SET SHIFTING IN ANOREXIA NERVOSA: AN EXAMINATION OF
COGNITIVE FLEXIBILITY AFTER RECOVERY

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Laura Elizabeth Irvine
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The Undersigned Faculty Committee Approves the

Thesis of Laura Elizabeth Irvine:

Set-Shifting in Anorexia Nervosa: An Examination of Cognitive

Flexibility After Recovery

[Signatures]

Claire Murphy, Chair
Department of Psychology

Sarah Mattson
Department of Psychology

Charles DeGenneffe
Department of Administration, Rehabilitation, and PostSecondary Education

J. Vincent Filoteo
Department of Psychology, University of California, San Diego

12/6/13
Approval Date
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DEDICATION

This thesis is dedicated to A.F.
ABSTRACT OF THE THESIS

Set-Shifting in Anorexia Nervosa: An Examination of Cognitive Flexibility After Recovery
by
Laura Elizabeth Irvine
Master of Arts in Psychology
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Anorexia Nervosa (AN) is a complex psychiatric disorder of unknown etiology. AN has strong neurobiological underpinnings that are reflected in observable differences in neural circuitry and cognitive functioning. One pathway to improving our understanding of the disease is through the study of underlying neuropsychological impairments. Previous studies of neurocognitive function in eating disorders have indicated impaired cognitive flexibility associated with AN. Specifically, this has been examined using a range of set-shifting tasks. Coupling our present understanding of the neural circuitry of set-shifting with current research into the neural correlates of AN will allow us to better understand and explain aberrant behaviors and cognitions typically associated with AN. The current study assessed set-shifting ability across multiple tasks in a cohort of 22 women recovered from restricting-type/purging-type AN (RAN) as compared with 22 healthy control women (CW). The Delis-Kaplan Executive Function System (D-KEFS) Trail Making, Verbal Fluency (VF), and Color-Word Interference (CWI) tests were used along with the Wisconsin Card Sorting Task (WCST). For each of the measures, the shift component was isolated from other task processes by computing a ratio score. It was hypothesized that the RAN group would have impaired set-shifting performance on each of these tasks relative to the CW group. There were no significant differences between groups on the ratio scores. The RAN group had slower completion times on all trials of the D-KEFS Trail Making and CWI tests as well as greater error totals on the WCST compared with CW. The fact that these did not translate to significant impairments when the switching components were isolated suggests that other component processes of these tasks, such as inhibition, may be contributing to between group differences. The RAN group performed better than the CW on the D-KEFS VF task. It was also hypothesized that within the RAN group there would be across-task correlation on the set-shifting measures, and that impaired set-shifting performance would be associated with increased perfectionism and obsessionality. There was a significant negative correlation within the RAN group between lifetime obsessionality and the WCST ratio score. Taken together, the findings of this study suggest that while the CW generally out-performs the RAN on most of the tasks, this cannot be attributed to a clear-cut group difference in set-shifting. Rather, it highlights the need for a nuanced approach to examining neuropsychological performance in AN with attention to task design, analysis, and the diagnostic characteristics of the sample in order to clarify the nature of any impairments.
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CHAPTER 1

INTRODUCTION

Anorexia nervosa (AN) affects approximately 0.3% to 0.7% of the general population (Bulik, Reba, Siega-Riz, & Reichborn-Kjennerud, 2005; Kaye, 2008). While this is a relatively small prevalence, eating disorders (ED), particularly AN, are among the most resistant to treatment and fatal of psychiatric disorders (Kaye, 2008). The etiology of these disorders remains as yet unknown, though research has explored sociocultural, genetic, neurobiological, and neurocognitive roots of the diseases. Given the chronic and sometimes intractable nature of the diseases, specifically AN, it is necessary to further our understanding of the disorders in order to improve treatment and, ultimately, prevention.

One pathway to increased understanding of ED is through the study of underlying neuropsychological impairments. Ultimately, the task at hand is for researchers to explore these impairments as they relate to the onset, duration, and the treatment of the disease. For example, if cognitive impairments are preexisting traits, how do they relate to the development and course of disease? If certain cognitive impairments can be conclusively related to ED, how do they relate to behavioral and personality characteristics of the disease? How can our understanding of cognitive functioning in AN improve treatment options and prognosis? The first step in this long line of questioning is to establish a clear methodology to assess neuropsychological function as it relates specifically to the deficits associated with ED. Thus far, neuropsychological studies of ED have used a wide range of tasks with varying results. However, the literature does show a broad range of set-shifting impairments in AN. The current study aimed to explore the use of several measures of set-shifting, which vary in modality, in a cohort of women who have recovered from AN as compared to women who have not suffered from the disease. Assessing cognitive flexibility in this group is of particular import given our burgeoning understanding of the neural correlates of AN, and the potential to relate observable cognitive impairments to disturbances in neural circuitry.
ANOREXIA NERVOSA

AN is characterized by a refusal to maintain a body weight above 85% of expected body weight, along with an intense fear of gaining weight, amenorrhea, and a disturbance in perception of body weight and shape despite low body weight (American Psychiatric Association, 2000). Additionally, individuals with AN tend to exhibit obsessionality, perfectionism, and rigid, inflexible thinking (Fassino et al., 2002; Halmi et al., 2000; Strober, 1980). Core clinical features of AN include highly repetitive and stereotyped behaviors and cognitions, specifically surrounding eating behavior (Steinglass, Walsh, & Stern, 2006). Notably, these cognitions and behaviors are very difficult to modify and may contribute to an extended duration or chronic case of the disease.

The diagnosis of AN can be further parsed into subtypes such as restricting-type AN purging-type AN, binging-type AN, or binging/purging-type AN. The utility of these diagnostic subtypes has been called into question due to the high incidence of cross-over: a recent longitudinal study found that during 7 years of follow-up approximately three-quarters of women with initial diagnoses of AN experienced cross-over either between anorexia subtypes (one-half of the women) or to bulimia nervosa (one-third) (Eddy et al., 2008). The authors conclude that, while the diagnostic distinction between anorexia nervosa and bulimia nervosa remains valid, distinguishing between anorexia subtypes may have limited clinical utility. However, this does not negate the potential usefulness of establishing meaningful clinical subtypes as means of assessing prognosis, treatment, and genetic underpinnings for research purposes.

Personality, Biology, and Development

Though, there is frequently overlap and/or transition between anorexia nervosa and bulimia nervosa, and both disorders are subject to anxious and obsessional symptomology that pre and post-date the illnesses, suggesting trait-related disturbances that may predispose these individuals to the development of ED (Anderluh, Tchanturia, Rabe-Hesketh, & Treasure, 2003; Deep, Nagy, & Weltzin, 1995). Similarly, there are a range of personality characteristics, including harm-avoidance, novelty-seeking, self-directedness and cooperativeness, that differentiate women with eating disorders from their healthy counterparts, even after recovery (Klump et al., 2004; Wagner et al., 2006). These
personality traits have been associated with either over-inhibition or extreme disinhibition in individuals with ED (Wagner et al., 2006). A disturbance in emotional processing is thought to be a core characteristic of eating disorders. In particular, individuals with eating disorders tend to score higher on scales of alexithymia, a cognitive-affective deficit associated with impaired recognition of emotional states, than control populations (Bydlowski et al., 2005). As such, they struggle to identify emotional states in themselves and others, and similarly struggle to distinguish between emotional and physical sensations. These processing difficulties may lead predisposed individuals to develop coping strategies that ultimately take the form of disordered eating behaviors.

In addition to establishing distinct behavioral and personality profiles in ED, recent research has made headway in highlighting neurobiological alterations that may be similarly associated with ED. Specifically, researchers have suggested that disturbances in the ventral (limbic) neurocircuit, comprised of the amygdala, insula, ventral striatum, and central components of the anterior cingulated cortex (ACC) and prefrontal cortex (PFC), and the dorsal (cognitive) circuit, which includes the hippocampus, portions of the caudate, the dorsolateral prefrontal cortex (DLPFC), and parietal cortex, may contribute to the behavioral, cognitive, and emotional traits exhibited in eating disorders (Kaye, Wagner, Fudge, & Paulus, 2011). These two circuits correspond with our ability to identify the emotional significance of stimuli and produce an affective response, and to control selective attention, planning, and emotional states, respectively. Dysregulation of these circuits can be associated with abnormal feeding behaviors in ED, as well as affective and cognitive disturbances. Furthermore, it is likely that these processing irregularities occur together to create a unique profile of the disease.

Researchers have proposed multifactorial neurodevelopmental models of eating disorders. In these models a combination of genetic, biological, psychosocial, intrapersonal, and cultural factors all interact to create a susceptibility to the disease in the presence of environmental stressors (Connan, Campbell, Katzman, Lightman, & Treasure, 2003; Lena, Fiocco, & Leyenaar, 2004). In AN, deficits in emotional regulation and processing, attributed to genetic and early life factors, could result in compensatory overdependence on cognitive rules and strategies as a means of self-management (Connan et al., 2003). This corresponds with possible disturbances in the ventral (limbic) neurocircuits that may lead to
overcompensation or hyperactivity by dorsal (cognitive) circuitry (Kaye et al., 2011).
Alternatively, the ventral neurocircuitry could be relatively unimpaired, but its functioning could be inhibited by dorsal-striatal pathways. These dysregulations in neurocircuitry may likewise contribute to traits such as perfectionism, obsessionality, and cognitive rigidity that are frequently associated with AN. The complex etiology of eating disorders lends itself to multiple avenues of research including genetics, brain imaging, personality and temperament assessment, and neuropsychological studies. Ultimately, information derived from research in these modalities can be collated to create a comprehensive picture of ED.

**Neuropsychological Studies of Anorexia Nervosa**

A number of studies have provided evidence of neuropsychological impairment associated with eating disorders. These studies have uncovered deficits in executive function, visual-spatial ability, divided and sustained attention, verbal function, and learning and memory (Lena et al., 2004). The majority of research in the field has focused primarily on deficits in executive function as exhibited in AN.

An early study that examined cognitive functioning in AN in comparison to a control group was done by Gillberg, Gillberg, Råstam, and Johansson (1996). The study, which used the Weschler Adult Intelligence Scale- Revised (WAIS-R), found that the AN group had significantly lower verbal IQ and object assembly subtest scores when compared with controls. These results are particularly noteworthy because approximately 90% of the AN group was weight restored, suggesting that the deficits were not necessarily disease-state dependent. Later studies have elucidated evidence of impaired cognitive flexibility, weak central coherence, poor abstraction, and attentional biases in anorexia nervosa (Fassino et al., 2002; Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Lopez, Tchanturia, Stahl, & Treasure, 2009; Steinglass et al., 2006; Tokley & Kemps, 2007; Wildson & Wade, 2006). In particular, cognitive flexibility, as measured by performance on a range of set-shifting tasks, has been implicated as a relatively consistent impairment in anorexia nervosa (Holliday et al., 2005; Nakazato et al., 2009; Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Steinglass et al., 2006; Tchanturia, Campbell, Morris, & Treasure, 2005; Zastrow et al., 2009). The neuropsychological profile of people with eating disorders suggests weaknesses in cognitive flexibility/set-shifting and response inhibition and relative strengths in terms of
fewer impulsive response errors, directed (explicit) learning, and attention to detail (Treasure, Tchanturia, & Schmidt, 2005)

Coupled with genetic, biological, and psychosocial factors, cognitive impairments may contribute to the development and chronicity of AN. Lena et al. (2004) propose that neuropsychological deficits underlie the etiology of ED and contribute to acute symptomology and relapse. In their model, the authors suggest that cognitive deficits in childhood and adolescence can impact physical and emotional maturation and, in the context of environmental stressors, predispose certain individuals to develop ED. For example, an otherwise high functioning individual with neuropsychological deficits in executive and attentional processing may struggle to handle the emotional, interpersonal, and maturational pressures of adolescence and develop maladaptive coping strategies. In the case of AN, attentional or perceptual impairments may cause an individual to develop rigid strategies of cognitive control that contribute to the development and perpetuation of disordered eating patterns. Studies of ill and recovered individuals show that neurocognitive deficits are often exacerbated during the acute stage of illness, but do not entirely remit with recovery (Gillberg et al., 2010; Lopez et al., 2009; Mikos et al., 2008; Tchanturia, Morris, et al., 2004). In fact, evidence from the Minnesota Starvation Experiment showed that restricting food intake led to increasingly rigid thinking and behavior surrounding food, presumably in a population without premorbid vulnerabilities to cognitive inflexibility (Friederich & Herzog, 2011). Additionally, certain neurocognitive disturbances may make some people particularly successful in maintaining eating disorder behavior and cognitions. For example, strict adherence to rules and attention to detail could contribute to highly restrictive and rigid eating pathology (Treasure et al., 2005). Steinglass and Walsh (2006) propose a model of AN whereby perseverative eating behaviors are mediated by impairments in non-declarative (habit) learning, such that dieting behavior is over-learned and becomes commensurately difficult to cease. This has profound implications for treatment, as effective intervention may require modifying the cognitive functioning that contributes to the disease in order to attain and maintain recovery.
SET-SHIFTING

Set-shifting refers to the ability to switch back and forth between several tasks, operations, mental sets, or behavioral objectives (Miyake et al., 2000). Set-shifting has been used as a measure of cognitive flexibility for many years using a range of tasks: the Wisconsin Card Sorting Task (WCST), the Trailing Making Test A and B (TMT), the Haptic Illusion Task, the Brixton Test, the CatBat task, Delis-Kaplan Executive Function System (D-KEFS), and the Cambridge Neuropsychological Test Automated Battery (CANTAB) set-shifting subtest. Of these, the WCST is a particularly well-known measure of set-shifting ability.

Set-shifting is not necessarily a unidimensional construct. Though a test such as the WCST may accurately test for what we call a set-shifting impairment, the mechanism for the impairment is not always clear. Researchers have categorized set-shifting based on a number of different factors, including relevance of the switching dimensions, type of dimension, response versus stimulus shifts, and component processes.

Owen et al. (1993) posit two types of potential impairments that might lead to a deficit in set-shifting: an inability to switch from a dimension that was previously attended to (‘perseveration’) or an inability to shift to a dimension that was previously irrelevant (‘learned irrelevance’). Conventional set-shifting tests are not designed to differentiate between the relative contributions of perseveration or learned irrelevance to an overall set-shifting deficit. Similarly, it may be that the different mechanisms that contribute to set-shifting impairments may be associated with different areas of neural functioning.

Within the domain of perseveration there are multiple mechanisms of perseveration. Sandson and Albert (1984) define perseveration as the “continuation or recurrence of experience or activity without the appropriate stimulus” (p. 715) and outline a new taxonomy of perseveration, which expands on taxonomies presented by previous researchers. The authors present three categories of perseveration: stuck-in-set, continuous, and recurrent, which are each distinct in process and, possibly, neuroanatomy (Sandson & Albert, 1984). Continuous perseverance refers to “the continuous and inappropriate repetition of a current behavior”, stuck-in-set refers to “the continuous and inappropriate maintenance of a current set of framework”, and recurrent perseverance refers to the “unintentional repetition, after cessation, of a previously emitted response” (Sandson & Albert, 1984, p. 717). In an
analysis of cognitive error types using a range of neuropsychological measures, Possin et al. (2005) found that stuck-in-set and recurrent perseverations represented two distinct types of perseveration, though continuous perseverations correlated with stuck-in-set perseverations. Overall, this research highlights the ways in which different neurocognitive tasks may tap distinctly different error types, and, correspondingly, unique neuroanatomical regions.

Set-shifting can also be examined based on the type of shift that is occurring: intradimensional versus extradimensional set-shifting. Intradimensional set-shifting refers to when the correct response requires a shift to a different level within a dimension, whereas an extradimensional shift requires a change to a different dimension from previous trial (Kramer et al., 2007). These shifting subtypes have been shown to correspond to different neuroanatomical structures within the frontal lobes: ventro-medial frontal structures and the dorso-lateral prefrontal cortex, respectively (Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Similarly, it may be that shifting between stimulus sets versus response sets activates different neural networks, and show differential impairments in a range of populations (Ravizza & Ciranni, 2002). Additionally, different types of set-shifting tasks have different component processes that are required to complete the task: motor speed, visual scanning, verbal and alphabet fluency, counting, sustained attention, learning, and hand-eye coordination (Kramer et al., 2007). Tasks such as the WCST also include positive and negative feedback in response to sorting choice. In examining performance on set-shifting tasks it is key to keep in mind the modality specific aspects of the task and consider that all tasks may not be equal across populations. Similarly, different tasks are likely to have different neuroanatomical correlates and some may be better suited for exploring functional deficits than others depending on population.

**Neural Correlates of Set-Shifting and Perseveration**

A number of studies have sought to explore the neuropsychological correlates of set-shifting using populations with regionally specific brain damage or dysfunction or functional magnetic resonance imaging (fMRI) techniques. The majority of these studies have implicated the frontal cortex in set-shifting ability, however non-frontal regions, such as the basal ganglia and parietal lobe have been implicated as well (Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The prefrontal cortex (PFC) is considered the site of higher level
executive functioning that allows us to control attention, process information, engage in complex cognitions, and set goals. It is highly interconnected to almost all other brain regions and serves as the mechanism by which behaviors are guided, directed, and integrated (Zillmer, Spiers, & Culbertson, 2008). In particular, fronto-striatal circuitry has been implicated in tasks requiring cognitive flexibility and set-shifting (Monchi et al., 2001; Shafritz, Kartheiser, & Belger, 2005; Simard et al., 2011).

In an examination of set-shifting deficits in patients with frontal-lobe epilepsy and temporal-lobe epilepsy and a comparison group, McDonald et al. (2005) found that the patients with frontal-lobe epilepsy showed significantly impaired visuomotor set-shifting compared with temporal-lobe epilepsy patients and controls. This finding corroborates previous studies, which suggest that deficits in set-shifting are mediated by the PFC (Ettlin et al., 2000; Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002).

It is important to note that the component processes inherent in different set-shifting tasks may confound our ability to specify the neural correlates of set-shifting. In an effort to control for component processes, Kramer et al. (2007) used both control and switching conditions of the D-KEFS Design Fluency tasks (a non-verbal paradigm) in patients with probable Alzheimer’s, frontotemporal dementia, or semantic dementia, as well as a healthy control group. Using magnetic resonance imaging to assess brain lobar volumes, the study found that only right and left frontal lobe volumes were significantly correlated with performance on the switching task. This relationship remained significant when controlling for working memory (WM), suggesting that, though there may be conceptual and functional overlap between WM and set-shifting, they are two distinct constructs. Another study that used the D-KEFS Design Fluency, Trail Making, and Color-Word interference tasks found that the switching conditions of the tasks correlated with grey matter volumes in the bilateral prefrontal cortex and the posterior parietal lobe (Pa et al., 2010). The same study measured component process of these tasks and found increased regional specificity as these components were statistically controlled for, specifically in the case of the Design Fluency task.

Event-related functional magnetic imaging has also allowed researchers to explore neural activity associated with particular stages of shifting tasks. In an examination of the WCST card sorting task, Monchi et al. (2001) found specific involvement of prefrontal
regions during different stages of the task. For example, the dorsolateral PFC (associated with WM) was activated in response to both positive and negative feedback, whereas a cortical basal ganglia loop, which included the mid-ventrolateral PFC, caudate nucleus, and mediosorsal thalamus, only showed increased activity during negative feedback, i.e. in situations necessitating a response shift (Monchi et al., 2001). The authors also found broad activation of the posterior prefrontal cortex during both feedback and response periods, and surmised that this region was implicated in response selection. Using similar methodology, a recent study by Simard et al. (2011) assessed brain activation in healthy subjects while they performed a modified version of the WCST designed to assess lexical set-shifting. The researchers found fronto-striatal activation consistent with findings using the original WCST, but also additional activity in the ventral lateral PFC, potentially associated with the phonological components of the task (Simard et al., 2011). These studies suggest that regions in the fronto-striatal circuit are consistently activated during set-shifting, but that there is regionally specific brain activation in response to different task components and different stimulus types.

Evidence of fronto-striatal activity in set-shifting performance has led researchers to evaluate the relative contribution of the basal ganglia to set-shifting ability. The basal ganglia are associated with motor function via inhibitory modulation of movement, but are also thought to play a role in non-motor functions (Hayes, Davidson, Keele, & Rafal, 1998). Previous studies have associated basal ganglia damage with impairment in both speed and accuracy of set-shifting in both cognitive and motor-based switching tasks (Hayes et al., 1998; Owen et al., 1993). Though the basal ganglia and the frontal cortex are closely linked neuroanatomically and work in concert, damage or dysfunction to the different regions may contribute to unique types of set-shifting deficits. Several studies have examined set-shifting in patients with Parkinson’s disease (PD), which is characterized by basal ganglia dysfunction, as compared with patients with specific damage to the prefrontal cortex. These have indicated significantly different deficits in performance between the two groups. In a comparison of error type on a visual discrimination task, Owen et al. (1993) found that while frontal lobe patients’ impairment on the task could be attributed to perseverative errors, the PD patients exhibited both perseveration and learned irrelevance. This suggests that frontal cortex is not uniquely responsible for certain types of shifts, such as shifting to a previously
irrelevant dimension. Owen et al. (1993) suggest that the basal ganglia may be partially responsible for facilitating this specific type of switching, a finding further supported by Hayes et al. (1998). In another study, which used an odd-man out shifting task, patients with PD only showed impairment in the presence of response competition, whereas patients with damage to the PFC showed broader impairment (Ravizza & Ciranni, 2002). The authors point out that their tasks may have not sufficiently tapped into basal ganglia function to show widespread impairment in the PD patients, and refer to studies that suggest the basal ganglia may be primarily responsible for response set-shifts rather than stimulus set-shifts.

Based on a review studies of set-shifting in both medicated and unmedicated patients with PD, Price, Filoteo, and Maddox (2009), propose that rule shifting in response to feedback, as required by the WCST, depends on the function of the dorsal fronto-striatal circuit as a whole, rather than the independent performance of the PFC or the striatum. In a study using the WCST, Monchi et al. (2001) found increased striatal activation during negative feedback, i.e. conditions requiring a set-shift, while dorsolateral and posterior PFC activation was observable across stages of the task.

Overall, neuropsychological studies of set-shifting and its components suggest that the both frontal and striatal regions are involved in the process, with the potential for considerable specificity of these in regions for different elements of set-shifting tasks. These findings correspond with the high levels of interconnectivity between the regions as shown in anatomical studies (Alexander, DeLong, & Strick, 1986). Though our understanding of the neural networks involved in set-shifting is still evolving, current knowledge allows us to consider disruptions or deficits in specific regions and circuits when interpreting data from neuropsychological assessments. This information can be particularly valuable in assessing the contributions of neural cognitive disturbances to a disease such as AN, which has already been associated with a range of persistent neural alterations.

Set-Shifting and Anorexia Nervosa

One of the primary purposes of examining set-shifting in AN is to seek out potential neuropsychological correlates for a disease that has been shown to have demonstrable neurobiological abnormalities (Kaye, 2008; Tchanturia et al., 2005). As mentioned earlier, AN is a disease that is frequently associated with particularly rigid and inflexible phenotypic
profile. A logical correlate of this, neuropsychologically speaking, would be set-shifting. The role of set-shifting in AN may be a predisposing factor in the disease, via disrupted neural pathways, a maintenance factor, or, likely, both (Schmidt & Treasure, 2006; Steinglass et al., 2006).

A research team led by Dr. Janet Treasure has made particular headway in examining the presence of set-shifting deficits in individuals suffering from eating disorders. In an early study of cognitive flexibility in AN and BN, Tchanturia, Morris, et al. (2004) found that, in a battery of 14 different measures of cognitive flexibility, the group suffering from AN performed significantly lower than controls on 6 of these. Despite the fact that the AN group had significantly higher obsession and depression scores, along with significantly lower BMI, the results remained significant when these variables were entered as separate covariates. In their collaborative research, Dr. Treasure and Dr. Kate Tchanturia have used a relatively consistent battery of neuropsychological assessments: the Haptic Illusion task, the Brixton task, the Trail Making task, and the CatBat task. In an effort to establish an endophenotypic profile of neuropsychological function in AN, Holliday et al. (2005) examined discordant sister pairs of individuals suffering or remitted from AN and their unaffected sisters, with a comparison group using the aforementioned battery. Ultimately, the researchers found that the sisters with and without AN showed impaired performance on the CatBat and Haptic Illusion tasks compared with the controls, and the AN group had significantly slower TMT times than the other groups. A more recent study by Roberts, Tchanturia, and Treasure (2010) found that unaffected sisters showed increased perseveration on the WCST relative to controls. These findings suggest that, given the relative similarities in set-shifting impairment among sister pairs, set-shifting deficits may be a trait-related characteristic of AN. Additional studies have similarly found deficits in set-shifting in AN as measured by the TMT, Haptic, Catbat, and, also, the WCST (Fassino et al., 2002; Roberts et al., 2007; Steinglass et al., 2006; Tchanturia, Anderluh, et al., 2004). In a meta-analytic review of set-shifting in ED, Roberts et al. (2007) noted a range of effect sizes of the different tasks pooled across studies. The authors suggest that the disparity in effect sizes could be the result of a difference in the “potency” of the set-shifting tasks e.g. the tasks may differ both in difficulty and modality. The Haptic, Brixton, and CatBat have been used
as a measure of set-shifting in ED almost exclusively by Dr. Treasure’s research group, however, both the TMT and the WCST have been used more broadly in ED research.

In a meta-analysis of studies using the WCST to assess set-shifting in AN, Roberts et al. (2007) found a medium effect size for the presence of increased perseverative errors in the AN group pooled across five studies. Included in this group was a study by Fassino et al. (2002) that found that acutely ill AN participants took significantly longer to classify the card category and made more errors in the WCST than the control participants. The two groups did not differ, however, on perseverative responses. Another study included in the analysis found that ill AN participants made significantly more total errors and perseverative errors than controls on the same task (Steinglass et al., 2006). This result was corroborated by Nakazato et al. (2009) who, in addition to having currently ill AN participants and a control group, also had a recovered AN group. In further studies comparing these three groups, the recovered group had intermediate performance scores, with the control and ill groups on either end, indicating a continued level of impairment despite recovery (Nakazato et al., 2010; Roberts et al., 2010; Tenconi et al., 2010). It could be that impaired cognitive flexibility is exacerbated in the disease state, which remits somewhat upon recovery.

Additional evidence for this stems from a recent, large-scale study that used the WCST and found impaired performance in ill AN and BN groups relative to controls, and again, intermediate performance in the recovered AN group compared with the controls and ill AN (Tchanturia et al., 2012). It should be noted that, although a number of studies that have shown significant group differences on the WCST task, this finding has not always been consistent, with some researchers finding no evidence of significant group differences (Gillberg, Råstam, Wentz, & Gillberg, 2007; Wildson & Wade, 2006).

Efforts to associate set-shifting performance with clinical and personality features of the disease have been met with varied success. Some studies have found correlations between impaired set-shifting performance and increased anxiety, depression, perfectionism, and illness severity in eating disorder groups (Ohrmann et al., 2004; Roberts et al., 2010; Tchanturia, Morris, et al., 2004). Conversely, there have been several studies that, despite finding group differences in such clinical factors as obsessionality and depression, failed to find any significant association with cognitive flexibility (Tokley & Kemps, 2007; Wildson & Wade, 2006). Further investigation is required to understand how features that may be
associated with group membership, i.e. eating disorder groups and subtypes compared with controls, may map onto aspects of executive functioning or, alternatively, remain independent of these.

The fronto-striatal neural correlates of set-shifting have the potential to map onto our current understanding of AN as having underlying dysregulation between ventral and dorso-striatal pathways. Furthering our understanding of cognitive functioning in AN has utility for enhancing our understanding of overt behavioral characteristics associated with the disease, but can also allow further insight into the nature of the neurobiological alterations that are being elucidated through the use of brain imaging technology.

LIMITATIONS OF PREVIOUS RESEARCH

Based on the results of a range of studies of neuropsychological function in AN, there is a general consensus that there are deficits in executive functioning and, specifically cognitive flexibility. However, these studies often present somewhat differing findings or fail to replicate significant results. These inconsistencies can potentially be attributed to widely varied methodologies. First of all, there is quite a bit of variability in terms of participant characteristics. A large number of studies use acutely ill AN participants, which could render findings murky with state-related confounds. In particular, the use of ill participants makes it difficult to determine if group differences are the result of disease-state specific factors, such as malnutrition, rather than trait-specific characteristics. Within the AN participant populations, most studies do not control for subtype (restricting-type AN vs. binging/purging-type AN), nor do they have accurate measures of disease severity or duration beyond BMI. In assessing recovered AN participants, there is broad range of criteria used to establish recovery from simply weight-restored to a stable BMI for over a year. The current study aims to control for all of these issues by using strict psychiatric guidelines to establish both recovery and subtype.

In addition to irregularity in participant group composition, there is not yet an established neuropsychological battery that is used in ED research. Additionally, even in tasks that are used frequently in ED studies, there is not necessarily across-study consistency in the outcome analysis of these tasks. For instance, in using the WCST, studies have generally reported perseverative errors, but not perseverative responses. Furthermore,
outcome measures on set-shifting tasks are not always computed with consideration for the baseline component processes and/or measures of general cognitive ability. In the current study, the shifting component for each of the tasks was established using a ratio score that accounted for performance on baseline measures.

**HYPOTHESES**

The current study examined set-shifting performance in individuals recovered from AN, as well as healthy controls, using the Delis-Kaplan Executive Function Verbal Fluency, Trail Making, and Color-Word Interference Tasks, as well as the Wisconsin Card Sorting Tasks. The primary hypothesis, based on the review of previous literature, was that the recovered AN group would show broad-ranging, across-task impairment on these measures of set-shifting relative to controls. Furthermore, this impairment would persist even when the baseline component processes of the tasks are controlled for in statistical analysis.

It was further hypothesized that the set-shifting impairments would be correlated with one and other across tasks and within-groups. Additionally, it was anticipated that in the AN group, set-shifting impairment would be associated with heightened levels of perfectionism and obsessionality as measured by the Multidimensional Perfectionism Scale (MPS; Frost, Marten, Lahart, & Rosenblate, 1990) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleishmann, et al., 1989), respectively.
CHAPTER 2

METHODS

The following section describes participant recruitment, measures, and methodology of this study and discusses planned statistical analysis.

PARTICIPANTS

Participants for this research study were recruited through the University of California San Diego’s Eating Disorders Treatment and Research Program. Forty-four women between the ages of 18 and 45 were recruited for this study, of these 22 met criteria for recovery from restricting-type or purging-type anorexia nervosa (RAN) and 22 were healthy control women (CW). Of the RAN group, 86.3% were Caucasian and 13.6% were Asian, with one individual identifying as Hispanic/Latina. The CW group was comprised of 81.8% Caucasian and 18.2% Asian participants, with three individuals identifying as Hispanic/Latina. Within the group of recovered women, seven had a lifetime diagnosis of purging-type anorexia nervosa and 15 had a lifetime diagnosis of restricting-type anorexia nervosa. One CW participant did not complete the neuropsychological examination and was removed from the data set leaving a total of 21 CW for analysis. The study included only female participants due to the low prevalence of ED in males, as well as the potential for atypical symptomology in that group. All participants were right-handed, and screened using the Edinburgh Handedness Inventory (Oldfield, 1971).

The RAN group met the following criteria for inclusion: (a) must have, at some point in their life, met DSM-IV diagnosis for AN, (b) onset of illness must be 4 years prior to participation in the study, (c) the lifetime diagnosis must be for restricting-type or purging-type AN with no history of binge eating (as defined by the DSM-IV). In order to establish recovery in the RAN group, they met the following criteria: (a) no restrictive eating or other eating disorder related behaviors for 12 months prior to study participation, (b) maintenance of stable weight (± 3.0 kg) between 90% - 120% ideal body weight (IBW) for the past 12 months, (c) regular menstrual cycles for the past twelve months, (d) no current alcohol or
substance abuse/dependence, (e), no current diagnosis of a severe major affective disorder, anxiety disorder, or other psychopathology that may interfere with participation, (f) no use of psychoactive medication or antidepressants, (g) no presence of major neurological or medical disorders.

The CW group did not have or have had any stigmata suggestive of an eating disorder or any history of serious psychiatric, medical, or neurological illness. Additionally, they had maintained an IBW between 90% and 120% since menarche.

**DIAGNOSTIC AND BEHAVIORAL ASSESSMENTS**

All participants underwent a screening interview with a psychiatrist using the either the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Gibbon, Spitzer, & Williams, 1996) or the MINI-International Neuropsychiatric Interview Plus (MINI) (Sheehan et al., 1998), as well as the Module H of SCID I (modified to characterize eating disorder diagnoses), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleishmann, et al., 1989), and the Schedule for Affective Disorders and Schizophrenia Lifetime and Childhood Anxiety Section (modified) (SADS-L; Edicott & Spitzer, 1978; Fyer, Edicott, Mannuzza, & Klein, 1985). In addition, current psychopathology, temperament and personality characteristics were assessed using a range of self-report questionnaires that were filled out using surveymonkey.com. These standardized questionnaires were comprised of the Beck Depression Inventory (BDI; Beck, Ward, & Mendelson, 1961), the Spielberger State-Trait Anxiety Inventory-Version Y (STAI-Y; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Eating Disorders Inventory-2 (EDI-2; Garner, 1991), the Multidimensional Perfectionism Scale (MPS; Frost et al., 1990), the Sensation Seeking Scale (SSS; Zuckerman, Eysenck, & Eysenck, 1978), the Barratt Impulsivity Scale – 11th Revision (BIS-11; Barratt, 1983), and the Temperament and Character Inventory (TCI; Cloniger, Przybeck, & Svrakic, 1994).

**NEUROPSYCHOLOGICAL ASSESSMENTS**

In order to assess overall cognitive functioning as well as set-shifting ability in multiple modalities, a range of validated neuropsychological tasks were used.
General Intelligence and Achievement

The Wechsler Abbreviated Scale of Intelligence provided a measure of IQ by assessing performance on four subscales: Vocabulary, Block Design, Similarities, and Matrix Reasoning, which are designed to measure verbal knowledge, visual information processing, spatial and nonverbal reasoning, as well as crystallized and fluid intelligence (WASI; Wechsler, 1999). The WASI additionally provided estimates of verbal and performance IQ. The Wide Range Achievement Test Reading subtest provided a measure of academic achievement (WRAT4; Wilkinson & Robertson, 2006).

Delis-Kaplan Executive Function System

Three subtests from the Delis-Kaplan Executive Function System were used to explore set-shifting performance: Trail Making Test, Color-Word Interference, and Verbal Fluency (D-KEFS; Delis, Kaplan, & Kramer, 2001). The raw scores for these measures were assessed manually and outcome reports were generated using the D-KEFS Scoring Assistant Version 2.0 (2001).

D-KEFS Trail Making Test

The participants completed Conditions 3 (letter sequencing) and 4 (number-letter switching) from the D-KEFS Trail Making Test (TMT). Condition 3 required the participants to sequentially connect only letters on a stimulus page that contained both letters and numbers. Condition 4 required participants to sequentially switch back and forth between letters and numbers on the stimulus page. Using Condition 3 in conjunction with Condition 4 controls for component processes such as visual scanning, motor speed, and letter fluency. Performance on the task was measured by completion time along with sequencing and set-loss errors.

D-KEFS Color-Word Interference

Participants completed all four conditions of the Color-Word Interference (CWI) task. In Condition 1 (CWI-Color Naming), participants named patches of color as quickly as possible in order to provide a baseline measure of naming skills. Condition 2 (CWI-Word Reading) required participants to read the color words as quickly as possible as means of controlling for reading ability. Condition 3 (CWI-Inhibition) is an adapted Stroop paradigm
that entailed inhibiting the salient and automatic task of reading words to instead name discordant ink colors as quickly as possible. Lastly, Condition 4 (CWI-Inhibition/Switching) required participants to switch back and forth between reading the word and saying the ink color, thereby inhibiting the word. Again, completion time was the overall measure of task performance in conjunction with corrected and uncorrected errors.

**D-KEFS Verbal Fluency**

All three conditions of the Verbal Fluency (VF) task were administered. Condition 1 (VF-Letter Fluency) asked participants to name as many words beginning with the criterion letter (F, A, and S) in four 15-second intervals. The primary performance measure was the total number of correct words named in each 60-second trial with additional scores for repetition and set-loss errors. In Condition 2 (VF-Category Fluency), participants named as many words as possible in a target category (Animals and Boys’ Names in four 15-second intervals). Again, outcome measures are total number of words named in the 60-second intervals along with repetition and set-loss errors. Lastly, in Condition 3 (VF-Category Switching) the participants switched between naming items from two target categories (Fruits and Vegetables). In this condition, a total switch accuracy score was generated, in addition to independently derived naming scores and repetition and set-loss errors.

**Wisconsin Card Sorting Task**

Participants completed a computerized version of the Wisconsin Card Sorting Task (WCST; Computer Version 4, Psychological Assessment Resources). The computerized WCST is based on the standardized 128-card task developed by Heaton, Chelune, Talley, Kay and Curtiss (1993) and requires participants to match a stimulus card that appears at the bottom of a screen to one of four key cards that appears at the top of the screen. These cards are comprised of a one red triangle, two green stars, three yellow crosses, and four blue circles. As such, the matching rule can be based on color, number, or shape. Participants are given feedback after each trial on whether they correctly matched the card, however, the sorting rule changes unpredictably over the course of the task. The participants must first generate and correctly infer the correct sorting rule, and they must also be receptive to feedback and make an appropriate switch when the rule changes. Performance on the WCST was assessed using several computer generated scores including the total trials administered
and number of categories completed, as well as response and error analysis (perseverative responses, perseverative errors, nonperseverative errors, and conceptual level responses).

**DATA ANALYSIS**

Data analysis was performed using SPSS, Version 20.0 (IBM, 2011).

**Between-Group Analyses**

Preliminary between group comparisons of age, education, IBW and BMI, estimated IQ, and academic achievement were run using independent samples t tests. If significant group differences exist on any of the measures, they were included as covariates in the analysis of the neuropsychological variables.

For each of the four neuropsychological tasks, D-KEFS-TMT, D-KEFS-CWI, D-KEFS-VF, and WCST, a ratio or difference score that controlled for component processes and isolated the shift component was computed and analyzed to test the primary hypothesis.

**D-KEFS TRAIL MAKING TEST**

A one-way ANVOCA was run on a ratio difference score for time to completion of Conditions 3 (Letter Sequencing) and 4 (Number-Letter Switching) with WRAT 4 Reading as a covariate. The ratio difference score was calculated as follows: Ratio difference score = Condition 4 Time - Condition 3 Time / Condition 4 Time + Condition 3 Time. Follow-up comparisons and correlations were run on trial times, sequencing, set-loss, and time-discontinue errors.

**D-KEFS COLOR-WORD INTERFERENCE**

A one-way ANVOCA was run on a ratio difference score for time to completion of Conditions 3 (Inhibition) and 4 (Inhibition-Switching) WRAT 4 Reading as a covariate. The ratio difference score was calculated as follows: Ratio difference score Time = Condition 4 Time - Condition 3 Time / Baseline Time. The Baseline Time is the average completion times for Conditions 1 (Color Naming) and 2 (Word Reading). Follow-up comparisons were run on error totals for each condition.
**D-KEFS Verbal Fluency**

A one-way ANOVA was run on a ratio difference score for total correct responses of Animal Naming subtest of Condition 2 (Category Fluency) and 3 (Category Switching Fluency) with WRAT 4 Reading as a covariate. The Animal Naming subtest was chosen in lieu of the Category Fluency total score based on evidence that indicates that the processing and retrieval of proper nouns (Boys’ Names) as opposed to common nouns (Animal Names) may engage different semantic and neural networks (Fine, Delis, Paul, & Filoteo, 2011).

Ratio difference score = \( \frac{\text{Condition 2 (Animal) Total} - \text{Condition 3 Total}}{\text{Condition 3 Total} + \text{Condition 2 (Animal) Total}} \). Follow-up comparisons and correlations were run on correct response by trial, set-loss, and repetition errors for each condition.

**Wisconsin Card Sorting Task**

A one-way ANCOVA was run on the ratio of Perseverative Errors to Total Errors with WRAT4 Reading as a covariate. Follow-up comparisons will look at additional outcome measures of the WCST including categories to completion, trials to first category, trials administered, conceptual level responses, and failure to maintain set.

**Within-Group Analyses**

Within-group analyses will be run to assess correlations of the aforementioned shifting components across tasks. Additionally, within-group correlations will be run to assess associations between set-shifting performance and overall perfectionism using the MPS and lifetime worst obsessions score using the Y-BOCS. Follow-up analyses will also look at clinical characteristics such as lifetime low BMI and disease duration.
CHAPTER 3

RESULTS

The results are organized by the outcome variables of interest: D-KEFS Trail Making Test, D-KEFS Color-Word Interference, D-KEFS Verbal Fluency, and Wisconsin Card Sorting Task. Preliminary analyses were run on demographic and self-report variables, as summarized in Tables 1 and 2, and follow-up correlation analyses were run within-groups and are presented at the end of this section.

Table 1. Means (M), Standard Deviations (SD) and Independent Samples t-test of Participant Characteristics for Women Recovered for Anorexia Nervosa (RAN) and Healthy Control Women (CW)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RAN (n=22)</th>
<th>CW (n=21)</th>
<th>t(41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.91 (7.54)</td>
<td>24.38 (5.12)</td>
<td>-1.21</td>
<td>0.21</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.77 (1.79)</td>
<td>22.53 (2.52)</td>
<td>1.14</td>
<td>0.261</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.55 (3.07)</td>
<td>15.57 (1.21)</td>
<td>-1.36</td>
<td>0.18</td>
</tr>
<tr>
<td>WASI Full 2 IQ</td>
<td>113.95 (14.27)</td>
<td>112.90 (11.33)</td>
<td>-0.266</td>
<td>0.79</td>
</tr>
<tr>
<td>WRAT Reading</td>
<td>65.32 (2.68)</td>
<td>63.48 (3.59)</td>
<td>-1.19</td>
<td>0.06</td>
</tr>
<tr>
<td>Low BMI (kg/m²)</td>
<td>14.64 (1.59)</td>
<td>20.4 (1.19)a</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease Duration (months)</td>
<td>69.38 (68.78)b</td>
<td>0 (0.00)a</td>
<td>-2.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note. BMI = body mass index; WASI = Weschler Abbreviated Scale of Intelligence; WRAT = Wide Range Achievement Test; YBOCS = Yale-Brown Obsessive Compulsive Scale.

*a n =20. b n =21.

This section will summarize the results of the between-group analyses of the demographic variables and shifting components for each task. Assumptions of normality, linearity and homogeneity of variance and regression were examined and met in accordance with Tabachnick and Fidell (2007).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RAN</th>
<th></th>
<th></th>
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<th>CW</th>
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<tr>
<td></td>
<td>n</td>
<td>M (SD)</td>
<td>n</td>
<td>M (SD)</td>
<td>t</td>
<td>df</td>
<td>p</td>
<td></td>
<td></td>
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<tr>
<td>Beck Depression Inventory</td>
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<tr>
<td>(BDI)</td>
<td>22</td>
<td>2.14 (2.61)</td>
<td>20</td>
<td>0.25 (0.44)</td>
<td>-3.34</td>
<td>22.34</td>
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<tr>
<td>STAI-Y</td>
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<tr>
<td>State</td>
<td>22</td>
<td>27.73 (8.05)</td>
<td>20</td>
<td>23.95 (3.83)</td>
<td>-1.97</td>
<td>30.66</td>
<td>0.06</td>
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<tr>
<td>Trait</td>
<td>22</td>
<td>28.45 (6.62)</td>
<td>20</td>
<td>24.05 (3.82)</td>
<td>-2.67</td>
<td>34.12</td>
<td>0.01</td>
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<td>Eating Disorder Inventory</td>
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<tr>
<td>Drive for Thinness</td>
<td>22</td>
<td>0.95 (1.36)</td>
<td>20</td>
<td>0.20 (0.52)</td>
<td>2.41</td>
<td>27.57</td>
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<td>Bulimia</td>
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<td>20</td>
<td>0</td>
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<td>Body Dissatisfaction</td>
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<td>2.50 (3.73)</td>
<td>20</td>
<td>1.15 (3.10)</td>
<td>-1.27</td>
<td>40</td>
<td>0.21</td>
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<td>Ineffectiveness</td>
<td>22</td>
<td>0.32 (1.09)</td>
<td>20</td>
<td>0.30 (0.80)</td>
<td>-0.06</td>
<td>40</td>
<td>0.91</td>
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<td>Perfectionism</td>
<td>22</td>
<td>5.95 (3.57)</td>
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<td>4.85 (3.84)</td>
<td>-0.97</td>
<td>40</td>
<td>0.34</td>
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<td>Interpersonal Distrust</td>
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<td>0.77 (1.99)</td>
<td>20</td>
<td>0.35 (0.93)</td>
<td>-0.86</td>
<td>40</td>
<td>0.39</td>
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<td>Interoceptive Awareness</td>
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<td>20</td>
<td>0.15 (0.49)</td>
<td>-1.18</td>
<td>23.6</td>
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<td>Maturity Fears</td>
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<td>20</td>
<td>1.50 (1.96)</td>
<td>1.17</td>
<td>40</td>
<td>0.25</td>
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<td>Asceticism</td>
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<td>1.64 (1.09)</td>
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<td>2.15 (1.23)</td>
<td>1.44</td>
<td>40</td>
<td>0.16</td>
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<td>Impulse Regulation</td>
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<td>20</td>
<td>0.30 (1.13)</td>
<td>-0.44</td>
<td>40</td>
<td>0.67</td>
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<tr>
<td>Social Insecurity</td>
<td>22</td>
<td>0.91 (1.23)</td>
<td>20</td>
<td>0.50 (0.76)</td>
<td>-1.28</td>
<td>40</td>
<td>0.21</td>
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<tr>
<td>Multidimensional Perfectionism Scale (MPS)</td>
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<tr>
<td>Concern of Mistakes</td>
<td>22</td>
<td>18.27 (4.89)</td>
<td>20</td>
<td>15.00 (4.85)</td>
<td>-2.18</td>
<td>40</td>
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<td>Personal Standards</td>
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<td>40</td>
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<td>Parental Expectation</td>
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<td>39</td>
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<td>20</td>
<td>6.15 (2.01)</td>
<td>-3.69</td>
<td>29.29</td>
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<td></td>
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</tr>
<tr>
<td>Doubting of Actions</td>
<td>22</td>
<td>7.91 (2.79)</td>
<td>20</td>
<td>6.70 (2.18)</td>
<td>-1.53</td>
<td>40</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td>22</td>
<td>25.41 (3.59)</td>
<td>20</td>
<td>23.35 (4.84)</td>
<td>-1.58</td>
<td>40</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Perfectionism</td>
<td>22</td>
<td>74.68 (14.39)</td>
<td>20</td>
<td>61.45 (12.82)</td>
<td>-3.13</td>
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<td>0.003</td>
<td></td>
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</tr>
<tr>
<td>Sensation Seeking Scale</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>19</td>
<td>2.47 (1.61)</td>
<td>16</td>
<td>3.38 (2.25)</td>
<td>1.34</td>
<td>26.64</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boredom</td>
<td>19</td>
<td>1.74 (1.41)</td>
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<td>1.44 (0.96)</td>
<td>-0.72</td>
<td>33</td>
<td>0.48</td>
<td></td>
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</tr>
<tr>
<td>Thrill-seeking</td>
<td>19</td>
<td>6.05 (2.84)</td>
<td>16</td>
<td>7.81 (2.40)</td>
<td>1.96</td>
<td>33</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experience-seeking</td>
<td>19</td>
<td>5.53 (2.12)</td>
<td>16</td>
<td>5.50 (1.59)</td>
<td>-0.04</td>
<td>33</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>15.68 (5.39)</td>
<td>16</td>
<td>18.06 (5.34)</td>
<td>1.31</td>
<td>33</td>
<td>0.2</td>
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</tbody>
</table>

(table continues)
## Table 2. (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RAN</th>
<th></th>
<th>CW</th>
<th></th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M (SD)</td>
<td>n</td>
<td>M (SD)</td>
<td></td>
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</tr>
<tr>
<td>TCI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Novelty Seeking</td>
<td>21</td>
<td>18.00 (5.65)</td>
<td>19</td>
<td>19.79 (6.37)</td>
<td>0.94</td>
<td>38</td>
<td>0.35</td>
</tr>
<tr>
<td>Harm Avoidance</td>
<td>21</td>
<td>10.86 (5.89)</td>
<td>19</td>
<td>6.37 (4.14)</td>
<td>-2.76</td>
<td>38</td>
<td><strong>0.01</strong></td>
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<tr>
<td>Reward Dependence</td>
<td>21</td>
<td>19.10 (2.86)</td>
<td>19</td>
<td>17.84 (4.03)</td>
<td>-1.14</td>
<td>28</td>
<td>0.26</td>
</tr>
<tr>
<td>Persistence</td>
<td>21</td>
<td>5.81 (2.29)</td>
<td>19</td>
<td>4.89 (2.21)</td>
<td>-1.28</td>
<td>38</td>
<td>0.21</td>
</tr>
<tr>
<td>Self-Directedness</td>
<td>21</td>
<td>39.24 (3.96)</td>
<td>19</td>
<td>39.00 (3.86)</td>
<td>-0.19</td>
<td>38</td>
<td>0.85</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>21</td>
<td>38.62 (1.75)</td>
<td>19</td>
<td>37.79 (7.12)</td>
<td>-0.52</td>
<td>38</td>
<td>0.61</td>
</tr>
<tr>
<td>Self-Transcendence</td>
<td>21</td>
<td>15.76 (6.55)</td>
<td>19</td>
<td>12.68 (6.69)</td>
<td>-1.47</td>
<td>38</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Note. p < 0.05 in boldface.*

## Demographics

Independent samples t-tests were run on age, BMI, years of education, WASI Full-2 IQ, and WRAT 4 Reading subtest, as well as lifetime low BMI and YBOCS worst obsessions scores to assess for differences between the RAN and CW groups (see Table 1). The groups were significantly different lifetime low BMI $t(40) = 13.2, p < 0.001$, with the RAN group having significantly lower lifetime BMI ($M = 14.64, SD = 1.59$) than the CW group ($M = 20.4, SD = 1.19$). The RAN group also had significantly higher YBOCS worst obsessions scores ($M = 3.73, SD = 5.94$) than the CW group ($M = 0.0, SD = 0.0$), $t(40) = -2.8, p < 0.001$. The WRAT 4 Reading subtest scores, designed as a measure of academic achievement, approached significance between groups $t(41) = -1.19, p = 0.06$, with the RAN group having slightly higher scores ($M = 65.32, SD = 2.68$) than the CW group ($M = 63.48, SD = 3.59$). In order to account for any variability overall academic achievement might contribute to set-shifting ability, WRAT 4 Reading scores were added as a covariate to outcome analyses. Additional independent $t$-tests were run on the outcome scores from the self-report assessment. See Table 2 for the means, standard deviations and independent samples $t$-test for the self-report assessments.

## D-KEFS Trail Making Test

A one-way ANCOVA was run on the ratio difference score for Conditions 3 (Letter Sequencing) and 4 (Number-Letter Switching) by diagnosis using WRAT Reading scores as a covariate (see Table 3). Condition 4 scores were missing from one RAN participant for
Table 3. Means (M), Standard Deviations (SD), and ANCOVA for the Delis-Kaplan Executive Function System Trail Making Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAN (n=21)</th>
<th>CW (n= 21)</th>
<th>F(1,39)</th>
<th>p</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails Ratio score</td>
<td>0.30 (0.13)</td>
<td>0.31 (0.12)</td>
<td>0.04</td>
<td>0.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Letter Seq.: Time (seconds)</td>
<td>34.67 (9.63)</td>
<td>29.81 (7.06)</td>
<td>4.97</td>
<td><strong>0.03</strong></td>
<td>0.11</td>
</tr>
<tr>
<td>Letter Seq: Set-Loss Errors</td>
<td>0</td>
<td>0.05 (0.22)</td>
<td>1.39</td>
<td>0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>Letter Seq: Sequencing Errors</td>
<td>0</td>
<td>0.05 (0.22)</td>
<td>0.24</td>
<td>0.62</td>
<td>0.01</td>
</tr>
<tr>
<td>Letter Seq: Time Discontinue Errors</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number-Letter Switch: Time (seconds)</td>
<td>66.81 (22.60)</td>
<td>57.10 (14.64)</td>
<td>4.95</td>
<td><strong>0.03</strong></td>
<td>0.11</td>
</tr>
<tr>
<td>Number-Letter Switch: Set-Loss Errors</td>
<td>0.05 (0.22)</td>
<td>0.10 (0.3 )</td>
<td>0.57</td>
<td>0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>Number-Letter Switch: Sequencing Errors</td>
<td>0.38 (0.59)</td>
<td>0.10 (0.3 )</td>
<td>4.37</td>
<td><strong>0.04</strong></td>
<td>0.1</td>
</tr>
<tr>
<td>Number-Letter Switch Time Discontinue Errors</td>
<td>0.05 (0.22)</td>
<td>0</td>
<td>0.64</td>
<td>0.43</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Note. All analyses were run with Wide Range Achievement Test Reading Scores as a covariate. Letter Sequencing and Number-Letter Switching Time scores were both square root transformed to account for positive skewness. A small effect size (partial η²) is > 0.01, a moderate effect size is > 0.06, and a large effect size is > 0.14. 

p < 0.05 in boldface.

this analysis, so this participant was excluded from the dataset. There were no significant group differences based on this analysis, \( F(1,39) = 0.04, \ p = 0.85, \) partial η² = 0.10. To further explore this outcome, analyses were run on the time scores for Conditions 3 and 4. Square root transformations were made on these variables to account for positive skewness. Homogeneity of regression was violated for Condition 4 at \( F(1,39) = 5.06, \ p = 0.03, \) however the covariate was retained in order to maintain consistency with the primary outcome of interest. An independent one-way ANCOVA for Condition 3 revealed that the RAN group was significantly slower than the CW women, \( F(1,39) = 4.97, \ p = 0.03, \) partial η² = 0.11. Similarly, an independent one-way ANCOVA for Condition 4 revealed that the RAN group was again significantly slower than the CW group, \( F(1,39) = 4.95, \ p = 0.03, \) partial η² = 0.11. In light of the absence of a significant finding in the analysis of the ratio score, it can be inferred that this deficit was not due to the set-shifting component in \( M \) Condition 4, but a general difficulty across conditions in the RAN group compared to controls. One-way ANOCVAs of sequencing errors, set-loss errors, and time discontinue errors for each condition by group using WRAT Reading score as a covariate, revealed a significant group difference for Condition 4 sequencing errors \( \text{(SE)}, \ F(1,39) = 4.37, \ p = 0.04, \) partial η² = 0.10, with the RAN group having a higher number of average SE errors \( = 0.38, SD = 0.59 \) than the CW group \( M = .10, SD = 0.30 \). There were no other group differences in error types.
**D-KEFS Color-Word Interference**

Two control participants had incomplete test results for the D-KEFS CWI interference task. As a result the analysis was based on a cohort of 22 RAN and 19 CW participants. A one-way ANCOVA was run on the ratio difference score of Conditions 3 (Inhibition) and Condition 4 (Inhibition-Switching) by diagnosis with WRAT Reading scores as a covariate (see Table 4). Preliminary analysis of the computed ratio score revealed an outlier in the AN group with a z-score of 3.896. The source of this was a particularly slow completion time on the Switching condition, leading to both positive skewness and kurtosis of the ratio score dataset. However, no observable reason suggested that this participant be removed from the data set. In order to assess the effect of the outlier, the analysis was run on ratio scores with and without the outlying participant. Square root transformations were made to account for skewness and kurtosis of the dataset with the outlier. The dataset without the outlier met all assumptions and required no transformations. The ANCOVA with the outlier was not statistically significant, \( F(1,38) = 0.38, p = 0.54, \) partial \( \eta^2 = 0.01. \) Similarly, the ANCOVA without the outlier was not significant, \( F(1,37) = 1.45, p = 0.24, \) partial \( \eta^2 = 0.04. \) Based on an examination of the means (Table 4), the groups were very similar on the Condition times, and though the AN group was slightly slower than the CW group on Condition 3 and 4, the relative difference between the conditions was actually greater for the CW group than the AN group, suggesting an absence of shift cost. In order to explore the variable two more ratio scores were computed: the Inhibition ratio: Condition 3\_Time / Baseline and Switching ratio: Condition 4\_Time / Baseline. Independent one-way ANCOVAs, with WRAT 4 remaining as a covariate, revealed that the RAN group had a significantly higher Inhibition ratio score than the CW group, \( F(1,38) = 10.69, p = 0.002, \) partial \( \eta^2 = 0.22, \) indicating accounting for baseline performance, the RAN group was impaired on the Inhibition condition relative to the CW group. This difference did not hold over when comparing the Switching ratio, which was not statistically significant, \( F(1,38) = 1.90, p = 0.18, \) partial \( \eta^2 = 0.05. \) It appears that any difficulty that the RAN group had with the task could be contributed to difficulty in the inhibition condition rather than any added cost of shifting. There were no group differences on within-condition errors.
Table 4. Means (M), Standard Deviations (SD), and ANCOVA for the Delis-Kaplan Executive Function System Color Word Interference Task (CWI)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAN (n=22)</th>
<th>CW (n=19)</th>
<th>F(1,38)</th>
<th>p</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CWI Ratio Score</td>
<td>0.36 (0.50)</td>
<td>0.41 (0.36)</td>
<td>0.38</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>CWI Inhibition Ratio Score</td>
<td>1.95 (0.28)</td>
<td>1.75 (0.24)</td>
<td>10.69</td>
<td><strong>0.002</strong></td>
<td>0.22</td>
</tr>
<tr>
<td>CWI Switching Ratio Score</td>
<td>2.31 (0.47)</td>
<td>2.15 (0.34)</td>
<td>1.9</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>Color Naming: Time (seconds)</td>
<td>26.32 (3.20)</td>
<td>26.11 (4.77)</td>
<td>0.05</td>
<td>0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Color Naming: Total Errors</td>
<td>0.23 (0.53)</td>
<td>0.37 (0.68)</td>
<td>0.59</td>
<td>0.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Word Reading: Time (seconds)</td>
<td>18.77 (2.67)</td>
<td>10.21 (3.46)</td>
<td>1.47</td>
<td>0.23</td>
<td>0.04</td>
</tr>
<tr>
<td>Word Reading: Total Errors</td>
<td>0.23 (0.43)</td>
<td>0.16 (0.50)</td>
<td>0.12</td>
<td>0.66</td>
<td>0.005</td>
</tr>
<tr>
<td>Inhibition: Time (seconds)</td>
<td>43.86 (8.06)</td>
<td>40.16 (6.47)</td>
<td>5.84</td>
<td><strong>0.02</strong></td>
<td>0.13</td>
</tr>
<tr>
<td>Inhibition: Total Errors</td>
<td>0.95 (1.46)</td>
<td>0.95 (1.51)</td>
<td>0.15</td>
<td>0.71</td>
<td>0.004</td>
</tr>
<tr>
<td>Inhibition/ Switching: Time (sec)</td>
<td>51.86 (11.04)</td>
<td>49.58 (10.08)</td>
<td>0.93</td>
<td>0.34</td>
<td>0.02</td>
</tr>
<tr>
<td>Inhibition/ Switching: Total Errors</td>
<td>1.68 (1.76)</td>
<td>1.47 (1.84)</td>
<td>0.52</td>
<td>0.47</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note. All analyses were run with Wide Range Achievement Test Reading Scores as a covariate. CWI Ratio Score was square root transformed to account for positive skewness and kurtosis. A small effect size (partial η²) is > 0.01, a moderate effect size is > 0.06, and a large effect size is > 0.14. p < 0.05 in boldface.

**D-KEFS Verbal Fluency**

A one-way ANCOVA was run on the ratio difference score for Conditions 2 (Animal Category Fluency) and 3 (Category Switching Fluency) by diagnosis using WRAT Reading scores as a covariate (see Table 5). There were no significant group differences based on this analysis, $F(1,40) = 0.09$, $p = 0.77$, partial $\eta^2 = 0.002$. Follow-up analyses of the number of correct responses for each of these conditions did not reveal any significant results. In an independent one-way ANOCVA with WRAT4 Reading scores as a covariate, the AN group had significantly more total correct responses than the CW for the Condition 1 Letter Fluency task, $F(1,40) = 4.59$, $p = 0.04$, partial $\eta^2 = 0.10$, but this group difference did not translate to other conditions of the Verbal Fluency test. There were no significant group differences on repetition or set-loss errors for the conditions.

**Wisconsin Card Sorting Task**

Two control participants and two AN participants had incomplete test results for the WCST task. As a result the analysis was based on a cohort of 20 RAN and 19 CW participants. A one-way ANCOVA was run on the ratio of Perseverative Errors to Total Errors by diagnosis with WRAT Reading scores as a covariate (see Table 6). There were no
Table 5. Means (M), Standard Deviations (SD), and ANCOVA for the Delis-Kaplan Executive Function System Verbal Fluency Task

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAN (n=21)</th>
<th>CW (n=22)</th>
<th>F(1,40)</th>
<th>p</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency Ratio Score</td>
<td>0.16 (0.12)</td>
<td>0.17 (0.09)</td>
<td>0.09</td>
<td>0.77</td>
<td>0.002</td>
</tr>
<tr>
<td>Letter Fluency: Naming Score</td>
<td>49.05 (12.12)</td>
<td>41.57 (8.37)</td>
<td>4.59</td>
<td>0.04</td>
<td>0.1</td>
</tr>
<tr>
<td>Letter Fluency: Repetition Errors</td>
<td>0.45 (0.74 )</td>
<td>0.38 (0.92 )</td>
<td>0.05</td>
<td>0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Letter Fluency: Set-Loss Errors</td>
<td>0.55 (0.67)</td>
<td>0.43 (0.75)</td>
<td>0.83</td>
<td>0.37</td>
<td>0.02</td>
</tr>
<tr>
<td>Category Fluency (Animals): Naming Score</td>
<td>23.27 (4.45)</td>
<td>22.95 (4.38)</td>
<td>0.19</td>
<td>0.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Category Fluency (Animals): Repetition Errors</td>
<td>0.55 (1.06)</td>
<td>0.29 (0.64)</td>
<td>1.19</td>
<td>0.28</td>
<td>0.03</td>
</tr>
<tr>
<td>Category Fluency (Animals): Set-Loss Errors</td>
<td>0.14 (0.47)</td>
<td>0</td>
<td>1.39</td>
<td>0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>Category-Switching: Naming Score</td>
<td>16.50 (2.16)</td>
<td>16.10 (2.32)</td>
<td>0.99</td>
<td>0.32</td>
<td>0.02</td>
</tr>
<tr>
<td>Category-Switching: Switch Accuracy</td>
<td>15.23 (2.51)</td>
<td>14.43 (2.38)</td>
<td>1.87</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>Category-Switching: Repetition Errors</td>
<td>0.23 (0.43)</td>
<td>0.19 (0.60)</td>
<td>0.14</td>
<td>0.71</td>
<td>0.003</td>
</tr>
<tr>
<td>Category-Switching: Set-Loss Errors</td>
<td>0.55 (0.86)</td>
<td>0.67 (1.02)</td>
<td>0.12</td>
<td>0.73</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Note. All analyses were run with Wide Range Achievement Test Reading Scores as a covariate.
A small effect size (partial η²) is > 0.01, a moderate effect size is > 0.06, and a large effect size is > 0.14.
p < 0.05 in boldface.

significant group differences on the ratio score, F(1,36) = 3.14, p = 0.09, partial η² = 0.08.
The CW group did have slightly higher ratio scores (M = 0.54, SD = 0.09) than the AN group (M = 0.49, SD = 0.02). Follow-up analyses revealed that the group did not differ on number of perseverative responses or perseverative errors, however, a one-way ANCOVA on total number of errors by diagnosis with WRAT4 Reading as covariate showed that the AN group had significantly higher total errors compared with CW, F(1,36) = 4.74, p = 0.04, partial η² = 0.12. This value is presumably driven by the significantly higher number of non-perseverative errors demonstrated by the AN group compared with the control group, F(1,36) = 5.78, p = 0.02, partial η² = 0.14, however this statistic may be driven by the presence of two AN individuals with non-perseverative error values over three standard deviations from the group mean. Rerunning the analysis without these participants reduces the group difference to p = 0.11. In addition, an one-way ANCOVA of total trials administered by diagnosis with WRAT4 Reading as covariate revealed the AN group had significantly more trials administered than controls, F(1,36) = 6.29, p = 0.02, partial η² = 0.15. The groups did not differ on conceptual level responses, failure to maintain set, categories to completion, trials to first category, or learning to learn.
Table 6. Means (M), Standard Deviations (SD), and ANCOVA Results for the Wisconsin Card Sorting Task (WCST)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAN (n=20)</th>
<th>CW (n=19)</th>
<th>F(1,36)</th>
<th>p</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCST Ratio score</td>
<td>0.49 (0.02)</td>
<td>0.53 (0.09)</td>
<td>3.14</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Trials Administered</td>
<td>101.25 (22.73)</td>
<td>85.84 (18.63)</td>
<td>6.29</td>
<td><strong>0.02</strong></td>
<td>0.15</td>
</tr>
<tr>
<td>Total Correct</td>
<td>70.30 (12.99)</td>
<td>68.32 (5.51)</td>
<td>0.47</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Perseverative Errors</td>
<td>14.25 (10.83)</td>
<td>9.26 (8.01)</td>
<td>2.37</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Non-Perseverative Errors</td>
<td>16.70 (16.14)</td>
<td>8.26 (7.64)</td>
<td>5.78</td>
<td><strong>0.02</strong></td>
<td>0.14</td>
</tr>
<tr>
<td>Perseverative Responses</td>
<td>16.05 (13.03)</td>
<td>9.84 (9.23)</td>
<td>2.64</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>Total Errors</td>
<td>31.00 (24.72)</td>
<td>17.53 (15.48)</td>
<td>4.74</td>
<td><strong>0.04</strong></td>
<td>0.12</td>
</tr>
<tr>
<td>Categories Completed</td>
<td>5.00 (1.89)</td>
<td>5.74 (0.81)</td>
<td>2.94</td>
<td>0.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Trials to First</td>
<td>21.10 (26.70)</td>
<td>14.58 (6.35)</td>
<td>1.05</td>
<td>0.31</td>
<td>0.03</td>
</tr>
<tr>
<td>Conceptual Responses</td>
<td>62.70 (17.62)</td>
<td>64.42 (6.07)</td>
<td>0.29</td>
<td>0.59</td>
<td>0.01</td>
</tr>
<tr>
<td>Failure to Maintain Set</td>
<td>0.95 (0.99)</td>
<td>0.53 (6.12)</td>
<td>2.69</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>Learning to Learn</td>
<td>-0.11 (2.14)</td>
<td>1.16 (3.42)</td>
<td>1.58</td>
<td>0.22</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Note. All analyses were run with Wide Range Achievement Test Reading Scores as a covariate. A small effect size (partial η²) is > 0.01, a moderate effect size is > 0.06, and a large effect size is > 0.14. p < 0.05 in boldface.*

**WITHIN-GROUP ANALYSES**

Bivariate correlations using Pearson’s product moment correlation were run within groups on each of the main outcome variables, the Trails ratio score, CWI ratio score, VF ratio score, and the WCST ratio score, as well as the overall perfectionism score from the MPS, and the lifetime worst obsessions score from the YBOCS (the CW group did not endorse any obsessions) (see Tables 7 and 8). See Figure 1 for a representation of the ratio scores for the shifting components across tasks and groups. For the RAN, group correlations were run between the aforementioned variables as well as lifetime low BMI (M = 14.64, SD = 1.59) and AN disease duration (in months) (M = 69.38, SD = 68.78). Within the RAN group, there was a significant negative correlation between the mean life time worst obsessions score from the YBOCS (M = 3.73, SD = 5.94) and the mean WCST ratio score (M = 0.49, SD = 0.02), indicating that those individuals with higher lifetime obsessions had a lower ratio of perseverative to total errors on the WCST, r(20) = -.46, p = 0.04, however it is worth noting that only 6 participant in the total RAN sampled endorsed any obsessionality on the YBOCS, thereby limiting the meaningfulness of the correlation. Within the CW group, there was a significant positive correlation between the mean VF ratio score (M = 0.17, SD =0.09) and the mean WCST ratio score (M = 0.53, SD = 0.09), showing that those
Table 7. Within-Group Correlations between the D-KEFS Trailing Making Test Ratio, Color-Word Inference (CWI) Ratio, Verbal Flency (VF) Ratio, Wisconsin Card Sorting Task (WCST) Ratio, Overall Perfectionism, Worst Obsessions, and Lowest Lifetime BMI for Women Recovered From Anorexia Nervosa

<table>
<thead>
<tr>
<th>Trails Ratio</th>
<th>CWI Ratio</th>
<th>VF Ratio</th>
<th>WCST Ratio</th>
<th>Perfectionism</th>
<th>Worst Obsessions</th>
<th>Low BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails Ratio</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CWI Ratio</td>
<td>.177</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>VF Ratio</td>
<td>.060</td>
<td>-.066</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>WCST Ratio</td>
<td>.027&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.297</td>
<td>-.223</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Perfectionism</td>
<td>.074</td>
<td>-.205</td>
<td>.083</td>
<td>-.391</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Worst Obsessions</td>
<td>-.148</td>
<td>-.087</td>
<td>.087</td>
<td>-.462&lt;sup&gt;*&lt;/sup&gt;</td>
<td>.416</td>
<td>---</td>
</tr>
<tr>
<td>Low BMI</td>
<td>.050</td>
<td>.207</td>
<td>-.013</td>
<td>-.047</td>
<td>.095</td>
<td>-.056</td>
</tr>
<tr>
<td>AN Duration</td>
<td>-.056</td>
<td>-.271</td>
<td>-.379</td>
<td>.058&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.086</td>
<td>-.237</td>
</tr>
</tbody>
</table>

Note. For Trails ratio n = 21, CWI ratio n = 22, VF ratio n = 22, WCST ratio n = 20, MPS n = 22, Low BMI n = 22, AN Duration n = 21. CWI = Color-Word Interference; VF = Verbal Fluency, WCST = Wisconsin Card Sorting Task; BMI = Body Mass Index. Overall perfectionism from the Multidimensional Perfectionism Scale (MPS) and worst obsessions from the Yale-Brown Obsessive Compulsive Scale (YBOCS).
<sup>aN = 19</sup>
<sup>*p < .05 level.</sup>

Table 8. Within-Group Correlations between the D-KEFS Trailing Making Test Ratio, Color-Word Interference (CWI) Ratio, Verbal Flency (VF) Ratio, Wisconsin Card Sorting Task (WCST) Ratio, and Overall Perfectionism for Healthy Control Women

<table>
<thead>
<tr>
<th>Trails Ratio</th>
<th>CWI Ratio</th>
<th>VF Ratio</th>
<th>WCST Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails Ratio</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CWI Ratio</td>
<td>-.163&lt;sup&gt;a&lt;/sup&gt;</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>VF Ratio</td>
<td>.040</td>
<td>.071&lt;sup&gt;a&lt;/sup&gt;</td>
<td>---</td>
</tr>
<tr>
<td>WCST Ratio</td>
<td>.170</td>
<td>.156&lt;sup&gt;+&lt;/sup&gt;</td>
<td>.486&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Perfectionism</td>
<td>-.179</td>
<td>.288&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-.112</td>
</tr>
</tbody>
</table>

Note. For Trails ratio n = 21, CWI ratio n = 19, VF ratio n = 21, WCST ratio n = 19, MPS n = 20. CWI = Color-Word Interference; VF = Verbal Fluency, WCST = Wisconsin Card Sorting Task. Overall perfectionism from the Multidimensional Perfectionism Scale (MPS).
<sup>aN = 19, bN = 18</sup> <sup>*N = 17</sup>
<sup>*p < .05 level.</sup>
Figure 1. Mean ratio scores on the D-KEFS Trail Making Test, the D-KEFS Color-Word Interference Task, the D-KEFS Verbal Fluency Task, and the Wisconsin Card Sorting Task of women recovered from anorexia nervosa (RAN) and control women (CW). Error bars represent standard deviation. Higher values indicate greater shifting impairment.

Individuals who had a higher VF ratio score, indicating a greater switch cost, also had a higher ratio of perseverative errors to total errors on the WCST, $r(19) = -0.49, p = 0.04$. There were no other significant correlations between variables within the two groups.
CHAPTER 4

DISCUSSION

The goal of this study was to examine set-shifting performance in individuals recovered from AN, as well as healthy controls, using the Delis-Kaplan Executive Function Verbal Fluency, Trail Making, and Color-Word Interference Tasks, as well as the Wisconsin Card Sorting Tasks. It was hypothesized that women recovered from anorexia nervosa would show impairment on these tasks relative to controls when the baseline component processes of the tasks were controlled for by using a ratio score, thereby isolating the set-shifting components of the tasks. It was further hypothesized that the set-shifting impairments would be correlated with one and other across tasks and within-groups. Additionally, it was anticipated that in the AN group, a set-shifting impairment would be associated with heightened levels of perfectionism and obsessionality as measured by the Multidimensional Perfectionism Scale (MPS; Frost et al., 1990) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodmann, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989), respectively.

Each of the set-shifting tasks was analyzed using a ratio score computed to control for component processes with WRAT4 reading scores as a covariate. Though the RAN group had slower completion times than the CW group for the switching condition of the D-KEFS Trail Making Task (TMT), the absence of a significant group difference on the ratio score for the task indicates that the slower times for the RAN group may not reflect a shifting impairment. Further evidence for this are the slower completion times of the RAN group compared to controls for the letter sequencing condition. This indicates that the RAN group may be slower due to a component process, such as visual scanning, motor speed, or hand-eye coordination. Furthermore, the RAN group had a greater number of sequencing errors, but not set-loss errors, than the CW for the switching condition. Given this, the RAN group struggled with the appropriate ordering of the letters or numbers, but not switching between the two. The findings for this task highlight the utility of using a ratio score to examine task performance: what would otherwise be a possible finding of set-shifting impairment in the
RAN group based on switching condition times is deconstructed to reveal that factors other than cognitive flexibility may be at play. Several previous studies which have examined the TMT in both ill and recovered AN as compared with controls have shown a similar directionality of findings with the AN groups have slower completion times than healthy controls, without demonstrating significant group differences (Nakazato et al., 2010; Steinglass et al., 2006). The nature of the TMT task, which has been useful in the diagnosis of brain damage and focal lesions, may make it inadequate to successfully identify potentially subtle deficits in ability in high-functioning diagnostic groups such as AN (Reitan & Wolfson, 1995).

Again, the use of a ratio score to compare switching between the RAN and CW groups on the D-KEFS Color-Word Interference Task (CWI) indicated that the RAN group was not significantly impaired on the switching component of the task. In fact, the RAN group was significantly slower than the CW group on the Inhibition condition, but not the Switching condition further indicating that slower completion times are not a product of shift cost. The fact that the RAN group were slower on the Inhibition condition, even when baseline processes were accounted for using an additional ratio score, suggests that this may be a fruitful avenue of exploration in future research. While inhibition is commonly considered as a factor in the phenotypic profile of AN, it is not entirely clear how evidence of inhibition as exhibited clinically (fasting, strict adherence to rules, etc.) may map measures of inhibition from a neuropsychological standpoint (Butler & Montgomery, 2005; Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006). In the case of the current study, the slower completion times on the Inhibition condition by the RAN group can be interpreted in multiple ways. The RAN group could be exerting a greater amount of effortful control in order to inhibit the pre-potent word reading response and name the color word. This could be due neural imbalance between inhibition and disinhibition in AN that requires greater “top-down” processing in order to inhibit the salient response. Conversely, it could be that RAN, who have exhibited greater verbal fluency relative to controls in other domains, may have simply have greater difficulty blocking the automatic processing of the word due to their generally superior verbal ability. The majority of set-shifting tasks in current research include an inhibitory component, whether it be inhibiting a previously learned rule to allow for another choice (the WCST), a pre-potent and more salient response as in the
CWI, or the sequencing within a learned category in order switch to another (Verbal Fluency and Trails). It may be that what has been interpreted as a set-shifting deficit on these and other tasks in neuropsychological research of anorexia nervosa can attributed to the inhibitory processes involved. Neither the CWI interference task, based on the classic Stroop paradigm, nor the Stroop have been widely used in eating disorder neuropsychological research. The majority of studies in the field involving a Stroop paradigm have modified it to include stimuli that are targeted to ED pathology such as words relating to food or shape (Ben-Tovim & Walker, 1991; Ben-Tovim, Walker, Fok, & Yap, 1989; Dobson & Dozois, 2004; Fadardi & Bazzaz, 2011; Fassino et al., 2002). Two studies that have included the classic Stroop, which does not include a shifting component, failed to show group differences in the Stroop interference score between ill AN and control participants (Ben-Tovim et al., 1989; Steinglass et al., 2006). It is noteworthy that these previous studies did not include a baseline measure in the calculation of the inference score. Ultimately, the paucity of studies that include this paradigm and the small samples sizes make it difficult draw inferences regarding the role of attentional processing and Stroop performance among AN without the benefit of further research.

There was no evidence of set-shifting impairment in the RAN group on the D-KEFS Verbal Fluency task. In fact, the RAN group slightly outperformed the CW on this task and was particularly good at the Letter Fluency condition of the task. This supports findings that women with anorexia nervosa show strengths, particularly verbal, in some areas of neurocognitive research and are frequently considered a highly achievement oriented population (Kaye, 2008; Stedal, Landro, & Lask, 2013). Compared to the other tasks in this study, the Verbal Fluency task is the only one to require the creative generation of responses. Additionally, it is the only task that does not require visual attention or processing. Both of these factors could contribute to relative success the RAN group exhibited on this task compared with the others.

There were no significant group differences on the ratio score of the WCST. However, the RAN group had a greater number of total errors and total trials administered compared with the CW. These values were not driven by a significantly greater number of perseverative errors on the part of the RAN group, suggesting that an inability to shift set was not necessary driving force behind any general difficulty they exhibited on the task.
These findings are in keeping with studies that have found that recovered AN groups show some overall difficulty with the task based on error totals, trials administered, or trials to first category completion (Nakazato et al., 2010; Nakazato et al., 2009; Tchanturia et al., 2012). Previous studies of both ill and recovered AN have found greater numbers of perseverative responses or errors, but without accounting for other error types and total errors, it becomes contentious to interpret these as indicative of a clear set-shifting deficit. Based on previous research, there does seem to be substantial evidence that ill individuals are impaired on this task, both in terms of overall task performance as well on indices of perseveration (Fassino et al., 2002; Ohrmann et al., 2004; Sato et al., 2013; Steinglass et al., 2006; Tenconi et al., 2010). There are many cognitive processes involved in the WCST that could play a role in overall task performance including basic motor processes, sustained attention, rule maintenance, and response to feedback. In fact, the task is unique from the others used in this study, in that the computerized version provides immediate visual and verbal feedback on whether the trial was successfully completed. Response to feedback, particularly increased sensitivity to negative feedback, has identified as potentially fruitful area of exploration in AN (Bischoff-Grethe et al., 2013; Kaye, Fudge, & Paulus, 2009). If individuals with AN are differentially affected by the trial feedback and feedback valence relative to controls, this could impact overall task performance without necessarily indicating an impairment in set-shifting. Overall, further studies are needed that include this task in both ill and recovered AN populations with particular attention to the component processes of the task via either task modification or appropriate controls in analysis.

Evidence of impairment on neuropsychological tasks in an ill state, but improved or only subtly impaired performance in a recovered population lends itself to several interpretations and gets at the crux of the issues that arise when studying ill and recovered populations. It is possible that, given the relatively consistent findings of a set-shifting deficit among individuals ill with AN, but less conclusive findings among recovered individuals, the deficit is a state-related impairment that mostly remits upon recovery. Furthermore, any lasting impairments could be a scar of the disease state. Evidence of mild set-shifting difficulties among healthy sisters of individuals with AN suggest, however, that there may be some genetic predisposition to cognitive inflexibility in this population (Holliday et al., 2005; Tenconi et al., 2010). An additional, and important consideration, is
that the current study was comprised of a population of women who met strict criteria for full and sustained recovery from AN. These criteria, in an effort to explore trait-related components of the eating disorder neuropsychological profile, are among the most rigid in the field. However, there are a significant portion of women with AN who have either a chronic course of the disease or are able to attain only partial recovery (Steinhausen, 2002). It is possible that these individuals may have greater premorbid impairments in cognitive flexibility, which contribute to the chronicity of their disorder, compared with women who fully recover. Indeed, perhaps women who are able to recover from this extraordinarily intractable disease are unique in their premorbid cognitive profile or in their ability to adapt cognitive traits in order to support recovery.

There are some limitations to the current study that should be noted. First, though the RAN group was diagnostically free of any binge-eating behavior, the group did include purging-type anorexia nervosa individuals. There has been some evidence that restricting-type AN and binge-purging type AN differ on set-shifting performance, and there is additional evidence that patients with bulimia nervosa may have a distinct neurocognitive profile from those with AN (Galimberti, Martoni, Cavallini, Erzegovesi, & Bellodi, 2012; Roberts et al., 2010; Van Autreve, De Baene, Baeken, van Heeringen, & Vervaet, 2013). This suggests that further studies would benefit from strict diagnostic differentiation of eating disorder subtypes in order clarify how different neurocognitive abilities may map on to different manifestation of the disease. Furthermore, it can be difficult operationalize disease severity for the purposes of research. This study was strict in its determination of past AN diagnosis based on DSM-IV criteria and weight history, but did not account for duration, age of onset, chronicity or relapse history, all factors which could impact long-term neurological functioning. This study was limited by its modest sample size, which is a common barrier in research among eating disorder populations, particularly when the study participants must meet strict inclusionary criteria. In addition, though the RAN group was screened for current Axis I comorbidities, prior clinical history of Axis I disorders was not considered in analysis. The CW and RAN groups were comprised exclusively of Caucasian (84.1%) and Asian (15.9%) participants, with four participants identifying as Hispanic/Latina. Both the ethnic and geographic, primarily urban and suburban environments, backgrounds of participants limit the generalizability of the findings to the
United States population as a whole. Finally, given the small sample sizes and exploratory nature of the analysis, statistical corrections were not made to account for multiple comparisons. This could mean that any significant differences found between the two groups, in either the primary or secondary analyses could be the result of Type I error, and should be interpreted with caution.

With regards to the nature of this study, which was rigorous in diagnostic inclusion, standards of recovery, and attention to component processes in the neuropsychological tasks, several avenues of future research are warranted. First, the use of the ratio score suggests that what has been referred to as a “set-shifting” deficit may be more subtle or complex in this population than some studies indicate. Further effort is needed to deconstruct and delineate the components of cognitive flexibility in AN. This may require the application of novel tests that are able to distinguish subtle impairments in this particular population, as well as examine independent processes of cognitive and motor inhibition and differentiate between cognitive and behavioral shifts. Second, the field would benefit immensely from longitudinal examination of neurocognitive function across illness, recovery, and/or chronicity. Lastly, inclusion of additional disease subtypes (binging-purging type AN, BN) in further neuropsychological research could give insight into distinct cognitive profiles of the diseases. Our continued insight into the neuropsychological components of eating disorders can augment and inform our burgeoning understanding of the neurobiology of these disorders. Together, these findings could contribute to means of determining protective factors and early prognosis for eating disorders, and, ultimately, targeted and effective treatment to these deadly and confounding diseases.
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