



Is impaired set-shifting a feature of “pure” anorexia nervosa? Investigating the role of depression in set-shifting ability in anorexia nervosa and unipolar depression

Katrin E. Giel^{a,*}, Andreas Wittorf^b, Larissa Wolkenstein^c, Stefan Klingberg^b, Eyal Drimmer^a,
Michael Schönenberg^c, Alexander M. Rapp^b, Andreas J. Fallgatter^b, Martin Hautzinger^c, Stephan Zipfel^a

^a Medical University Hospital Tübingen, Department of Psychosomatic Medicine and Psychotherapy, Oslanderstr. 5, 72076 Tübingen, Germany

^b Department of Psychiatry and Psychotherapy, University Tübingen, Oslanderstr. 24, 72076 Tübingen, Germany

^c University of Tübingen, Department of Clinical Psychology and Psychotherapy, Schleichstraße 4, 72076 Tübingen, Germany

ARTICLE INFO

Article history:

Received 1 February 2012

Received in revised form

25 May 2012

Accepted 7 June 2012

Keywords:

Anorexia nervosa
Cognitive flexibility
Depression
Eating disorders
Neuropsychology
Set-shifting

ABSTRACT

Impaired set-shifting has been reported in patients with anorexia nervosa (AN) and in patients with affective disorders, including major depression. Due to the prevalent comorbidity of major depression in AN, this study aimed to examine the role of depression in set-shifting ability. Fifteen patients with AN without a current comorbid depression, 20 patients with unipolar depression (UD) and 35 healthy control participants were assessed using the Trail Making Test (TMT), the Wisconsin Card Sorting Test (WCST) and a Parametric Go/No-Go Test (PGNG). Set-shifting ability was intact in patients with AN without a comorbid depression. However, patients with UD performed significantly poorer in all three tasks compared to AN patients and in the TMT compared to healthy control participants. In both patient groups, set-shifting ability was moderately negatively correlated with severity of depressive symptoms, but was unrelated to BMI and severity of eating disorder symptoms in AN patients. Our results suggest a pivotal role of comorbidity for neuropsychological functioning in AN. Impairments of set-shifting ability in AN patients may have been overrated and may partly be due to comorbid depressive disorders in investigated patients.

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1. Introduction

Set-shifting ability is a central ability of executive function and refers to “shifting back and forth between multiple tasks, operations, or mental sets” (Miyake et al., 2000, p. 55). Impaired set-shifting ability has been reported in patients with anorexia nervosa (AN), in recovered AN patients and even their unaffected sisters (Holliday et al., 2005; Roberts et al., 2007, 2010; Tchanturia et al., 2012), suggesting it as a possible endophenotype of AN (Holliday et al., 2005). Excessive control of eating and weight as well as a common overall cognitive and behavioral rigidity have been understood as clinical features of AN that are closely related with this neuropsychological impairment (Friederich and Herzog, 2011). Recently, cognitive remediation therapy (CRT) has been developed as a novel therapy approach targeting cognitive inflexibility in AN patients (Tchanturia et al., 2007; Genders and Tchanturia, 2010). By changes in thinking style, CRT is also supposed to enhance motivation and capacity to benefit from a psychotherapy targeting core symptoms of the eating disorder (Genders and Tchanturia, 2010).

However, based on the existing evidence it is not yet clear whether impaired set-shifting is a general characteristic of AN that broadly applies to most affected patients or whether impairments specifically apply only to certain subgroups of patients. In a recent case series, Rose et al. (2012) report a high variability in profiles of neuropsychological impairments between adolescent AN patients. These cases stem from a large patient sample which has undergone neuropsychological assessment using the Ravello Profile, a global standard neuropsychological test battery. Preliminary findings by the Ravello Profile work group rather suggest that there are subgroups of patients constituting distinct clusters of neuropsychological functioning with one cluster representing AN patients with even normal performance (Rose et al., 2012).

Such relevant subgroups could form around disorder-specific aspects such as subtype of AN, severity or duration of AN. Roberts et al. (2010) report that set-shifting performance was associated with the binge/purging subtype of AN, a longer duration of illness and more severe eating disorder rituals, but was unrelated to BMI. However, other possible factors contributing to neuropsychological functioning in AN patients possibly include medication and comorbid disorders, such as depression (Fowler et al., 2006; Rose et al., 2012).

Prevalence data indicate that major depression is the most common comorbid disorder in AN with reported lifetime rates up to 86% (O'Brien and Vincent, 2003). There is consistent evidence that

* Corresponding author. Tel.: +49 7071 2986710; fax: +49 7071 294541.
E-mail address: katrin.giel@med.uni-tuebingen.de (K.E. Giel).

set-shifting ability is impaired in patients suffering from depression (Veiel, 1997; Austin et al., 2001) and also other affective disorders (Godard et al., 2011; Solé et al., 2011). Notably, in a meta-analysis on neuropsychological functioning in patients with major depressive disorder, set-shifting ability was the neuropsychological function revealing the largest differences between patients and healthy control subjects among all neuropsychological functions included (Veiel, 1997). Parallel to the field of eating disorder research, set-shifting is currently discussed as a potential endophenotype of mood disorders as it has been demonstrated in euthymic patients with unipolar depression (UD) and healthy relatives of patients with bipolar disorder (Austin et al., 2001; Clark et al., 2005).

Due to the large clinical overlap between AN and depression and shared patterns of neuropsychological impairments in both patient groups, the question raises whether depression is a possible confounding variable in the current evidence of set-shifting ability in AN. To what extent can impaired set-shifting be explained by the eating disorder versus a comorbid depression?

This question is hard to clarify by the current body of research as earlier studies have widely neglected possible effects of comorbidity on set-shifting in AN. In their systematic review and meta-analysis, Roberts et al. (2007) mention that most studies on set-shifting in AN have not even reported comorbidity in their patient samples. The evidence of the few studies accounting for possible effects of comorbid depression is inconclusive. While the title of the study by McDowell et al. (2003) states that “cognitive impairment in AN is not due to depressed mood”, this work group has used the Wechsler Adult Intelligence Scale which assesses rather intellectual ability than neuropsychological functions such as set-shifting. While neuropsychological functions can be understood as aspects contributing to overall intelligence, intellectual ability goes beyond the sum of basic neuropsychological abilities and in comparison to them, is conceptualized as a trait that is far more stable. Notably, Fowler et al. (2006) who have defined major depression disorder as exclusion criterion in their study found no set-shifting impairments in AN patients. In their investigation of set-shifting ability in a large sample of patients with different eating disorders Roberts et al. (2010) found no differences between those with intact and poor set-shifting in lifetime comorbidity, but levels of self-report depression were somewhat elevated in patients with poor set-shifting. However, conclusions for AN are difficult due to the mixed sample. In a recent study, most group differences in set-shifting performance between AN patients and healthy participants disappeared after controlling for depression severity (Abbate-Daga et al., 2011).

In order to investigate the role of depression in set-shifting ability in AN patients we chose a novel approach by comparing set-shifting ability of AN patients without a current comorbid depression with those of patients currently suffering from UD and healthy control participants (HC) who fit the patients roughly on age and were matched for gender and education. The inclusion of this psychiatric comparison group allows for the investigation of the specificity of possible impairments which is highly relevant for the advancement of disorder-specific etiological and treatment models (Dudley et al., 2011). We hypothesized that (a) both patients with AN and UD would show set-shifting impairments compared to HC, (b) patients with UD would show larger set-shifting impairments compared to patients with AN, and (c) the extent of set-shifting impairments would be related to the extent of depressive symptoms in both patient groups.

2. Methods

2.1. Sample collection

We investigated three groups of subjects: Patients with AN without a comorbid depression, patients with UD and healthy control participants (HC). Participants were recruited during a period of 16 months (March 2009–July 2010) within a larger

research project investigating the specificity of cognitive biases in different psychiatric disorders (Wittorf et al. 2012).

General prerequisites for study participations for all three groups comprised of: (a) age between 18 and 59 years, (b) verbal intelligence ≥ 80 according to a standardized German vocabulary test (Lehrl, 1992). General exclusion criteria for study participations for all three groups comprised of: (a) impairments of the central nervous system, (b) current psychotic disorder, (c) current or earlier substance dependence, (d) current substance abuse, and (e) intake of benzodiazepines in the last 7 days before testing. The exclusion criteria (b), (c) and (d) were assessed using the “Structured Clinical Interview for DSM-IV Axis I Disorders” (SCID-I; Wittchen et al., 1997), while exclusion criteria (a) and (e) were assessed by a medical anamnesis.

Patients with AN: Fifteen female patients with AN according to DSM IV (American Psychiatric Association, 2000) were recruited from specialized inpatient, day treatment and outpatient services of the University Hospital Tübingen. Nine patients were identified as belonging to the restricting subtype and six belonged to the binge/purging subtype. Specific exclusion criteria comprised of: (a) a BMI $< 12 \text{ kg/m}^2$ and (b) current major depressive episode, recurrent major depressive disorder or dysthymic disorder. If patients were on psychoactive medication during study participation, intake had to be stable for the last 4 weeks for selective serotonin reuptake inhibitors (SSRIs) and for the last week for antipsychotics. Of these 15 AN patients, four were on low-dose antipsychotics and three took an SSRI.

Patients with UD: Twenty male and female patients with a current diagnosis of a single major depressive episode without psychotic symptoms ($n=3$), a recurrent major depressive disorder without psychotic symptoms ($n=12$) and a dysthymic disorder ($n=5$) according to DSM IV (American Psychiatric Association, 2000) were recruited from the specialized outpatient service at the Department of Clinical Psychology of the University Tübingen. Specific exclusion criteria comprised of: (a) severity of depressive symptoms < 11 as assessed by the Quick Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003) (b) a BMI $< 19 \text{ kg/m}^2$, (c) current AN, and (e) intake of antipsychotics in the last 30 days prior to testing. If patients were on SSRI intake during study participation, intake had to be stable for the last 4 weeks. Twelve patients were on SSRI medication.

Control group: For each participating patient, a healthy control participant was recruited from the general community via public advertisement, resulting in 35 healthy control participants. Each control participant was recruited to fit roughly with respect to age (± 5 years) and was matched to the respective patient according to gender and education (highest graduation). Specific exclusion criteria comprised of: (a) a BMI $< 19 \text{ kg/m}^2$ and $> 25 \text{ kg/m}^2$, (b) current or earlier AN, (c) current or earlier major depressive episode, recurrent major depressive disorder or dysthymic disorder, (d) current or earlier psychotic disorder, and (e) current or earlier intake of psychoactive medication.

2.2. Demographic and clinical assessment

All participants were asked for their gender, age, highest graduation and medication intake. Patients were also asked for the duration of and the time of first treatment for their current disorder. In AN patients and their matched control participants, height and weight were measured in order to calculate BMI. UD patients and their matched control participants were asked for their height and weight in order to assess possible exclusion criteria. We used the “Structured Interview for Anorexic and Bulimic Disorders for DSM-IV and ICD-10” (SIAB-Ex; Fichter and Quadflieg, 2001) for diagnosis of the eating disorder in AN patients and the “Structured Clinical Interview for DSM-IV Axis I Disorders” (SCID; Wittchen et al., 1997) for diagnosis and exclusion of Axis I disorders in all study participants. All participants filled in the “Quick Inventory of Depressive Symptomatology” (QIDS-SR; Rush et al., 2003) to assess depressive symptomatology. AN patients and their matched control participants additionally filled in the Eating Disorder Inventory (EDI-2; Paul and Thiel, 2005) to assess symptoms related to the eating disorder.

2.3. Neuropsychological assessment

Set-shifting ability was assessed using three different tasks: The Trail Making Test (TMT; Reitan, 1992) and the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993), which are two established instruments extensively used in earlier studies both with AN and depressed patients (Austin et al., 2001; Roberts et al., 2007; Tchaturia et al., 2012), and a Parametric Go/No-Go test (PGNG; Langenecker et al., 2007) comprehending different levels of difficulty which is therefore especially sensitive to detect subtle differences in performance.

TMT: Part B of the TMT requires participants to connect orderless numbers and letters in ascending alphanumeric sequence. We have used the paper-pencil-version of the TMT (Reitan, 1992). Time required to complete part B is assessed as measure of set-shifting ability. For the TMT B, a test–retest–reliability of 0.84 was reported (Langenecker et al., 2007). Construct validity of the TMT has been confirmed in numerous studies (Sánchez-Cubillo et al., 2009).

WCST: The WCST requires participants to sort stimulus cards. The card sorting rule can either be according to color, shape or number of the displayed symbols, however, this rule has to be inferred by the participant and switches unpredictably during task administration. Sticking to an obsolete sorting rule despite

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