**Supplementary Table 1: Studies on cognitive functioning in patients with adrenal insufficiency**

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| **Study** | **Design and patients** | **Measures**  | **Main Findings** | **Comments** |

**Studies on patients with PAI vs. healthy controls**

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| Van´t Westeinde et al (2022) | Cross-sectional67 pts. with PAI on GRT vs. 80 healthy matched controls | - **Cognitive Tests** for verbal and non-verbal intellectual ability, learning, memory and executive functioning (WAIS-IV Vocabulary; Digit Span; Span Board Test; WMS-III Coding, Stroop Task, WMS-III List Learning Test) - **Self-experienced problems with executive function** (BDEFS-SF)- **Anxiety/depression** (HADS)- **Fatigue** (MFI) | - Worse intellectual ability (p=0.042) and visuo-spatial working memory (p= 0.020) in PAI pts.; however, performance within average range compared to population norms-PAI pts. reported more problems with executive functions (p= 0.030) and on the subscales self-organization (p=0.005) and emotion regulation (p= 0.017) than controls- Significant interaction with sex for the total BDEFS-SF scale (p = 0.049) and the self-organization subscale ( p = 0.011), with only female patients reporting more problems on the total scale- Self-experienced problems with executive functions in both sexes were associated with increased mental fatigue and lower GC replacement doses | - Extensive neuropsychological test battery - Executive Function, fatigue and depression assessed by self-rating- No exclusion of patients treated for mood disorders (e.g.depression), however patients on antidepressant medication were statistically considered- Selection bias possible (high neuropsychological test scores of controls, young median patient age) - Heterogenous GRT (52 IR-HC, 15 MR-HC) |
| Henry et al. (2017) | Cross-sectional, repeated measures, experimental design with a wake and a sleep condition10 pts. with PAI on conventional GRT vs. 10 healthy matched controls | - **Cognitive tests** evaluating declarative memory and procedural memory(Rey-Auditory- Verbal Learning Test; Finger Tapping Test)- **Psychiatric disorders** (Mini International Neuropsychiatric Disorders Interview)- **Depression** (BDI-II)- **Intelligence** (Shipley-2 Intelligence Test)- **Sleep** (Actigraph and Pittsburgh Sleep Diary) | - PAI pts. experienced disrupted, poor-quality sleep compared to controls - PAI pts. did not benefit from a period of sleep in terms of memory consolidation - Impaired verbal learning and memory (p=0.07) | - Authors used latent variable models to describe associations between sleep and (neuro)psychological impairments in PAI patients- Memory deficits in PAI may be associated with disrupted sleep pattern that interfere with memory consolidation - Participants with BDI-II scores > 29 were excluded |
| Tiemensma et al. (2016) | 31 pts. with PAI vs. 31 healthy matched controls | **Cognitive tests** evaluating memory and executive functioning (WMS; Rey-Verbal Learning Test; Rey Complex Figure Test; FAS; DST; Stroop task; TMT A/B; SART; GIT-2)  | - Patients with PAI performed worse on auditory and visual memory tasks (all p <0.024) and executive functioning tasks (all p <0.012).- Postponement of morning HC showed no effect- PAI pts. reported more difficulties with attention, memory and executive functioning than controls | - Mild cognitive deficits in PAI patients on long-tern HC- Patients were excluded in case of any neurological diagnosis- Presence of depressive symptoms as a confounder was not evaluated |
| Henry et al. (2015) | Cross-sectional60 pts. with PAI vs. 60 healthy matched controls | **Self-report questionnaire on cognition** (Cognitive Failures Questionnaire) **Quality of life** (SF-36)**Depression** (BDI-II) **Sleep** (PSQI) | - PAI pts. reported poorer QoL, more depressive symptoms, more sleep disruptions, more memory impairment than controls (statistically significant in several domains of the respective questionnaires)- No direct effect of PAI, but significant effect of sleep disturbances on neuropychological functioning.  | - Cognition only assessed by means of self-rating- Study design intended to assess effect of sleep pattern on neuropsychological functioning- Controlled for depression as a confounder (Bonferroni correction) |
| Schultebraucks et al. (2015) | Cross-sectional30 pts. with PAI compared to 30 healthy matched controls- | - **Cognitive tests** evaluating executive function, concentration, verbal memory, visual memory, working memory and autobiographical memory (AVLT; the Rey complex figure test; Digit Span; the Stroop task;, ZVT; AMT) - **Depression** (PHQ-9) - **Mood, fatigue** (MDBF) | - No differences in executive function, concentration, working memory, verbal memory, visuospatial memory and autobiographical memory between PAI pts. and controls but significantly worse performance in verbal learning (p=.007)- Significantly more depressive symptoms reported by PAI pts. (p= 0.014) | - No clinically relevant cognitive impairment in PAI pts. compared to controls -Significantly more pts. with mood disorders in PAI group (Bonferroni correction) |
| Henry et al. (2014) | Cross-sectional27 PAI pts. vs. 27 healthy matched controls | **- Brief test of adult cognition, administered by telephone** to assess episodic memory, working memory, executive functioning, reasoning and speed of processing- **BDI-II (depression)** | - No significant differences on attention, executive functioning, reasoning and speed of processing subtests between pts. and controls- PAI pts. performed significantly worse only on episodic memory subtest- Patients with a longer duration of illness performed more poorly across all domains (n.s.) | - Controlled for depression as a confounder (Bonferroni-correction) |
| Klement et al. (2010) | Cross-sectional10 pts. with PAI with acutely discontinued HC replacement vs. 10 healthy matched controls | - **Cognitive Tests** evaluating attention and memory (Stroop task) **- Mood** **assessments**- **Symptom scores****- Biochemical parameters** assessed before and after a high calorie free choice buffet meal (comfort food) and a low calorie salad meal | - Neuroglycopenic symptoms higher in PAI patients than in controls with improvement by comfort food in contrast to salad (p<0.04)- Reduced attention and impaired mood in PAI pts. compared to healthy participants. Pattern partially reversed after free-choice intake of comfort food | - Impaired attention in comparison to control subjects in the specific study design interpreted as neuroglycopenic feature of Addison’s disease |

**Studies on patients with PAI/SAI vs. healthy controls**

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| Krekeler et al. (2021) | Cross-sectional20 MR-HC pts. with AI compared with regard to etiology (PAI/SAI) and GRT dose (>20 mg/d); 18 of these MR-HC pts. compared to 18 matched conventionally treated patients  | - **Cognitive Tests** evaluating intellectual abilities and mindset, short-term memory, executive functioning, attention and psychomotor response capability (CFT20-R; MWT-A; DST; Digit Span; TMT-A; TMT-B; LCT; test battery for attentional performance)- **Quality of Life** (ADDIQoL, SF-36) - **Depression** (BDI)- **Sleep** (PSQI, ESS) | - Controls demonstrated significantly better psychomotor activity (p=0.037)and intellectual abilities/mindset (p= 0.031) than MR-HC treated patients- PAI pts. performed better on tasks assessing intellectual abilities (p= 0.038) executive functioning (p= 0.026) than SAI pts. - No significant impact of MR-HC dosage on cognition - Better subjective quality of sleep reported by AI pts. on high dose MR-HC (p= 0.028) than low dose MR-HC | - Extensive neuropsychological test battery, 8 a.m., standardized assessment- Small patient sample for multiple comparisons- Depression assessed but not investgated as a confounder for cognitive function- Differences between PAI and SAI pts. with regard to cognitive function |
| Blacha et al. (2021) | Cross-sectional,40 pts. with AI (21 PAI/ 19 SAI), all but 2 pts. on conventional GRT vs. 20 healthy matched controls  | **- Cognitive tests** evaluating memory, executive functioning, attention, psychomotricity and general intellectual ability (CFT20-R; MWT-A; DST; Digit Span; WAIS; TMT-A; TMT-B; LCT; test battery for attentional performance) | - Significantly prolonged reaction time (p=0.002), and impaired response to visual stimuli (p=0.005) in AI pts. compared to controls- Negative effect of high-dose GRT (> 25 mg/d) on several cognitive domains (attention, visual motoric skills, executive functioning). | - Extensive neuropsychological test battery, 8 a.m, standardized assessment- Heterogenous HC regimens- No differences between PAI and SAI with regard to cognitive function- Not controlled for depression as a confounder  |

**Studies under specific conditions**

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| Harbeck et al. (2016) | 14 pts. with PAI/SAI compared with regard to duration of HC replacement (≤15 years) | - **Cognitive tests** evaluating memory and executive functioning (WAIS; MWT-B; DST; LCT; digit span; TMT-A/B;battery for attentional performance) - **Quality of life** (unstandardized questionnaire and structured interview)- **Depression** (BDI)  | - No differences in cognition and QoL between pts. on long-term vs. short-term GRT | - Small sample size- Heterogenous HC regimens- Wide range of serum cortisol levels- Depression assessed but not investigated as a confounder for cognitive function |
| Werumeus Buning et al. (2015) | Double-blind cross-over47 pts. with SAI, investigated after 10 weeks on physiological high-dose (0.4-0.6 mg/kg body weight/d) and low-dose (0.2-0.3 mg/kg/body weight/d)  | **Cognitive tests** evaluating memory, attention, executive functioning and social cognition (RBMT; the 15 Words Test, Digit Span; the Rey Complex Figure test; the 15 Figures Test; test battery for attentional performance; FAS, TMT A/B, and the Reading the Mind in the Eyes Test) | No differences in cognitive performance were found between the two dose regimens | - Untreated growth hormone (GH) deficiency in 10 patients- Serum cortisol measured to confirm differences between high and low-dose GRT regimens- Patients with current psychiatric disorders were excluded |
| Harbeck et al. (2009) | 14 pts. with PAI (5) or SAI (9)  | - **Cognitive tests** evaluating memory, executive functioning, attention (WAIS; MWT-B; DST; LCT) after nocturnal i.v. hydrocortisone and 2-4 weeks later during oral GRT **- Biochemical parameters**- **Quality of life** (SF-36) - **Depression** (BDI)  | - Mimicking physiological cortisol rise over night by HC infusion was not associated with better cognition or better QoL in patients with PAI and SAI  | - Pilot study with small sample size- Depression assessed but not investgated as a confounder for cognitive function |

**Abbreviations:**

ADDIQoL Addison’s-disease-specific-Quality-of- life-questionnaire

AMT Autobiographical Memory test

AVLT Neuropsychological testing comprised the auditory verbal learning test

BDEFS-SF Barkley Deficits in Executive Functioning Scale short form

BDI Beck-Depressions-Inventar

CFT20-R Culture- fair-test

DST Digit symbol test

ESS Eppworth-Sleeping- Scale

FAS Verbal Fluency Test

GIT-2 Groninger Intelligence Test 2

GRT Glucocorticoid replacement therapy

HADS The Hospital Anxiety and Depression Scale

HC Hydrocortisone

IR-HC Immediate- release hydrocortisone

LCT d2 letter cancellation test

MDBF Mehrdimensionaler Befindlickeitsfragebogen

MFI The multidimensional fatigue inventory

MR-HC Modified -release hydrocortisone

MWT A/B Mehrfachwahl Wortschatz Intelligenztest A/B

PAI primary adrenal insufficiency

PHQ-9 Patient Health Questionnaire

PSQI Pittsburgh-Sleep-Quality-Index

RBMT The Rivermead Behavioral Memory Test

SAI Secondary adrenal insufficiency

SART Sustained Attention to Response Task

SF-36 Short- Form-36

TMT-A/B Trail-Making-Test A and B

WAIS Wechsler Adult Intelligence Scale (WAIS)-IV

WMS Wechsler Memory Scale

ZVT Number-Combination test