Young adult Swedish patients with autoimmune Addison’s disease report difficulties with executive functions in daily life despite overall good cognitive performance

Annelies van’t Westeinde a, Sara Ström b, Tatja Hirvikoski c,d, Per Dahlqvist e, Jeanette Wahlberg f,g, Anton Gezelius a, Olle Kämpe h, Sophie Bensing b,†, Svetlana Lajic a*,†

a Department of Women’s and Children’s Health, Karolinska Institutet, Pediatric Endocrinology Unit, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
b Department of Molecular Medicine and Surgery, Karolinska Institute and Department of Endocrinology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
c Department of Women’s and Children’s Health, Pediatric Neuropsychiatry Unit, Center for Neurodevelopmental Disorders at Karolinska Institutet (KIND), Karolinska Institutet, SE-171 77 Stockholm Sweden
d Unit for Habilitation & Health, Stockholm County Council, Sweden
e Department of Public Health and Clinical Medicine, Umeå University, SE-901 87 Umeå, Sweden
f Department of Endocrinology and Department of Medical and Health Sciences, Linköpings University, SE-581 83 Linköping, Sweden
g Department of Internal Medicine, School of Health and Medical Sciences, Örebro University, SE-702 81 Örebro, Sweden
h Department of Medicine (Solna), Center for Molecular Medicine, Karolinska Institutet, Sweden

ARTICLE INFO

Keywords:
Addison’s disease
Cognition
Executive function
Mental fatigue

ABSTRACT

Objectives: Sub-optimal replacement of glucocorticoids (GC) in autoimmune Addison’s disease (AAD) may affect cognitive functioning. The present study therefore sought to investigate cognitive performance and self-reported problems with executive functions in a cohort of young adult patients with AAD.

Design and methods: 67 patients with AAD (39 females), mean age 32 yrs. (range 19–41), and 80 control participants (43 females), mean age 29 yrs. (range 19–43), completed neuropsychological tests estimating verbal and non-verbal intellectual ability, learning, memory and executive functioning, in addition to self-report scales assessing problems with executive functions, fatigue and symptoms of anxiety and depression.

Results: Patients performed within the average range on all cognitive tests compared to population norms. Despite average performance in neuropsychological tests by both sexes, young adult female patients with AAD experience problems with executive functions in daily life. Coping with mental fatigue and optimization of pharmacotherapy may be important factors to be addressed in order to provide timely support for patients. Future research is needed to further determine other risk factors for experiencing executive function impairments in AAD.

1. Introduction

Autoimmune Addison’s disease (AAD) is characterized by autoimmune destruction of the adrenal cortex, leading to chronic glucocorticoid (GC) and mineralocorticoid (MC) deficiency (Charmandari et al., 2014). In addition, patients lack production of androgens from the adrenals, which leads to at least 50% reduction in androgen levels for female patients (Allochio et al., 2007). More than half of the patients are diagnosed with at least one other autoimmune disease, most commonly autoimmune thyroid disorders (Betterle and Morlin, 2011; Martin-Grace...
As GCs and MCs are essential for life, AAD is fatal without prompt treatment and patients require life-long steroid replacement therapy. Current standard therapy is oral replacement with immediate release hydrocortisone (IR-HC) administered 2–3 times daily, with the morning dose being at least 50% of the total daily GC dose, in addition to the once daily administered MC fludrocortisone (Lavås and Husebye, 2003). Some female patients receive androgen replacement, most commonly in the form of dehydroepiandrosterone (DHEA), though this is currently not standard treatment (Bornstein et al., 2016).

Whilst being lifesaving for the patients, the current treatment regimen fails to mimic normal cortisol secretion and results in a sub-optimal hormonal rhythmity consisting of a much smaller number of daily pulses (Choudhury et al., 2019). Achieving optimal replacement is difficult, as too high doses of GCs may have metabolic side-effects, while undertreatment may cause adrenal crises (Husebye et al., 2021). Recently, modified-release hydrocortisone formulas have been developed, allowing patients to take GC replacement only once daily (Johannsson et al., 2012; Stewart, 2019; Whithaker et al., 2014). While preventing sharp peaks and troughs in cortisol levels, the modified-release formula further abolishes any ultradian rhythmicity.

As the brain is a major target organ for corticosteroids (Joëls, 2018; McEwen et al., 1986), the disturbed cortisol rhythm in AAD might affect brain function and cognition in patients, both on the short- and the long-term (de Kloet et al., 2018; Kalafatakis et al., 2018). Many cognitive processes require precisely regulated GC levels, in which the dynamic hormonal oscillations under natural conditions are crucial (Kalafatakis et al., 2021, 2018; Øst et al., 2017). Elevated GC levels during stress are important for memory formation, working memory and emotion regulation, whereas prolonged exposure to high GC levels cause cognitive problems and symptoms of depression (Keller et al., 2017; Lupien et al., 2005). Cognitive control and emotion regulation are executive processes that are essential for optimal daily life functioning. Executive functions may be categorized as “hot” or “cold”, depending on the presence of emotion or reward-related processing (hot), or higher-order cognitive control (cold) (Nejati et al., 2018). However, both are involved in the regulation of goal-directed behaviour and use similar, yet distinguishable, brain networks (Nejati et al., 2018; Zähringer et al., 2018). Studies on cognition and well-being in AAD show inconsistent results. Some studies find difficulties with memory (Henry et al., 2017, 2014; Tiemensma et al., 2016), mental flexibility (Tiemensma et al., 2016), attention (Blacha et al., 2021; Klement et al., 2010, 2009), intellectual abilities (Krekeler et al., 2021) and verbal learning (Henry et al., 2017; Schultebraucks et al., 2015) in patients, others identify only small differences between patients and controls (Schultebraucks et al., 2015), or even better performance of patients on an attention task (Tiemensma et al., 2016). In addition, problems with cognition in AAD might partly be mediated by sleep disturbances (Henry et al., 2017) and by duration and severity of illness, where more cognitive problems are associated with longer illness duration and having experienced more adrenal crises (Henry et al., 2014).

Patients with AAD do consistently report of impaired health related quality of life (HRQoL) and show more depressive symptoms compared to the general population, with a higher percentage of the patients being out of work and receiving disability pension (Hahn et al., 2007; Lavås et al., 2010, 2002; Tiemensma et al., 2014). Patients also frequently complain about reduced vitality, fatigue and sleep disturbances (Lavås et al., 2003). However, the complex associations between executive dysfunctions on the one hand, and fatigue and mental ill-health on the other hand have not yet been thoroughly investigated. Most studies conducted are on cohorts of around 30–60 patients (Henry et al., 2014; Schultebraucks et al., 2015; Werumeus Buning et al., 2016), with a mean age of around 50 years (Henry et al., 2014; Schultebraucks et al., 2015; Tiemensma et al., 2016; Werumeus Buning et al., 2016). Studies on younger patients with AAD are rare, both due to the rarity of the disease, and the later average age of onset. Research on younger patients is needed to identify vulnerabilities to mental ill-health or areas where support might be needed, for example to complete education. In addition, we can gain better understanding of the sensitivity of the human brain to hormonal disturbances starting at a young age.

The present study sought to investigate cognitive functioning, in addition to self-reported problems with hot and cold executive functions in daily life, in a large cohort of young adult patients with AAD. In addition, we aimed to investigate if any observed impairments are associated with self-reported fatigue, mental ill-health (symptoms of anxiety and depression) and disease-related factors including disease duration, age of onset, number of adrenal crises and medication dose. Finally, we aimed to investigate sex differences.

2. Methods

2.1. Participants

In this report, we compare patients with AAD with Swedish population controls, as part of a larger study on primary adrenal insufficiency (Karlsson et al., 2017). Exclusion criteria for controls: GC treatment, autoimmune disease, psychiatric problems and treatment in the past or present, alcohol or drug abuse, magnetic resonance imaging (MRI) contraindications, abnormal fasting levels of cholesterol, triglycerides, and insulin, or abnormal blood pressure (24-h ambulatory blood pressure measurement).

Patients with AAD between 18 and 45 years, with more than two years since diagnosis, were recruited via the Swedish Addison Registry (Dalin et al., 2017). The positive response rate was 71%. Exclusion criteria for the patient group: autoimmune polyendocrine syndrome type-1, diabetes type 1, epilepsy, history of severe psychiatric problems (such as schizophrenia or burnout, which were established via a telephone interview, patients who described being diagnosed with severe mental health problems were excluded from participation). We allowed mild depression, anxiety or the neurodevelopmental disorder Attention Deficit Hyperactivity Disorder (ADHD) and the use of anti-depressants, anxiolytics or psychostimulants, because the presence of some of these symptoms was of interest to investigate. Hypothyroidism was also allowed, given the high comorbidity with AAD. All patients had tested positive for autoantibodies against 21-hydroxylase and were well-characterized and monitored at their clinics.

The final cohort comprised 80 (43 females) controls and 67 (39 female) patients with AAD, of which 29 (19 females) with hypothyroidism. Fifty-two patients were treated with IR-HC (2 or 3 daily doses) and 15 patients had modified-release hydrocortisone medication (MR-HC), (Plenadren®) once daily. The IR-HC equivalence dose of Plenadren® was calculated as Plenadren® dose in mg* 0.806 (Johannsson et al., 2012). Eight females received DHEA treatment. Eighteen patients had been diagnosed with AAD before 18 years of age. All participants gave written informed consent to take part in the study. The study was approved by the Regional Ethical Committee of Karolinska Institutet and by the Swedish Ethical Review Authority (dnr 99 32, 2020–00564).

2.2. Procedures

The neuropsychological tests were administered by a trained psychologist (see (Karlsson et al., 2017) for details) and included assessments of: verbal and non-verbal intellectual ability (Wechsler Adult Intelligence Scale (WAIS)-IV Vocabulary,WAIS-IV Matrices (Wechsler, 2008a)); executive functions, including working memory performance (WAIS-IV Digit Span (Wechsler, 2008a)); processing speed and interference control (Wechsler Memory

et al., 2020; Pazderska and Pearce, 2017). While AAD can start at any age, it most typically occurs in young adult and middle-aged individuals, and has a slight female predominance (Bensing et al., 2016; Erichsen et al., 2009; Martin-Grace et al., 2020).
Scale (WMS-III Coding (Wechsler, 2008b) and the ability to inhibit pre-potent responses (the Stroop Task (Golden and Freshwater, 1996)); learning and long-term memory (WMS-III List Learning Test (Wechsler, 2008b)) retrieval of the list after 30 min). WAIS results were converted to scaled scores (population norm M=10, SD=3) and Stroop results to T-scores (population norm M=50, SD=10) (Karlsson et al., 2017).

Experienced executive functioning problems in the past two weeks was assessed with the Barkley Deficits in Executive Functioning Scale short form (BDEFS-SF) (Barkley, 2011)). The BDEFS-SF consists of a 20-item total score, and five four-item sub-scale scores assessing the “hot” executive functions motivation and emotion regulation and the “cold” executive functions self-management, discipline and self-organization. American age-adjusted cut-off values were used for clinically relevant subscale scores (Barkley, 2011).

We assessed symptoms of depression and anxiety in the past week (the Hospital Anxiety and Depression Scale (HADS, (Pallant and Bailey, 2005); Zignmund and Snaith, 1983)), with two seven-item subscales; Anxiety and Depression, in addition to fatigue in the past two days prior to testing (the multidimensional fatigue inventory (MFI)), which gives five four-item subscales: general fatigue, mental fatigue, physical fatigue, reduced activity and reduced motivation (Hagelin et al., 2007). We used the subscales general and mental fatigue in the present study, as we considered these most relevant for cognitive function. All subscales had good internal consistency.

Patients also reported on dose and type of medication, time of medication intake, age at diagnosis, number of adrenal crises since diagnosis (an episode of adrenal insufficiency requiring immediate hospital treatment).

2.3. Statistical analyses

2.3.1. Demographics

We determined group differences between patients and controls in: proportion of males and females, education level (higher education defined as having completed at least 3 years of university studies) (Chi-square tests), illegal drug use (Fisher’s exact test), age and alcohol use (Wilcoxon test for non-parametric data), and among AAD patients: sex differences regarding hypothyroidism (Chi-square tests), total hydrocortisone replacement dose (either IR-HC or MR-HC) number of adrenal crises, age at diagnosis, and disease duration (Wilcoxon test for non-parametric data).

2.3.2. Covariate selection

Age was used as a covariate in the comparisons where BDEFS-SF scores were the outcome, as these do not have age-corrected norms. We did not correct for sex and education (Table 1). No multiple comparisons correction was applied to not miss small but potentially relevant clinical findings, but effect sizes are reported (Cohen’s d). The significance threshold was p < 0.05, data were approximately normally distributed and no outliers affected the results. Linear regression models were used unless otherwise specified.

Table 1

| Variable | AAD (n = 67) | Control (n = 80) | p-value |
|----------|-------------|-----------------|---------|
| Sex      |             |                 |         |
| % Female | 58.2%       | 53.8%           | 0.707   |
| Age      | Mean (SD), Range |               |         |
|          | 32.3 (6.7), 29.2 (7.4) | | 0.010   |
| Education| % With higher education | |         |
|          | 41.8%       | 40.0%           | 0.628   |
| Alcohol  | N per week  |                 |         |
|          | 1.3         | 1.2             | 0.598   |

Wilcoxon test for non-parametric data is applied for group differences in Age and Alcohol use. Chi-square test are applied for group differences in Sex and Education level.

2.3.3. Main group comparisons

We compared patients with AAD to controls on all neuropsychological tests and BDEFS-SF scales: 1) AAD versus controls, 2) the interaction between diagnosis and sex, and 3) post-hoc tests divided by sex for tests where a significant interaction effect was found. BDEFS-SF scales that differed significantly between groups were used for subsequent analyses. First, Chi-square were used to test group differences in the number of participants with clinically relevant symptoms of executive function (based on American cut-off values).

2.3.4. Associated factors

Next, within the patient group, we tested if the following factors were associated with those BDEFS-SF scales: 1) MFI mental tiredness and MFI general tiredness, 2) HADS depression and HADS anxiety, and 3) disease related factors: age at diagnosis, disease duration, medication dose, number of adrenal crises, and age at testing. We then combined the significantly associated factors in a new model to assess which were most relevant for executive function problems. We also tested the relationship between these BDEFS-SF scales and performance on neuropsychological tests of executive function (Digit span and Span Board tests (forward and backward)). Finally, we assessed group differences and interactions with sex for the HADS and MFI scales.

2.3.5. Sensitivity analyses and sub-group comparisons

Within the patient cohort, we tested the effect of time of testing, order of testing (neuropsychological testing before MR-scanning or vice versa), and time since last medication intake in minutes on neuropsychological tests that differed between patients and controls. Next, we compared 1) patients with (n = 29) and without (n = 38) hypothyroidism, 2) patients on MR-HC medication (n = 15) and patients on any dose of IR-HC replacement, 3) patients taking 1–2 (n = 24) doses IR-HC and patients taking 3–4 (n = 28) doses of IR-HC per day, and 4) female patients with (n = 8) and without (n = 31) supplementary DHEA treatment, on any test that differed between patients and controls.

All analyses were conducted using the open source R software, version 3.6.1 (Team, 2013).

3. Results

3.1. Demographics

Patients with AAD were on average 3 years older than the controls (p < 0.01). There were no group differences in sex distribution, education level or drug and alcohol use (Table 1). There were no significant sex differences within the patient group regarding total daily hydrocortisone replacement dose (either IR-HC or MR-HC) number of adrenal crises, age at diagnosis, disease duration or presence of hypothyroidism (Table 2).

3.2. Main group comparisons

3.2.1. WAIS-IV and WMS-III

Overall, we found few differences in performance on the neuropsychological tests between patients and controls (Table 3, data divided by sex). Patients did score somewhat lower on verbal intellectual ability (Mean (Standard Deviation (SD)) AAD: 10.1 (2.0), Mean (SD) Controls: 10.9 (2.3), B = −0.75, p = 0.042, Cohen's d = −0.34) and visuo-spatial working memory (Span Board forward) (Mean (SD) AAD: 10.0 (3.0), Mean (SD) Controls: 11.1 (2.6), B = −1.09, p = 0.020, Cohen's d = −0.41), see Fig. 1A & B. However, performance on these tasks was within average range compared to population norms, while the control group performed above-average. There were no interactions with sex.

3.2.2. Self-reported executive function problems (BDEFS-SF)

Patients with AAD reported more problems with executive functions on the total BDEFS-SF scale (see Table 3 for data divided by sex) (Mean
Table 2
Medication use and disease characteristics of the patients with AAD.

| Type of GC | All, n = 67 | Females (F), n = 39 | Males (M), n = 28 | p-value (Female vs Male) |
|-----------|-------------|---------------------|------------------|-------------------------|
| IR-HC (n) | 52          | 29                  | 23               | 0.648                   |
| GC dose (mg/m2) | 13.1 (3.5) | 13.0 (3.5)         | 13.2 (3.5)       | 0.847                   |
| (mean (SD)) | (3.5)     | (2.7)               | (2.7)            |                         |
| MR-HC (n) | 11.8        | 11.0 (2.3)          | 13.6 (2.9)       | 0.136                   |
| GC dose (mg/m2) | 2.6 (0.7)  | 2.6 (0.7)           | 2.5 (0.7)        | 0.980                   |
| (mean (SD), SD) | (2.7)     | (2.7)               | (2.7)            |                         |
| Doses/day (mean, SD) | 1.3 (0.6)  | 1.2 (0.4)           | 1.4 (0.9)        | 0.223                   |

Table 3
Mean scores on neuropsychological tests and self-reported executive function problems for the patients with AAD and controls, split by sex. Data are presented as mean (SD). Significant findings are indicated in bold, for the tests where an interaction was found between sex and diagnostic group. *Indicates p < 0.05 for the post-hoc group comparison between female patients with AAD and female controls.

| General intellectual ability | Females | Control (n = 39) | Males | Control (n = 28) |
|-----------------------------|---------|-----------------|-------|-----------------|
| Mean (SD)                   | 11.5 (3.6) | 12.1 (3.0)           | 11.6 (2.7) | 13.1 (3.2)       |
| WAIS-JV, Matrixes (S)       | 10.7 (2.6) | 11.0 (2.6)           | 11.0 (2.3) | 11.1 (2.7)       |
| WAIS-JV, Vocabulary (S)     | 10.4 (2.2) | 10.7 (2.0)           | 9.8 (1.9)  | 11.1 (2.7)       |
| Executive Functions         |         |                  |       |                 |
| WAIS-JV, Digit Span (S)     | 12.1 (2.3) | 12.3 (2.1)           | 10.3 (2.4) | 10.3 (2.4)       |
| WAIS-JV, Coding (S)         | 10.1 (3.2) | 10.8 (2.9)           | 9.9 (2.7)  | 11.4 (2.4)       |
| WMS-III, Span Board (Forward) (S) | 11.6 (2.0) | 12.1 (1.4)      | 11.2 (2.6) | 11.8 (2.0)       |
| WMS-III, Span Board (Backward) (S) | 55.8 (6.7) | 54.9 (6.5)       | 55.3 (6.8) | 55.2 (7.0)       |
| Stroop Interference (T)     | 12.8 (2.8) | 13.2 (1.9)           | 11.9 (2.2) | 12.7 (2.2)       |
| Learning and Memory |         |                  |       |                 |
| WMS-III, Word List (LTM) (S) | 34.7 (8.9)* | 30.8 (6.4)           | 29.4 (6.2) | 30.1 (8.6)       |
| BDFES-SF Total              |         |                  |       |                 |
| BDFES-SF Self Management    | 9.0 (3.1) | 7.9 (2.8)           | 8.0 (2.7)  | 8.0 (3.2)        |
| BDFES-SF Self Organization  | 7.1 (2.7) | 5.4 (1.8)           | 5.2 (1.7)  | 5.3 (1.9)        |
| BDFES-SF Self Discipline    | 6.1 (2.1) | 5.7 (1.8)           | 5.6 (1.9)  | 5.7 (2.0)        |
| BDFES-SF Motivation         | 5.0 (1.6) | 5.2 (1.5)           | 4.9 (1.2)  | 5.9 (2.4)        |
| BDFES-SF Emotion Regulation | 7.6 (3.3) | 6.6 (2.3)           | 5.7 (2.9)  | 5.3 (1.8)        |

Abbreviations: WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; LTM, Long-term memory, i.e., recall after 30 min; S, scaled score, population norm M = 10, SD = 3; T, T-score, population norm M = 50, SD = 10; BDFES-SF; Barkley Deficit in Executive Functioning Scale – Short Form.

3.3. Factors associated with BDFES-SF scores

3.3.1. Mental ill-health

There were no differences on the HADS scales between patients and controls (Table 4). However, when correcting for age at testing, patients had higher anxiety than controls (B = −1.29, p = 0.047).

Within the patient group, symptoms of anxiety (B = 0.59, p = 0.019) and depression (B = 0.86, p = 0.012) were associated with a higher total BDFES-SF score. In addition, symptoms of depression were associated with higher self-organization subscale scores (B = 0.24, p = 0.032), while symptoms of anxiety were associated with higher emotion regulation subscale scores (B = 0.27, p = 0.021). When excluding the patients on antidepressant treatment, only the associations between anxiety and total self-reported BDFES-SF score (B = 0.79, p = 0.002) and the emotion regulation subscale score (B = −0.27, p = 0.021) remained.

3.3.2. Fatigue

Patients with AAD reported more general tiredness compared to controls (B = −2.35, p = 0.003), and there was an interaction with sex for mental tiredness (B = −3.5, p = 0.009), with only female patients reporting more mental tiredness compared to controls (B = −2.65, p = 0.002) (Table 4). These results were not changed when correcting for age at testing, with (B = −2.21, p = 0.006) for general tiredness in the whole group and (B = −2.47, p = 0.004) for mental tiredness in females.

Within the patient group, mental tiredness, but not general tiredness, was associated with higher total BDFES-SF (B = −1.21, p < 0.001), self-organization (B = 0.34, p < 0.001) and emotion regulation (B = 0.30, p = 0.020) scores. The results remained the same after excluding patients on antidepressant treatment.

3.3.3. Disease-related factors

After correcting for age at testing, only the total GC replacement dose was significantly associated with self-reported problems on the emotion regulation subscale (B = −0.30, p = 0.013), i.e. patients with lower GC replacement dose experienced more subjective problems with emotion regulation. Since patients on MR-HC are on a slightly lower average replacement dose, we re-ran the same model without those 15 patients changing the results. In the IR-HC group, we now also found an
association between GC replacement dose and BDEFS-SF total scale (B = −0.67, p = 0.044), and a positive association between number of adrenal crisis and experienced problems with emotion regulation (B = 0.25, p = 0.020).

### 3.3.4. Combined model

We combined the factors that were significantly associated with the BDEFS-SF scales in one model per outcome scale (BDEFS-SF total score, self-organization and emotion regulation) to capture the unique
contribution of each predictor in the model for the patient group. When put in the same model, MFI mental tiredness ($B = 1.19, p < 0.001$) (Fig. 2A), but not HADS depression or HADS anxiety score were significantly associated with problems on the total BDEFS-SF score. For self-organization, only MFI mental tiredness ($B = 0.36, p < 0.001$) (Fig. 2B) was associated with problems on this scale, but not HADS depression. Finally, for emotion-regulation, both total GC replacement dose ($B = –0.28, p = 0.010$) (Fig. 2C) and MFI mental tiredness ($B = 0.24, p = 0.040$) (Fig. 2D), but not HADS anxiety, were associated with problems on this scale. These relationships remained the same when excluding patients on MR-HC.

### 3.3.5. Self-reported problems on BDEFS-SF related to neuropsychological tests of executive function

In patients with AAD there was a negative association between the BDEFS-SF total score and verbal working memory (the Digit span ($B = –1.25, p = 0.001$)), as well as visuo-spatial working memory (the Span Board forward test ($B = –0.74, p = 0.030$)). In addition, there was a negative association between BDEFS-SF self-organization and verbal working memory (the Digit span ($B = –0.40, p < 0.001$)).

### 3.4. Sensitivity analyses

Longer time since last medication intake was associated with better visuo-spatial working memory ($B = 0.006, p = 0.035$). Time of testing during the day and order of testing (neuropsychological testing before MR or vice versa) did not affect performance.

### 3.5. Hypothyroidism, MR-HC, and DHEA supplementation

There were no significant differences between: patients with vs without hypothyroidism; patients on IR-HC vs MR-HC; patients taking 1–2 vs 3–4 doses of IR-HC per day; female patients with vs without DHEA supplementation on any of the outcome measures that differed between groups (visuo-spatial working memory forward, verbal ability, BDEFS-SF total, BDEFS-SF self-organization and BDEFS-SF emotion regulation).

### 4. Discussion

Young adult patients with AAD performed well within the normal range of population norms on all cognitive tasks assessed in this study. Nevertheless, female patients experienced more problems with executive functions in daily life compared to controls. These self-reported problems in the patient cohort were associated with more mental fatigue and lower GC dose.

Previous studies on cognition in AAD have mostly reported problems with verbal learning and memory, with disease duration as well as sleep quality mediating reduced cognitive performance in patients (Henry et al., 2017, 2014; Klement et al., 2010, 2009; Schultebraucks et al., 2015). Here, we report only slightly poorer results for visuo-spatial working memory, which was due to our specific control cohort that

---

**Fig. 2.** Linear associations between mental tiredness, GC replacement dose and self-reported executive functions in daily life (BDEFS-SF scores) in patients with AAD. Significant linear associations were identified, based on the combined regression models, between A: the BDEFS-SF total score and MFI mental tiredness ($B = 1.19, p < 0.001$), B: the BDEFS-SF self-organization subscale and MFI mental tiredness ($B = 0.36, p < 0.001$), and C: the BDEFS-SF emotion regulation subscale and total GC replacement dose per m2 body surface ($B = –0.28, p = 0.010$). D: the BDEFS-SF emotion regulation subscale and MFI mental tiredness ($B = –0.24, p = 0.040$). The lines displayed in the figures represent the linear associations without any other covariates in patients with AAD. Simple Pearson correlations (without covariates) were A: $r = 0.65, p < 0.001$, B: $r = 0.54, p < 0.001$, C: $r = –0.33, p = 0.006$, D: $r = 0.41, p < 0.001$. Black dots represent females, grey dots represent males.
scored above average. Our findings are in line with studies that find relatively few problems with cognition (Henry et al., 2014; Schulte-brauckts et al., 2015). In contrast to the previous studies, our cohort consists of younger patients, with a mean age of 32 yrs compared to for example mean ages of 52 (Schulte-brauckts et al., 2015) and 49 yrs. (Tiemensma et al., 2016) in others. Our observations suggest that young AAD patients are able to perform well during testing situations, even when diagnosed earlier in life than usual for this disease (Saevik A et al., 2018).

Interestingly, despite performing in the average range on the neuropsychological tests, female patients with AAD did report problems with both hot and cold executive function in their daily lives. Potentially, patients are able to compensate by effort at the time of testing, while in complex and demanding daily life situations, they struggle completing their tasks. Patients specifically reported problems on the BDEFS-SF self-organization and emotion regulation subscales. The self-organization subscale assesses problems with cold executive functions, such as having difficulties with problem-solving and clear thinking. These experienced problems might be related to the brain-fog and fatigue that patients frequently report of (Lovás et al., 2005). Unsurprisingly, self-reported mental fatigue correlated strongly with reported problems on this scale. Moreover, symptoms of depression were significantly associated with this subscale, which is in line with previous studies finding executive function problems in patients with depression (Nuoju et al., 2021). However, the combined regression model revealed that while mental tiredness had a unique contribution on the self-organization subscale, symptoms of depression did not. Nonetheless, patients reporting problems with executive functions in combination with mental fatigue might be at risk of developing depression.

The emotion regulation subscale of BDEFS-SF taps into patients’ ability to calm down or regain control when experiencing emotions. As GCs are key regulators of emotional functions, difficulties with emotion regulation could be expected in AAD patients (Kalakataks et al., 2021, 2018). Indeed, studies have shown that an increase in cortisol is necessary to regain control over emotions in a stressful situation (Henckens et al., 2012; Hermans et al., 2014). Interestingly, in addition to mental tiredness, total GC replacement dose was also associated with problems on the emotion regulation subscale. In fact, a higher dose was associated with less emotion regulation problems, suggesting that undermedication might affect these executive functions negatively. These findings are in line with a previous report of a higher GC dose correlating with less general and mental fatigue and fewer symptoms of depression (Werumeus Buning et al., 2016).

Absence of hypothalamic-pituitary-adrenal axis flexibility and problems with emotion regulation are also observed in patients with depression and anxiety (Keller et al., 2017; Pico-Perez et al., 2017). Thus, emotion regulation difficulties could predispose patients to develop mood disturbances. Indeed, nearly 20% of patients in our study had clinically relevant problems on the emotion regulation subscale, especially females. In addition, after correcting for age at testing, both male and female patients reported more anxiety than controls. It may therefore be important to carefully monitor such patients for mental ill-health.

The most distinguishing feature between male and female patients with AAD is the 50% reduction in androgens in females. Androgens are known to have a neuroprotective effect and generally have a positive influence on cognition, in particular on working memory (do Vale et al., 2014; Konowsky, 2006) and have been shown to enhance emotion regulation abilities (do Vale and Escera, 2018). A previous study found that mental fatigue improved significantly during DHEA treatment, and worsened again after washout, but did not find a positive effect of DHEA on cognitive performance after 12 months treatment (Gurnell et al., 2009). In our cohort, only eight females had DHEA supplementation, which is too few to draw any conclusions, or deduce trendsetting results. Moreover, the number of adrenal crises experienced in females needs to be investigated as a potential factor contributing to EF problems, since we found a positive relationship between number of adrenal crises and experienced emotion regulation problems in the patient group on IR-HC. In addition, GC under-treatment in females could be associated both with adrenal crises as well as problems with emotion regulation. These observations are also in line with findings of increased prevalence of mood-related disorders in women (Zender and Ohlansky, 2009). In addition, sex differences may exist in the effect of cortisol on stress regulation, perceived stress (Kogler et al., 2015), and working memory (Schoofs et al., 2013). Hence, the lack of flexible cortisol response in patients may indeed affect males and females differently. Taken together, being female with AAD seems a risk factor for experiencing executive function problems. The combined regression models further showed that the most relevant factor contributing to self-reported executive function problems was mental fatigue, in addition to GC replacement dose specifically for emotion regulation. Optimizing medication with careful follow-up might improve emotion regulation. It is also important to note that in addition to direct disease-related factors, the fact that patients need to deal with a life-threatening disease on a daily basis might in itself contribute to the experience of executive function problems. We did not find significant differences between patients on IR-HC and MR-HC in terms of cognitive function or experienced executive function problems. An association between number of adrenal crises and experienced emotion regulation problems was found only in patients on IR-HC. The lack of this association in patients on MR-HC was probably due to the small group size, with most patients having experienced zero adrenal crises. However, this observation warrants further investigation.

4.1. Limitations

The high scores in the neuropsychological tests of control participants point at a selection bias in our sample. We did not exclude patients with a history of or on current treatment for psychiatric problems such as anxiety and depression. However, we did not find significant differences between groups on symptoms of anxiety and depression. Furthermore, the results were unchanged after excluding patients on medical treatment for mood disturbances. We did not control for variables such as time of testing during the day and time since last medication intake, which might be related to variability in hormone levels. However, these factors likely did not affect the self-rating questionnaires. Finally, we conducted many separate comparisons without correcting for multiple comparisons, not to miss associations that could be clinically relevant. This might have led to type I errors.

4.2. Conclusion

Patients with AAD performed generally at average level on neuropsychological tests. Female patients experienced difficulties with executive function in their daily lives, which were related to mental tiredness and GC replacement dose. Such issues could contribute to reduced quality of life and mood disturbances. Future studies need to investigate why women are more vulnerable. The use of screening tools for mental fatigue and self-perceived problems with executive functioning in a clinical setting might be needed to help identify patients in need of extra care.

Funding

This work was supported by the Marianne and Marcus Wallenberg Foundation, the Knut and Alice Wallenberg Foundation, the International Fund raising for Congenital Adrenal Hyperplasia (IFCAH)/European Society for Pediatric Endocrinology (ESPE), the Stockholm County Council (ALF-SLL), Swedish Research Council (DNR 2021-02440 to S. L.), Region Stockholm (clinical research appointment DNR RS 2019-1140 to S.L.), the Foundations of Lisa and Johan Grönlund, Stiftelsen Primurare Barnhuset i Stockholm, Samariten, Jerringfonden, Sällskapet
References

Allolio, B., Arlt, W., Hahner, S., 2007. DHEA: why, when, and how much–DHEA replacement in adrenal insufficiency. Ann. d.endocrinol. 68, 266–273.

Barkley, R.A., 2011. Barkley Deficits in Executive Functioning Scale (BDEFS for adults). Guilford Press.

Benning, S., Hulting, A.L., Huuseby, E.S., Kampe, O., Lovas, K., 2016. MANAGEMENT OF ENDOCRINE DISEASE: Epidemiology, quality of life and complications of primary adrenal insufficiency: a review. Eur. J. Endocrinol. 175, R107–R116.

Betteer, C., Martin, L., 2011. Autoimmune Addison’s disease. Endocr. Dev. 20, 161–172.

Blaha, A.K., Rahvar, A.H., Flitsch, J., van de Loo, I., Kropp, P., Harbeck, B., 2021. Impaired attention in patients with adrenal insufficiency - impact of urophysiological therapy. Steroids 167, 108788.

Boromans, S.R., Allolio, B., Arlt, W., Barthel, A., Don-Wauchope, A., Hammer, G.D., Huuseby, E.S., Merke, D.P., Murad, M.H., Stratakis, C.A., Torpy, D.J., 2016. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 101, 364–389.

Charmandari, E., Nicolasides, N.C., Chrousos, G.P., 2014. Adrenal insufficiency. Lancet 383, 2152–2167.

Choudhury, S., Lightman, S., Meinr, K., 2019. Improving glucocorticoid replacement profiles in adrenal insufficiency. Clin. Endocrinol. 91, 367–371.

Dall, F., Nordling Eriksson, G., Dahlqvist, P., Hallgren, Å, Wahlberg, O., Ekwoll, O., Soderberg, S., Ronnelid, J., Olen, P., Winquist, O., Catrina, S.B., Kristrom, B., Laudius, M., Inanson, M., Hallidin Stenlid, M., Gustafsson, J., Gebe-Mehdini, G., Björndotter, S., Janson, Å, Akerman, A.K., Åman, J., Duchen, K., Bergbroadtrotte, R., Johannson, G., Lundskog, E., Landin-Olsson, M., Ellving, M., Wadensten, E., Hulting, A.L., Kampe, O., Benning, S., 2017. Clinical and immunological characteristics of autoimmune Addison disease: a nationwide swedish multicenter study. J. Clin. Endocrinol. Metab. 102, 379–389.

de Koot, E.R., Meijer, O.G.C., de Nicolosi, A.F., de Rijk, R.H., Joels, M., 2018. Importance of the brain corticosteroid receptor balance in metaboliticy, cognitive performance and neuro-inflammation. Front. Neuroendocrinol. 49, 124–145.

de Vode, S., Escera, C., 2018. Dehydroepiandrosterone and dehydroepiandrosterone-sulfate and emotional processing. Vitam. Horm. 108, 413–459.

de Vode, S., Selinger, L., Martins, J.M., Gomes, A.C., Bicho, M., do Corno, L., Escera, C., 2014. The relationship between dehydroepiandrosterone (DHEA), working memory and distraction–a behavioral and electrophysiological approach. PLoS One 9, e104273.

Erichsen, M.M., Lovás, K., Skinningsrud, B., Wolff, A.B., Undlien, D.E., Svartberg, J., 2005. Stress hormones and humoral memory: evidence from the large-scale brain networks in response to acute stressors. Trends Neurosci. 37, 153–164.

Ericsson, S., Zetterberg, H., Skrtic, S., 2012. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a randomised controlled trial. Psychoneuroendocrinology 124, 105096.

Kalafatakis, K., Russell, G.M., Ferguson, S.G., Grabski, M., Harmer, C.J., Munro, N.R., Marchant, N., Wilson, A., Brooks, J.C., Thakrar, J., Murphy, P., Thai, N.J., Lightman, S.L., 2021. Glucocorticoid ultradian rhythmicity differentially regulates mood and resting state networks in the human brain: A randomised controlled clinical trial. Psychoneuroendocrinology 124, 105096.

Kalafatakis, K., Russell, G.M., Harmer, C.J., Munro, M.R., Marchant, N., Wilson, A., Brooks, J.C., Durant, C., Thakrar, J., Murphy, P., Thai, N.J., Lightman, S.L., 2018. Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. Proc. Natl. Acad. Sci. USA 115, E4091–E4100.

Karlsson, I., Gezelius, A., Hivrikiotis, T., Lajic, S., 2017. Cognitive impairment in adolescents and adults with congenital adrenal hyperplasia. Clin. Endocrinol. 87, 651–659.

Keller, J., Gomez, R., Williams, G., Lembre, A., Lazerzeroni, L., Murphy Jr., G.M., Schatzberg, A.F., 2017. HPA axis in major depression: cortical, clinical symptomatology and genetic variation predict cognition. Mol. Psychiatry 22, 527–536.

Klement, J., Kubod, C., Cords, H., Oltmanns, K.H., Hulting, A.L., Wahlberg, J., Svartberg, J., Peter, A., 2010. High-calorie glucose-rich food attenuates neurocognitive symptoms in patients with Addison’s disease. J. Clin. Endocrinol. Metab. 95, 5503–5508.

Klement, J., Kubod, C., Hulting, A.L., Loeck, C., Oltmanns, K.H., Hulting, A.L., Peter, A., 2009. Effects of glucose infusion on neurocognitive and cognitive parameters in Addison disease. Metab. Clin. Exp. 58, 1825–1831.

Kogler, G., Gar, R.C., Dernel, M., 2015. Sex differences in cognitive regulation of psychosocial achievement stress: brain and behavior. Hum. Brain Mapp. 36, 1028–1042.

Krekeler, C., Kropp, P., Blacha, A.K., Rahvar, A.H., Harbeck, B., 2021. Dual-releas of hydrocortisone and its benefits on cognitive function and quality of sleep. Endocr. Rev. 40, 1–21.

Laudius, M., Inanson, M., Hulting, A.L., Huppf, P.A., Chatterjee, V.K., 2010. Development of a disease-specific quality of life questionnaire in Addison’s disease. J. Clin. Endocrinol. Metab. 95, 545–551.

Lavás, K., Hulting, E.S., 2003. Replacement therapy in Addison’s disease. Expert Opin. Pharmacother. 4, 2145–2149.

Lavás, K., Hulting, E.S., Helsten, F., Björvatn, B., 2003. Sleep disturbances in patients with Addison’s disease. Eur. J. Endocrinol. 148, 449–456.

Lavás, K., Loge, J.H., Hulting, E.S., 2002. Subjective health status in Norwegian patients with Addison’s disease. Clin. Endocrinol. 56, 581–588.

Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., Tu, M.T., 2005. Stress hormones and memory function across the lifespan. Psychoneuroendocrinology 30, 225–242.

Marin-Graice, J., Dineen, R., Sherlock, M., Thompson, C.J., 2020. Adrenal insufficiency: physiology, clinical presentation and diagnostic challenges. Clin. Chim. Acta 505, 314–319.

McEwen, B.S., de Koot, E.R., Rostene, W., 1986. Adrenal steroid receptors and actions in the nervous system. Physiol. Rev. 66, 1121–1188.

Neajli, V., Salehinejad, M.A., Nitsche, M.A., 2018. Interaction of the left dorsolateral prefrontal cortex (DLPFC) and Right Orbitofrontal Cortex (OFC) in hot and cold executive functions: evidence from transcranial direct current stimulation (tDCS). Neuroscience 369, 109–123.

Núñez, L., Gómez-Beníto, J., Carmona, V.R., Pino, O., 2021. A systematic review of executive function and information processing speed in major depression disorder. Brain Sci. 11.

Oster, H., Challet, E., Ott, V., Arvat, E., de Koot, E.R., Dijk, D.J., Lightman, S., Vgontzas, A., Van Casteren, E., 2017. The functional and clinical significance of the 24-hour rhythmicity of circulating glucocorticoids. Endocr. Rev. 38, 3–45.

Pallant, J.F., Bailey, C.M., 2005. Assessment of the structure of the hospital anxiety and depression scale in musculoskeletal patients. Health Qual. Life Outcomes 3, 82.

Paulesu, A., Lightman, S.L., 2021. Glucocorticoid ultradian rhythmicity differentially regulates mood and resting state networks in the human brain: A randomised controlled clinical trial. Psychoneuroendocrinology 124, 105096.

Garcia, H., Alos, I., Matellán, S., Bensimon, G., Pereira, A., 2012. Thinking about stress and its effects on health and well-being. Rev. Esp. Salud Pública 86, 195–203.
Schultebraucks, K., Wingenfeld, K., Heimes, J., Quinkler, M., Otte, C., 2015. Cognitive function in patients with primary adrenal insufficiency (Addison’s disease). Psychoneuroendocrinology 55, 1–7.

Stewart, P.M., 2019. Modified-release hydrocortisone: is it time to change clinical practice? J. Endocr. Soc. 3, 1150–1153.

Team, R.C., 2013. R: A language and environment for statistical computing. Team, R.C., 2013. R: A language and environment for statistical computing.

Tiemensma, J., Andela, C.D., Biermasz, N.R., Romijn, J.A., Pereira, A.M., 2016. Mild cognitive deficits in patients with primary adrenal insufficiency. Psychoneuroendocrinology 63, 170–177.

Tiemensma, J., Andela, C.D., Kaptein, A.A., Romijn, J.A., van der Mast, R.C., Biermasz, N.R., Pereira, A.M., 2014. Psychological morbidity and impaired quality of life in patients with stable treatment for primary adrenal insufficiency: cross-sectional study and review of the literature. Eur. J. Endocrinol. 171, 171–182.

Wechsler, D., 2008a. WAIS-IV Administration and Scoring Manual. Wechsler, D., 2008b. WMS-III: Wechsler Memory Scale, Third ed. Psychological Corporation, San Antonio, TX.

Werumeus Buning, J., Brummelman, P., Koerts, J., Dullaart, R.P., van den Berg, G., van der Klauw, M.M., Sluiter, W.J., Tucha, O., Wolfennbuttel, B.H., van Beek, A.P., 2016. Hydrocortisone dose influences pain, depressive symptoms and perceived health in adrenal insufficiency: a randomized controlled trial. Neuroendocrinology 103, 771–778.

Whitaker, M., Debono, M., Huatan, H., Merke, D., Arlt, W., Ross, R.J., 2014. An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure. Clin. Endocrinol. 80, 554–561.

Zaehringer, J., Falquez, R., Schubert, A.L., Nees, F., Barnow, S., 2018. Neural correlates of reappraisal considering working memory capacity and cognitive flexibility. Brain Imaging Behav. 12, 1529–1543.

Zender, R., Olshansky, E., 2009. Women’s mental health: depression and anxiety. Nurs. Clin. N. Am. 44, 355–364.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.