological performance.

Results

Demographics and clinical assessments

RAN and CW individuals were of similar age and BMI. RAN individuals completed significantly more years of education than CW [$F(1, 71) = 4.99, p = 0.029$]. RAN also scored significantly higher than CW on the Beck Depression Inventory [$F(1, 71) = 7.99, p = 0.006$], and on State-Trait Anxiety Inventory State [$F(1, 71) = 5.44, p = 0.023$] and Trait [$F(1, 71) = 6.37, p = 0.014$] Anxiety. RAN individuals with and without a past BN diagnosis did not differ significantly on any of the demographic variables, self-report questionnaire scores, or CWIT performance (Table 1).

Neuropsychological assessment

Controlling for education, differences in performance between CW and RAN, trended toward significance on Inhibition Ratio [$F(1, 71) = 3.19, p = 0.08$], but there were no significant differences on Inhibition/Switching Ratio [$F(1, 71) = 0.01, p = 0.93$].

A model including State Anxiety and Group (CW vs. RAN), including education as a covariate, revealed a significant independent effect of State Anxiety [$\beta = 0.27, t(46) = 2.28, p = 0.026$] on Inhibition Ratio, but not of Group ($p = 0.09$) nor their interaction ($p = 0.177$) (Table 2). Neither interaction nor main effect significantly predicted Inhibition/Switching Ratio. Regressing State Anxiety on CWI Inhibition among the RAN group alone was significant [$\beta = 0.37, t(46) = 2.63, p = 0.012$] but in CW alone was not ($p = 0.54$) (Figure 1).

Table 1 One-way ANOVA analyses comparing Groups on demographic variables and clinical assessments

| | CW | | RAN | | F | p |
|--------------------------------------|--------|------|--------|------|------|-------|
| | n = 24 | | n = 47 | | | |
| | M | SD | M | SD | | |
| Age | 25.08 | 6.11 | 26.68 | 1.83 | 2.32 | 0.13 |
| BMI | 22.08 | 6.93 | 21.76 | 1.72 | 0.28 | 0.6 |
| Education | 15.65 | 4.75 | 16.61 | 1.92 | 4.99 | 0.03* |
| Beck Depression Inventory Depression | 0.42 | 0.86 | 1.89 | 2.41 | 7.99 | 0.01* |
| STAI State Anxiety | 24.35 | 3.45 | 28.86 | 8.2 | 5.44 | 0.02* |
| STAI Trait Anxiety | 24.5 | 4.33 | 28.75 | 6.56 | 6.37 | 0.01* |
| CWI Inhibition Ratio | 1.77 | 0.24 | 1.91 | 0.31 | 3.7 | 0.06 |
| CWI Inhibition/Switching Ratio | 0.34 | 0.37 | 0.35 | 0.47 | 0.01 | 0.91 |

CW, control women; RAN, participants remitted from anorexia nervosa; M, mean; SD, standard deviation; STAI, Spielberger State Trait Anxiety Inventory; CWI, Color-Word Interference Test.

* $p < 0.05$.

Table 2 Linear regression model assessing the ability of Group and State Anxiety to predict CWI Inhibition Ratio scores

| | Unstandardized coefficients | | Standardized coefficients | | t | Sig. |
|-----------------------------------|-----------------------------|------------|---------------------------|--|------|--------|
| | B | Std. Error | Beta | | | |
| Constant | 1.35 | 0.29 | | | 4.64 | <0.001 |
| Group (CW vs. RAN) | 0.15 | 0.09 | 0.24 | | 1.72 | 0.09 |
| Education | 0.01 | 0.02 | 0.04 | | 0.37 | 0.71 |
| State Anxiety | 0.01 | 0.00 | 0.27 | | 2.28 | 0.03 |
| Group × State Anxiety Interaction | 0.02 | 0.02 | 0.18 | | 1.36 | 0.18 |

CW, control women; RAN, participants remitted from anorexia nervosa; STAI, Spielberger State Trait Anxiety Inventory.

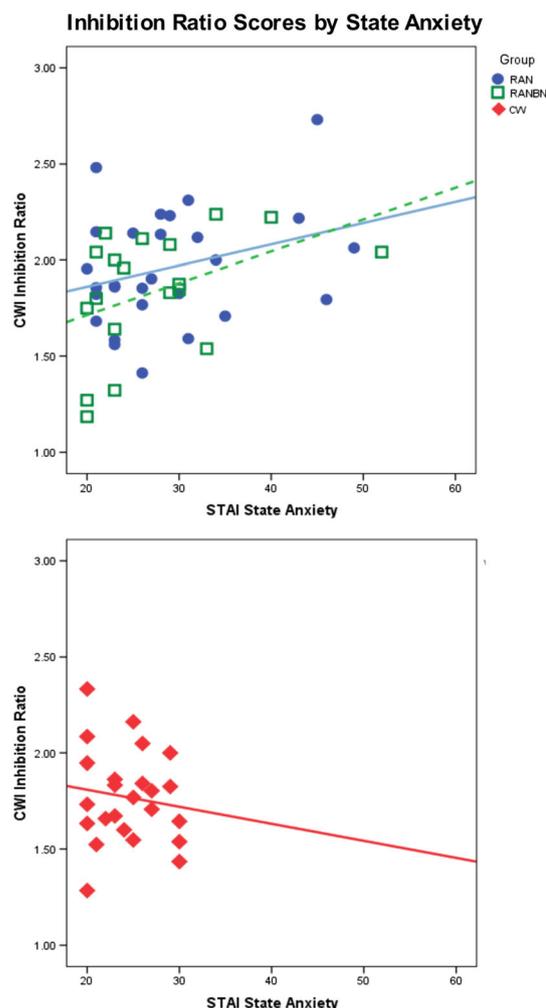


Figure 1. CWI Inhibition Ratio scores by State Anxiety among individuals remitted from anorexia nervosa with a history of bulimia nervosa (RANBN) and without (RAN), and among control women (CW). Increased ratio scores indicate worse performance. RAN and RANBN did not differ significantly. State anxiety predicted CWI Inhibition Ratio scores among individuals with eating disorder histories ($p = 0.012$) but not among CW ($p = 0.54$)

Discussion

These findings suggest that cognitive control impairments in AN may be related to anxiety. History of ED, whether AN or AN then BN, was not related to significant impairment in inhibition or task-switching on the CWIT as compared with healthy controls. However, State Anxiety was significantly predictive of performance only in the ED group. Cognitive rigidity and set-shifting are widely considered an endophenotype of AN (e.g. Holliday et al., 2005) but recent research suggests that the relationship between neuropsychological performance and AN may be more nuanced. A meta-analysis and a systematic review of set-shifting in children and adolescents (Lang, Stahl, Espie, Treasure, & Tchanturia, 2014) show attenuated differences between younger participants with AN and controls and suggest that a more subtle neuropsychological disturbance may become aggravated by the illness. Talbot and colleagues (Talbot, Hay, Buckett, & Touyz, 2015) have shown that set-shifting is not impaired in individuals with lifetime histories of AN. We failed to show differences in cognitive inhibition and task-switching in a remitted sample.

Alterations in performance on Stroop tasks using food or body shape words in ill AN have been attributed to deficits in interference control (Dobson & Dozois, 2004). To our knowledge, these studies did not assess the impact of anxiety. It is possible that anxiety produced by the emotionality of the disease-specific stimuli may be responsible for these findings rather than a true neuropsychological deficit. Research on cognition may benefit from the assessment of clinical variables such as state anxiety and their impact on performance.

There were several limitations to this study. Because we used a remitted sample, we may have seen more attenuated differences between groups than had we tested ill subjects. However, the finding that anxiety continues to contribute to cognitive function even upon remittance of symptoms is clinically relevant. Similarly, given the cross-sectional design, it is unclear whether inhibition performance influences anxiety or vice versa. The sample size was relatively small, although post-hoc power analyses conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) suggested power (0.823) to detect medium effect sizes. Level of depression did not appear to influence performance, inconsistent with recent research (Abbate-Daga et al., 2015). The Wisconsin Card Sorting Test and Trail Making Test are more commonly

used to assess set-shifting than the CWIT. The lack of significant differences in task-switching in our sample may be attributable to differences in task administration (i.e. computerized versus not), or to differences in the type of cognitive function measured, as other measures of set-shifting incorporate aspects of working memory or problem-solving (Lehto, 1996; Lie, Specht, Marshall, & Fink, 2006; Sanchez-Cubillo et al., 2009), which may contribute to performance deficits. Further, it may be that cognitive deficits exist only in subgroups of patients, or, as this study suggests, that clinical variables mediate the relationship between AN and altered neuropsychological functioning. Despite limitations, findings add to the literature supporting the persistence of differences in cognitive performance related to clinical variables in recovery from AN.

This is the first study we are aware of that identifies interference control as potentially susceptible to the effects of anxiety on executive function in AN. Anxiety has been linked to poor outcome and low BMI in AN (Dellava et al., 2010; Kaye et al., 2004). The current findings raise the possibility that difficulties with interference control may be related to elevated State Anxiety. Steinglass and colleagues (2010) have demonstrated that acute pre-meal anxiety in weight-restored AN participants was significantly predictive of reduced intake. It has been posited by others that the efficacy of family-based treatments for adolescent AN is predicated on their ability to treat the anxiety related to the disorder (Hildebrandt, Bacow, Markella, & Loeb, 2012). State anxiety is thus a potentially valuable target for treatment given the demonstrated negative effects on cognitive performance and symptom severity found by others. Future research is warranted to determine the nature of this effect in actively ill participants and to explore the relationship between cognitive performance and clinical variables in ED more generally.

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