Cognitive flexibility and Agouti-related protein in adolescent patients with anorexia nervosa

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Summary
Introduction: Cognitive flexibility and the flexible learning and relearning of stimulus-reward-associations are important for decision-making and goal-directed behavior. Studies on patients with anorexia nervosa (AN) have shown difficulties in cognitive functions associated with malnutrition and extreme underweight. However, to date we find a lack of neuropsychological studies on cognitive flexibility among adolescent patients with AN. Furthermore, the underlying biological mechanisms remain unclear. Therefore, we aim to examine cognitive functions, especially reward association learning, as a measure of cognitive flexibility in adolescent patients with AN and investigate the relationship between Agouti-related protein (AGRP) and cognitive functions.

Methods: The study population consists of 30 patients with AN (M_age = 16.2 ± 1.2) and a healthy control group (CG) of 28 female adolescents (M_age = 16.3 ± 1.3). All subjects completed a neuropsychological test battery including the probabilistic Object Reversal Task, the Digit Symbol Test and the Trail Making Test. Patients with AN were explored before and after weight gain, the CG initially and after 3 months.

Results: Subtle deficits in cognitive flexibility were found in patients with AN compared to the CG. After weight gain, the AN group improved relative to their baseline values in most of the variables but did not reach CG values. They still showed slight impairments. Moreover the study revealed a clear association between AGRP levels and cognitive flexibility.

Discussion: Cognitive flexibility plays an important role in AN and may be modulated by abnormal levels of the appetite-regulating peptide AGRP. Even subtle impairments in cognitive flexibility can be relevant for the ability to fully engage in therapy and therefore may hinder a prosperous treatment.

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1. Introduction

AN is a severe psychiatric disorder with a long course of disease. The point prevalence varies between 0.4% and 3.4% (Gonzales et al., 2007) and the mortality rate amounts to 5.6% per decade of illness (Sullivan, 1995). A multifactor aetiology model including biological, intrapersonal, psychosocial, cultural and familial factors has been claimed regarding the genesis of AN (Herpertz-Dahlmann, 2003).

Two subtypes of AN are distinguished: the binge-purging type (AN-BP) and the restricting type (AN-R). Patients with AN-BP seem to be similar to patients with bulimia nervosa (BN) regarding personality traits, whilst differing from patients with AN-R (Vervoet et al., 2004; Rosval et al., 2006). The personality profile of patients with AN-BP and BN is similar in terms of increased impulsivity (Hueg et al., 2006). In contrast common clinical features in patients with AN-R are high levels of compulsivity, perfectionism, persistence and rituals as well as a rigid adherence to familiar and practiced paradigms, which hampers the flexible adaptation to a changing environment (Hueg et al., 2006; Schneider et al., 2008). These characteristics reduce the ability to fully engage in the therapy and hinder therefore a successful treatment. The described features in patients with AN may result from abnormalities in cognitive functions. Several studies have found difficulties in cognitive functioning, visual–spatial ability, attention, learning and memory (Lena et al., 2004). Various groups have shown that patients with AN exhibit difficulties in cognitive flexibility (Tchanturia et al., 2005; Wilsson and Wade, 2006). Cognitive flexibility is the ability to vary thoughts and behaviors in order to adapt to changing environmental conditions (Schneider and Fink, 2006). Steinglass et al. (2006) reported a reduced flexibility in AN compared to healthy control subjects regarding perseverative errors in the Wisconsin Card Sorting Test. Moreover there is a possible association between cognitive inflexibility with malnutrition and extreme underweight (Kingston et al., 1996; Ponicke et al., 2005). Nevertheless Tchanturia et al. (2004) found continued impairment of cognitive flexibility in patients who had recovered from AN. They suggested reduced cognitive flexibility to be an endophenotype of AN and therefore maybe a risk factor for developing disordered eating (Lena et al., 2004). Despite the different personality styles of patients with AN-R and AN-BP, most of the studies included both subtypes without a differentiated analysis. Solely Tchanturia et al. (2004) highlighted that the two subtypes show comparable neuropsychological performance.

The reported studies have dealt with adult patients, whilst only little is known about adolescent patients with AN (Bühren et al., 2008). This is remarkable as AN typically occurs during adolescence with a peak between the age of 15 and 19 (Steinhausen, 2005). Furthermore, cognitive impairments that occur during adolescence may exacerbate the course of disease. Early cognitive deficits may also hinder treatment efforts to a greater extent than during adulthood. Moreover there is a higher risk for chronication. There are some studies investigating cognitive functions among adolescent patients with AN but having several limitations. Witt et al. (1985) found impairments in learning ability in patients with AN, associated with duration of illness, whereas no difficulties were detected in attention, visual memory learning and psychomotor ability compared to healthy control subjects. Blanz et al. (1997) found a significantly higher IQ in patients with AN compared to patients with other disorders. Bradley et al. (1997) found no differences in cognitive functions between patients with AN and healthy control subjects at baseline assessment. At follow-up patients with AN showed a significant improvement on visuospatial tasks compared to the healthy control subjects. Neumärker et al. (2000) examined intelligence and number processing in patients with AN and healthy control subjects. The number processing performance was significantly lower in patients with AN. After weight gain, patients with AN showed significant changes in general intelligence test and number processing. Grunwald et al. (2002) reported difficulties in the haptic perception in patients with AN associated with a functional disturbance of the right parietal cortex. Fowler et al. (2006) examined 25 patients with AN and 25 healthy control subjects and found no remarkable deficits in cognitive flexibility. Accordingly, Castro-Fornielles et al. (2007) found no significant differences in cognitive functions between patients with AN and healthy control subjects. Finally, Hatch et al. (2010) found impairments on sensorimotor speed tasks in patients with AN. Nevertheless, patients with AN showed a superior working memory compared to the healthy control subjects. After weight gain, patients with AN were significantly faster on attention and cognitive function tasks. They exhibited superior verbal fluency, working memory, and a significantly superior ability to inhibit well-learnt responses.

Albeit there are some studies on cognitive functions in adolescent patients with AN, only few studies investigated cognitive flexibility in particular and only two studies included a follow-up for patients and healthy control subjects (Bradley et al., 1997; Hatch et al., 2010). Again there are no differentiated analysis for the both subtypes of AN. Furthermore, most of the studies based on small sample sizes and none of these studies aimed to investigate underlying biological mechanism.

Although there is increasing evidence for a relationship between malnutrition and cognitive functions, the underlying biological mechanisms remain unclear. Recent research has established links between cognition and appetite-regulating peptides. For example, leptin, a hormone secreted by fat cells which communicates the abundance of available energy stores to the CNS (Elmquist et al., 1999; Zhang et al., 2005), plays an important role in cognition. In this context, Morrison (2009) stated that its receptors are present in many brain areas, including cortical regions and the hippocampus related to learning and memory abilities. Leptin ameliorates hippocampal-dependent learning and memory by influencing one form of synaptic plasticity known as long-term potentiation (Harvey, 2007). Its absence in the CNS, for example in Alzheimer’s disease, has been supposed to be a direct cause of cognitive impairment (Paz-Filho et al., 2010). In AN leptin plasma levels are also suppressed (Moriya et al., 2006; Hebebrand et al., 2007), which may lead to cognitive impairments, too. Certainly, to our knowledge there is only information about the relationship between leptin and cognitive functions in general but not for cognitive flexibility in particular.

Agouti-related protein (AGRP) is another appetite-regulating peptide. It is expressed in the hypothalamus, inhibited by leptin and acts as a powerful orexigenic mediator that
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