From the Department of Women's and Children's Health
Karolinska Institutet, Stockholm, Sweden

BRAIN STRUCTURE AND FUNCTION IN PRIMARY ADRENAL INSUFFICIENCY

Annelies van't Westeinde

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Brain structure and function in primary adrenal insufficiency

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By

Annelies van't Westeinde

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Principal Supervisor:
Professor Svetlana Lajic
Karolinska Institutet
Department of Women's and Children's Health
Division of Pediatric Endocrinology

Co-supervisor(s):
Associate Professor Sophie Bensing
Karolinska Institutet
Department of Molecular Medicine and Surgery

Nelly Padilla, MD, PhD
Karolinska Institutet
Department of Women's and Children's Health
Division of Neonatology

Opponent:
Professor Alberto M. Pereira Arias
Amsterdam UMC
Department of Endocrinology and Metabolism

Examination Board:
Associate Professor Daniel Ferreira Padilla
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Clinical Geriatrics

Associate Professor Erika Comasco
Uppsala University
Department of Women's and Children's Health
Division of Neuropsychopharmacology

Professor Thomas Sejersen
Karolinska Institutet
Department of Women's and Children's Health
Division of Pediatric neurology

"Trying to put the processes of nature into words is as complicated as trying to drink up the ocean with a fork."

Alan Watts

Populärvetenskaplig sammanfattning

Primär binjurebarkssvikt kan orsakas av olika sjukdomar bl.a medfödd binjurebarkshyperplasi (CAH) och autoimmun Addisons sjukdom. Individer som drabbas av dessa sjukdomar saknar de livsviktiga hormonerna kortisol och aldosteron som produceras av binjurarna. Kortisol hjälper kroppen att få tillräckligt med energi när det behövs, särskilt när man är stressad och kroppen behöver mer energi än vanligt. Hos friska människor producerar binjurarna kortisol med en specifik dygnsvariation med högst produktion och utsöndring på morgonen när man skall vakna. Kortisol produceras också i högre mängd när man är stressad eller blir sjuk och får feber. Att helt sakna kortisol och aldosteron är livsfarligt och det är därför viktigt att individer som har primär binjurebarkssvikt dagligen behandlas med läkemedel som ersätter dessa hormoner. Att styra denna behanding kan vara svårt och det finns en risk att patienterna antingen får för mycket eller för lite kortisol. De suboptimala kortisolnivåerna kan påverka kroppen negativt. Utöver metabolismen så påverkar kortisol också hjärnans struktur och funktion. Kortisol är viktigt för hjärnans normala tillväxt och för utvecklingen av den vita substansen i hjärnan. En optimal nivå av kortisol i hjärnan krävs även för att klara av olika kognitiva funktioner såsom minne, arbetsminne och för att reglera våra känslor, särkilt när man har varit stressad. Vi tror därför att sub-optimala kortisolnivåer hos individer med binjurebarkssvikt kan påverka hjärnans struktur och funktion negativt. Denna avhandling har studerat just denna hypotes. Vi har undersökt om individer med CAH och Addisons sjukdom har förändringar i hjärnans struktur och funktion och om de upplever problem med olika kognitiva funktioner. Vi har även försökt förstå relationen mellan doserna av kortisol som patienterna behandlas med och deras kognitiva funktioner och eventuella förändringar i hjärnans struktur och funktion. Vårt mål är att försöka förstå hur sjukdomen påverkar patienternas hjärna och om vi behöver utveckla bättre medicin i framtiden för att skydda hjärnan på långt sikt. Våra resultat visar att framförallt patienter med CAH har många förändringar i hjärnans struktur. De har mindre grå substans i regioner som man använder när man aktiverar sitt arbetsminne. Individer med CAH hade även problem med själva arbetsminnet, vilket kan bero på de strukturella hjärnförändringarna. De hade även förändringar i den vita substansen som kopplar ihop olika regioner i hjärnan. Vi såg dock ingen tydlig koppling mellan dessa förändringar och deras medicinintag vid den tidpunkt när man gjorde testerna/hjärnavbildningarna. Patienter med Addison sjukdom mådde däremot relativt bra. De angav

dock att de upplevde problem med att klara olika uppgifter i sin vardag. Särskilt kvinnor med Addisons sjukdom sade att de upplever problem med att reglera sina känslor. De upplevde även att de var trötta, vilket skulle kunna förklara deras kognitiva problem till viss del. Individer med Addisons sjukdom hade även ett annat aktivitetsmönster i hjärnan i vila. Vi vet i nuläget inte vad det betyder, då vi inte hittade någon koppling mellan hjärnans aktivitet och deras kognitiva problem, eller deras upplevda trötthet. Såsom för CAH hittade vi inte heller någon tydlig koppling mellan deras medicinintag (i samband med testning) och hjärnans funktion. Patienter med Addison sjukdom hade nästan inga förändringar i hjärnans struktur. Skillnaden mellan dessa två sjukdomar kan bero på att individer med CAH har haft sin sjukdom sedan födelsen då den är medfödd, medan de med Addisons sjukdom blev sjuka när de var vuxna och hjärnan hade då redan utvecklats till stor del. Sammanfattningsvis har vi funnit att hjärnan hos individer med CAH och Addisons sjukdom har påverkats av sjukdomen, men på olika sätt. Vi behöver studera vidare hur den ackumulerade dosen av läkemedel påverkar hjärnans funktion över tid, hur olika typer av nya kortisolläkemedel påverkar hjärnan samt hur patientens upplevda trötthet kan förbättras så att de lättare kan klara av sin vardag.

Abstract

Individuals with primary adrenal insufficiency (PAI), i.e., congenital adrenal hyperplasia (CAH) and autoimmune Addison's disease (AAD), suffer from impaired production of the adrenal gland hormones cortisol and aldosterone, and in the case of AAD, also androgens. Replacement medication for these hormones is sub-optimal due to the difficulties in replicating the natural rhythms of cortisol secretion. The hormones are known to affect brain function via many mechanisms, and both pre- and postnatal hormone dysregulation may affect cognitive functioning, brain structure and brain function. Therefore, studying brain health in PAI is of interest and is needed to optimise treatment and patient wellbeing. The present thesis investigated brain structure related to cognitive functioning in individuals with CAH, and cognitive functioning, brain structure and resting-state functional connectivity in individuals with AAD. We found that individuals with CAH have impairments in white matter microstructure, as well as cortical thinning of the frontoparietal network that was related to weaker performance on a visuospatial working memory task. On the other hand, individuals with AAD performed equally to control subjects on most measures of cognitive functions assessed with standardized tests during the lab-visit, but they self-reported executive function problems in daily life, which were related to experienced mental fatigue. As opposed to individuals with CAH, those with AAD did not have profound differences in the structure of the brain, apart from smaller total brain volumes. However, they displayed increased resting-state functional connectivity, particularly in primary visual regions and the orbitofrontal cortex. Our results suggest that the effects of adrenal hormone insufficiency affect individuals with CAH and AAD differently. This difference may be related to the onset of the disease, which is from conception for those with CAH and in adolescence or adulthood for those with AAD. Long-term follow-up studies are needed to assess whether the observed differences contribute to increased cognitive decline later in life and how to optimise replacement medication to sustain brain health.

List of scientific papers

I. **van't Westeinde, A.,** Karlsson, L., Thomsen Sandberg, M., Nordenström, A., Padilla, N. and Lajic, S. (2020). Altered gray matter structure and white matter microstructure in patients with congenital adrenal hyperplasia: relevance for working memory performance. *Cerebral Cortex,* 30(5):2777-2788.

II. **van't Westeinde, A.,** Ström, S., Hirvikoski, T., Dahlqvist, P., Wahlberg, J., Gezelius, A., Kämpe, O., Bensing, S. and Lajic, S. (2022). Young adult Swedish patients with autoimmune Addison´s disease report difficulties with executive functions in daily life despite overall good cognitive performance. *Psychoneuroendocrinology,* 140, 105714.

III. **van't Westeinde, A.,** Padilla, N., Siqueiros Sanchez, M., Fletcher-Sandersjöö, S., Kämpe, O., Bensing, S. and Lajic, S. (2022). Brain structure in autoimmune Addison's disease. *Cerebral Cortex*, 1-12.

IV. **van't Westeinde, A.,** Padilla, N., Fletcher-Sandersjöö, S., Kämpe, O., Bensing, S. and Lajic, S. Increased resting-state functional connectivity in autoimmune Addison's disease, *manuscript.*

Scientific papers not included in this thesis

van't Westeinde, A., Karlsson, L., Messina, V., Wallensteen, L., Brösamle, M., Dal Maso, G., Lazzerini, A., Kristensen, J., Kwast, D., Tschaidse, L., Auer, M., Nowotny, H., Persani, L., Reisch, N. and Svetlana Lajic. (2023). An update on the long-term outcomes of prenatal dexamethasone treatment in congenital adrenal hyperplasia. *Endocrine Connections*, in press.

van't Westeinde, A., Zimmermann, M., Messina, V., Karlsson, L., Padilla, N. and Lajic, S. (2022). Brain activity during visuospatial working memory in congenital adrenal hyperplasia, *Cortex*. 159, 1-15.

Messina, V., **van't Westeinde, A.,** Padilla, N. and Lajic. S. (2022). First trimester dexamethasone treatment is not associated with alteration in resting-state connectivity at adolescent or adult age. *The Journal of Clinical Endocrinology & Metabolism***,** 107, 2769–2776.

Messina, V., **van't Westeinde, A.,** Padilla, N. and Lajic, S. (2022). Changes in resting-state functional connectivity in patients with congenital adrenal hyperplasia. *NeuroImage Clinical, 35*, 103081.

van't Westeinde, A. and Patel, K.D. (2022). Heartfulness meditation: a yogic and neuroscientific perspective. *Frontiers in Psychology: Hypothesis and Theory,* 13, 806131.

van't Westeinde, A., Zimmermann, M., Messina, V., Karlsson, L., Padilla, N. and Lajic, S. (2020). First trimester DEX treatment is not associated with altered brain activity during working memory performance in adults. *The Journal of Clinical Endocrinology & Metabolism,* 105(11), e4074-e4082.

van't Westeinde, A., Karlsson, L., Nordenström, A., Padilla, N. and Lajic, S. (2020). First-trimester prenatal dexamethasone treatment is associated with alterations in brain structure at adult age. *The Journal of Clinical Endocrinology & Metabolism,* 105(8).

Cauvet, E.,*** van't Westeinde, A.,*** Toro, R., Kuja-Halkola, R., Neufeld, J., Mevel, K. and Bölte, S. (2020). The social brain in female autism: a structural imaging study of twins. *Social Cognitive and Affective Neuroscience,* 15(4), 423-436.

Neufeld, J., Hagström, A., **van't Westeinde, A**., Lundin, K., Cauvet, E., Willfors, C., Isaksson, J., Lichtenstein, P. and Bölte, S. (2020). Global and local visual processing in autism – a co-twin-control study. *Journal of Child Psychology & Psychiatry,* 61(4):470-479.

van't Westeinde, A.,* Cauvet, E.,* Toro, R., Kuja-Halkola, R., Neufeld, J., Mevel, K. and Bölte, S. (2019). Sex differences in brain structure: a twin study on restricted and repetitive behaviours in twin pairs with and without autism. *Molecular Autism, 11,* 1.

Cauvet, E.,*** van't Westeinde, A.,*** Toro, R., Kuja-Halkola, R., Neufeld, J., Mevel, K. and Bölte, S. (2019). Sex differences along the Autism Continuum: A twin study of brain structure. *Cerebral Cortex, 29* (3), 1342-1350.

Isaksson, J., **van't Westeinde, A.,** Cauvet, E., Neufeld, J., Lundin, K. Willfors, C. and Bölte, S. (2019). Social Cognition in Autism and other Neurodevelopmental Disorders - A co-twin control study. *Journal of autism and developmental disorders,* 1-11.

Myers, L., **van't Westeinde, A**., Kuja-Halkola, R., Tammimies, K., & Bölte, S. (2018). 2D: 4D ratio in neurodevelopmental disorders: a twin study. *Journal of autism and developmental disorders*, *48*, 3244-3252.

* shared first-author

Contents

List of abbreviations

21-OH	21-hydroxylase
AAD	Autoimmune Addison’s disease
ACC	Anterior cingulate cortex
AD	Axial diffusivity
AddiQoL	Addison's quality of life
ACTH	Adrenocorticotropic hormone
ANS	Autonomic nervous system
APA	American Psychological Association
APS	Autoimmune polyglandular syndrome
BBB	Blood-brain barrier
BDEFS-SF	Barkley deficits in executive functioning scale – short form
BLA	Basolateral nucleus of the amygdala
BOLD	Blood-oxygen-level-dependent
BMI	Body mass index
CA1	Cornus ammonics 1
CA3	Cornus ammonics 3
CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndrome
CAR	Cortisol awakening response
CD	Cushing’s disease
CEN	Central executive network
CRH	Corticotrophin releasing hormone
DEX	Dexamethasone
DG	Dentate gyrus
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone-sulfate

DMN	Default mode network
DN	Dorsal attention network
DTI	Diffusion tensor imaging
EF	Executive function
FA	Fractional anisotropy
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GC	Glucocorticoid
GR	Glucocorticoid receptor
HRQoL	Health-related quality of life
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamus-pituitary-adrenal
ICV	Intracranial volume
IR-HC	Immediate-release hydrocortisone
IQ	Intelligence quotient
KSQ	Karolinska Sleep Questionnaire
LTM	Long-term memory
LTP	Long-term potentiation
MADRS	Montgomery-Åsberg Depression Rating scale
MC	Mineralocorticoid
MD	Mean diffusivity
MFI	Multidimensional Fatigue Inventory
MS	Multiple sclerosis
MR	Mineralocorticoid receptor
MR-HC	Modified-release hydrocortisone
MRI	Magnetic resonance imaging
NC	Non-classic
NMDA	N-methyl-D-aspartate
OCC	Occipital cortex

OFC	Orbitofrontal cortex
PAI	Primary adrenal insufficiency
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
PVN	Paraventricular nucleus
QoL	Quality of life
RD	Radial diffusivity
REM	Rapid eye movement
rs-fc	Resting-state functional connectivity
RSN	Resting-state network
SAI	Secondary adrenal insufficiency
SAM	Sympathetic-adrenomedullary
SF-36	Short-form 36
SHBG	Sex hormone-binding globulin
SCN	Suprachiasmatic nucleus
SN	Salience network
STM	Short-term memory
SV	Simple virilising
SW	Salt-wasting
SWS	Slow-wave sleep
TFCE	Threshold-free cluster enhancement
WAIS	Wechsler Adult Intelligence Scale
WM	Working memory
WMS	Wechsler Memory Scale

Introduction

Primary adrenal insufficiency (PAI) is characterised by a lack of vital steroid hormone production from the adrenal cortex. Its leading causes are autoimmune Addison's disease (AAD) and congenital adrenal hyperplasia (CAH) (1). PAI was first described in the 19th century when Thomas Addison reported cases of adrenal tuberculosis in 1855. Addison noted the characteristic bronze pigmentation of the skin (2). Eleven years (y) later, the first case of CAH was described by Luigi De Crecchio, a pathologist reporting on a female individual, living as a man, who presented with a 6 cm long phallos (3, 4). PAI was invariably fatal until the discovery of synthetic cortisone halfway through the previous century, which could replace the lack of glucocorticoid (GC) hormones (5). Both CAH and AAD are managed by life-long oral replacement of GCs as well as mineralocorticoids (MC) (6, 7). Although the availability of this medication means that patients can live until old age, replicating the natural rhythmic secretion of adrenal hormones remains difficult. Patients are therefore regularly exposed to sub-optimal levels of GC, MC and other adrenal hormones, in addition to having reduced flexibility of the hypothalamus-pituitary-adrenal (HPA) axis. Adrenal hormones have a wide range of physiological effects and target almost all tissues in the body, including the brain. Thus, disturbances in managing optimal levels of adrenal hormones might contribute to numerous physiological problems, leading to poor quality of life (QoL). Given the brain's sensitivity to GCs, PAI's long-term effects might negatively impact cognitive functioning, brain structure and brain function. To date, little research has focused on these domains in PAI, particularly when it comes to AAD, for which no brain imaging research had been conducted until recently. Identifying problem areas related to cognition and the brain in individuals with PAI might lead to optimised treatment strategies and form the foundation of research to develop novel drugs that consider brain health as a clinical endpoint so that the patient's QoL may ultimately be improved. With this background, the present thesis aims to assess the long-term effects of having PAI on baseline cognitive functioning, brain structure and brain function in individuals with CAH and AAD.

1 Literature review

1.1 Steroid hormones from the adrenal cortex

Adrenal hormones are involved in many physiological systems, and cortisol affects nearly all body tissues (figure 1). Accordingly, disturbances in adrenal hormone balance can have a great variety of effects. Although the brain is one of the main target organs of cortisol and androgens, the interaction with other physiological systems (e.g., peripheral glucose regulation and immune function) must be considered. Any differences observed in cognitive functioning and the brain in PAI are therefore likely to be the result of the complex interactions between adrenal hormones and the physiological systems they are impacting, aside from the psychological effects of dealing with a potentially life-threatening disease. This chapter briefly summarises adrenal hormone production and regulation.

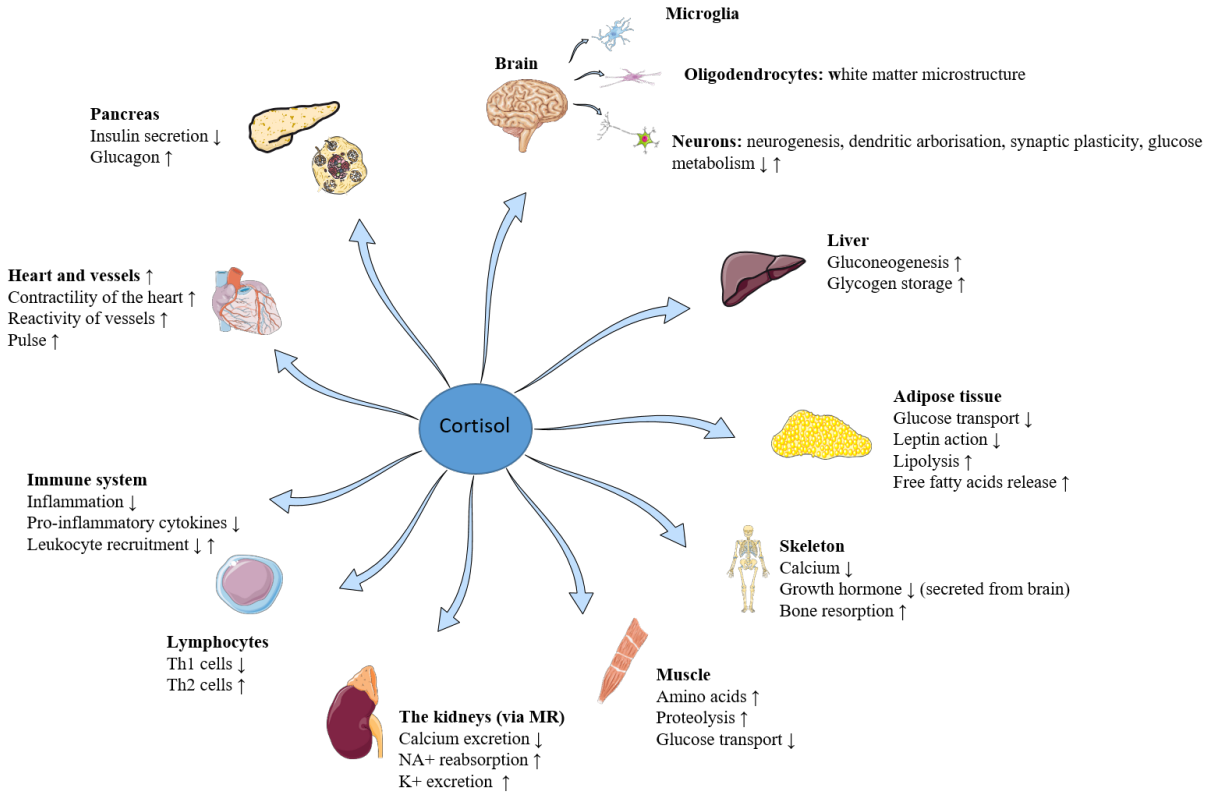


Figure 1. *Overview of some of the physiological effects of cortisol. This image was produced using medical images from smart.servier.com. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).*

1.1.1 The adrenal cortex

PAI primarily affects the hormone production of the adrenal cortex. Healthy adrenal glands consist of an internal catecholamine-producing medulla and a steroid-hormone-producing cortex. The cortex is subdivided into the mineralocorticoid-producing zona glomerulosa, the glucocorticoid-producing zona fasciculate and the androgen-producing zona reticularis. All steroid hormones from the adrenal cortex are derived from cholesterol and converted to aldosterone, cortisol and androgens through a series of enzymatic reactions (figure 2).

1.1.2 Cortisol

Both the MC aldosterone and the GC cortisol are crucial for life, and loss of these hormones leads to salt-wasting (SW) crises and circulatory collapse, culminating in death. Aldosterone secretion from the zona glomerulosa is regulated via the renin-angiotensin-aldosterone axis, while cortisol secretion from the zona fasciculata is regulated via the HPA axis. Aldosterone is primarily involved in maintaining blood pressure as it regulates the salt balance in the kidneys (8, 9). For the present thesis, however, the focus will be on the role of cortisol.

Cortisol is mainly bound to corticosteroid-binding globulin and serum albumin in the bloodstream, rendering it inactive, with only approximately 5% being free and metabolically active (10, 11, 12). Free cortisol easily crosses cell membranes because of its lipophilic nature and binds to both the MC and GC receptors (MR and GR) in the cytosol of cells. The GR is coded by the *NR3C1* gene and can be produced in two isoforms resulting from alternative splicing (13, 14). It is a complex receptor with co-chaperones; for example, *FKBP5* codes for a GR co-chaperone (15). When bound, GRs regulate gene expression, which constitutes the slow response of cortisol, sometimes only an hour after a cortisol peak (16, 17, 18). In addition, cortisol may bind to membrane-associated corticosteroid receptors thought to have rapid non-genomic effects within minutes (min) of a cortisol peak (19).

Cortisol production usually increases in response to stress and has stimulating, inhibiting and preparative effects for maintaining homeostasis (20). The various functions that cortisol has on the body mediate these processes, but its primary function is to regulate energy metabolism by promoting the body's catabolic state. This role of cortisol entails that the body can ensure energy availability for vital

organs during stress by promoting gluconeogenesis in the liver and inhibiting insulin (21, 22). For this reason, prolonged stress can lead to insulin resistance (23, 24). Cortisol also inhibits the immune system and is therefore used to treat inflammation (25), can help regulate blood pressure by increasing vasoconstriction (26) and affects bone growth, with excess cortisol leading to osteoporosis, having a negative effect on osteoblasts and suppressing growth hormone secretion (27, 28).

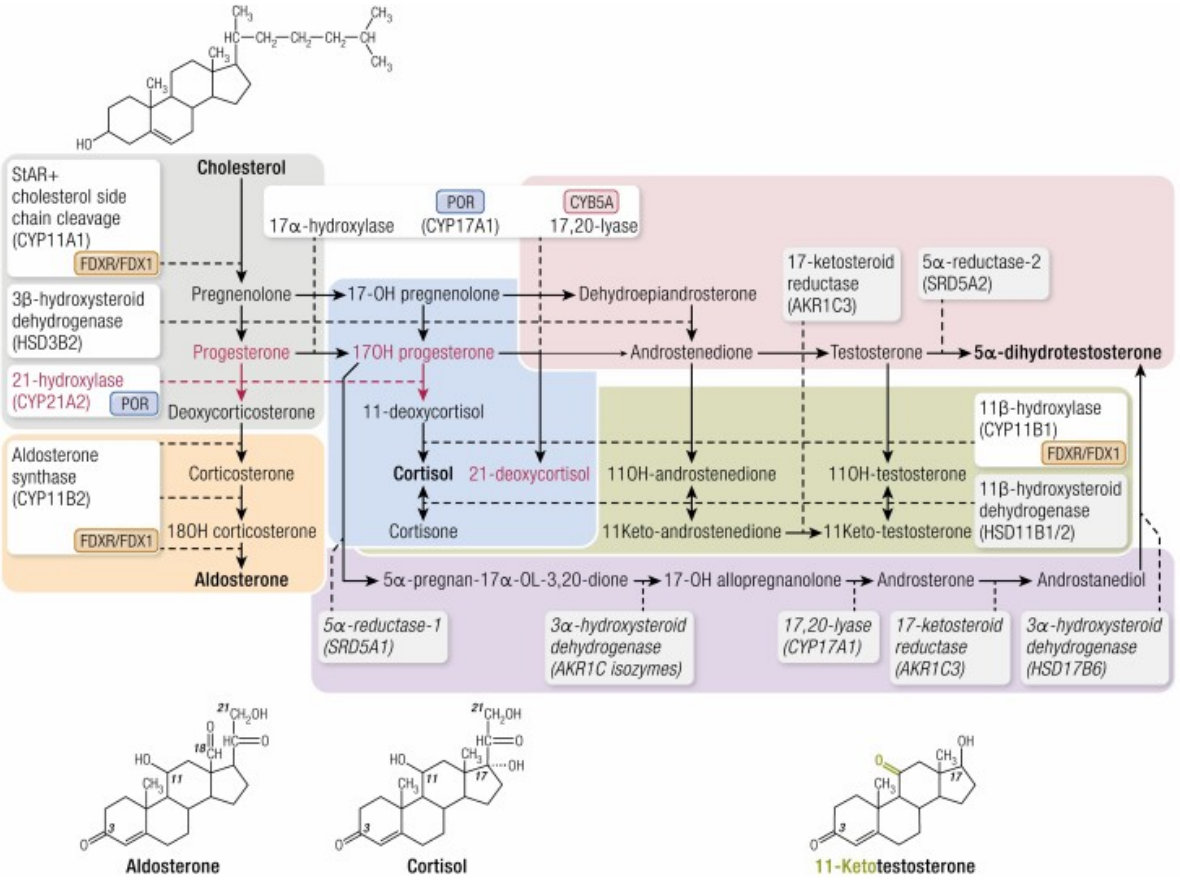


Figure 2. *Adrenal cortex steroid-hormone synthesis. Reproduced with permission from Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, et al. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocrine reviews. 2022;43(1):91-159. Copyright The Authors 2021 (29).*

1.1.2.1 HPA axis rhythms

The HPA axis regulates cortisol secretion with circadian and ultradian rhythmicity (30, 31, 32, 33, 34). In short, the HPA axis consists of a feedback and feedforward loop of hormone secretions from the hypothalamus, pituitary and adrenal glands (figure 3). This feedback-feedforward loop is thought

to be the main constituent of the ultradian secretion rhythm (35), which is approximately an hourly rhythm but may vary substantially across individuals (31, 36, 37). With low levels of circulating cortisol, corticotropin-releasing hormone (CRH) releases from the paraventricular nucleus (PVN) of the hypothalamus, which triggers the release of adrenocorticotropic hormone (ACTH) from the pituitary gland into the blood stream. ACTH stimulates cortisol secretion from the adrenals, and the subsequent rise in cortisol exerts negative feedback, among other upon CRH production in the hypothalamus. This pulsatile rhythm is thought to be needed to safeguard GR sensitivity and maintain HPA axis responsiveness to stress, though in a brain-region-dependent way (32, 33, 34).

The circadian rhythm is regulated by an internal biological clock, mastered by the suprachiasmatic nucleus (SCN) of the hypothalamus. In addition to this master clock, there are circadian oscillators in specific tissues, such as the heart and adrenal glands (38). For example, adrenal gland sensitivity to ACTH is affected by circadian oscillations (39). Cortisol might play a role in synchronising bodily rhythms by mediating between central and peripheral clocks (40). Cortisol levels usually start to rise early in the morning (about 3-4 am), presumably due to the brain's energy demand), with cortisol making more glucose available (41). The morning rise shows a characteristic pattern termed the cortisol awakening response (CAR), which is thought to help people wake up (41, 42, 43). CAR entails a 50-60% cortisol increase for about an hour (h), peaking 30 min after awakening (44). Cortisol levels then fall again throughout the day, reaching nadir around midnight, although smaller peaks are observed around midday and afternoon (45, 46). The circadian rhythm exists not only for cortisol but also for its regulators, CRH and ACTH, whose rhythms occur in parallel and peak in the morning, with nadirs at midnight (47).

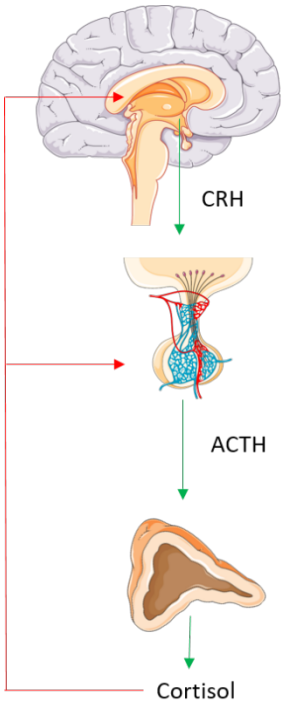


Figure 3. *HPA axis. Corticosteroid-releasing hormone (CRH) is released from the hypothalamus in response to stress, which stimulates adrenocorticotrophic hormone (ACTH) release from the pituitary gland, which in turn stimulates cortisol production by the adrenal cortex. Cortisol exerts negative feedback (red arrows) on the level of the pituitary gland as well as the hypothalamus and other brain regions. This image was produced using medical images from smart.servier.com. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).*

1.1.2.2 The stress response

The HPA axis is crucial for generating an adequate stress response to maintain homeostasis (22). Both physiological and psychological stressors can trigger neurons in the paraventricular nucleus of the hypothalamus, thereby activating both the sympathetic-adrenomedullary (SAM) axis, which constitutes the fast, autonomic nervous system (ANS) response culminating in the release of adrenaline from the adrenal medulla, and the HPA axis, which constitutes a slow hormonal response, resulting in the release of cortisol from the adrenal cortex (22). Of note, as explained above, cortisol itself also has a fast and slow-response, depending on the receptors it activates, either membrane-bound (fast non-genomic) or in the cytosol (slow genomic) (16, 19). Regulation of the stress response may vary between physiological and psychological stressors (22). Physiological stress depends more on the brainstem and

limbic forebrain regions. In contrast, psychological stress depends on the connections between the prefrontal cortex (PFC) and hippocampus, and the hippocampus and amygdala, with the hippocampus exerting an inhibitory control over the HPA axis (48, 49, 50). The HPA axis response is further regulated by the modulating effects of the catecholaminergic pathway on the PVN (51, 52, 53). The fast SAM response prepares the body for a fight or flight response, while the slow hormonal response of cortisol exerts its glucose-sparing effects and other functions to maintain homeostasis (20). Interestingly, the cortisol response to a stressor might be more effective when in the rising phase of an ultradian cycle, emphasising the importance of maintaining pulsatile rhythmic secretion of adrenal hormones (37, 54).

1.1.3 Androgens

Androgens are produced by the zona reticularis of the adrenal cortex through several enzymatic pathways, and include dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone (see figure 2). DHEA can be sulfated into its inactive ester DHEA-sulfate (DHEAS) by SULT2A1 (55, 56, 57, 58). DHEA is a prohormone metabolised chiefly into active sex hormones in the adrenal glands, ovaries and testis or in target tissues such as the brain (59, 60, 61). DHEA and DHEA-S are predominantly produced by the adrenals, as opposed to the gonads, amounting to 75-90% of total bodily DHEA production (62, 63). However, they are substrates for gonadal testosterone production, particularly relevant for females, as evidenced by the almost undetectable circulating testosterone levels in women with AAD (64). In healthy premenopausal women, adrenal-derived DHEA contributes 40-75% of the circulating sex hormone level, increasing to 100% in postmenopausal women. In men, metabolised DHEA accounts for only 5% of total circulating testosterone and 30% of DHEA-derived sex hormones (65, 66, 67).

Circulating DHEA is much more prevalent in its sulfated form, which has a longer half-life than DHEA and a higher affinity for the carrier proteins, either albumin or sex hormone-binding globulin (SHBG) (58, 68, 69). Circulating DHEA-S taken up by cells is usually converted back to the active form of DHEA and then converted to the relevant sex hormone for the tissue, which depends on the cell type (61). Although DHEA can bind the androgen and estrogen receptors, it is a weak agonist and is usually converted to the more potent testosterone and estradiol (60, 62). No high-affinity DHEA receptor has been identified (70).

Unlike cortisol, the precise physiological role of DHEA is not yet clear. Its role may include effects on bone health (bone mineral density) (71, 72), insulin sensitivity (73), improving the immune response (74) and sexual function (70, 75). Both DHEA and cortisol have a role in maintaining homeostasis. However, as opposed to cortisol, DHEA stimulates the anabolic state. Because it promotes glucose oxidation, it is thought to have anti-glucocorticoid properties, which might contribute to its neuroprotective effects (71, 72, 73).

Androgen production and release from the adrenals are regulated by ACTH (62, 74). DHEA secretion does not follow a precise circadian rhythm; however, it is responsive to stress and GCs and, in combination with its relatively short half-life, it is released in an episodic fashion (68). While a stress response involves increased cortisol production, DHEA secretion is diminished (75), and as opposed to cortisol and CRH, adrenal androgens cannot exert negative feedback on the HPA axis (76). DHEA-S, on the other hand, is relatively stable throughout the day, partly due to the long half-life and low clearance rate (77, 78). DHEA production does follow a typical age-related trajectory, with a pre-pubertal surge at adrenarche in childhood, a peak in the early 20s and then a steady decline after the third decade of life by about 10% per decade until it eventually reaches prepubertal levels again (74, 79). DHEA decline may cause physical and mental health issues in post-menopausal women, and DHEA supplementation is sometimes given to help alleviate symptoms. However, the evidence for its efficacy is inconclusive (80, 81).

1.2 Congenital adrenal hyperplasia

CAH comprises a collection of inherited autosomal recessive disorders occurring in approximately 1:10,000-1:15,000 newborns (29, 82, 83, 84, 85). Because the disease is congenital, it starts already in utero and affects boys as much as girls (29, 87-89). See figure 4 for a summary of the disease.

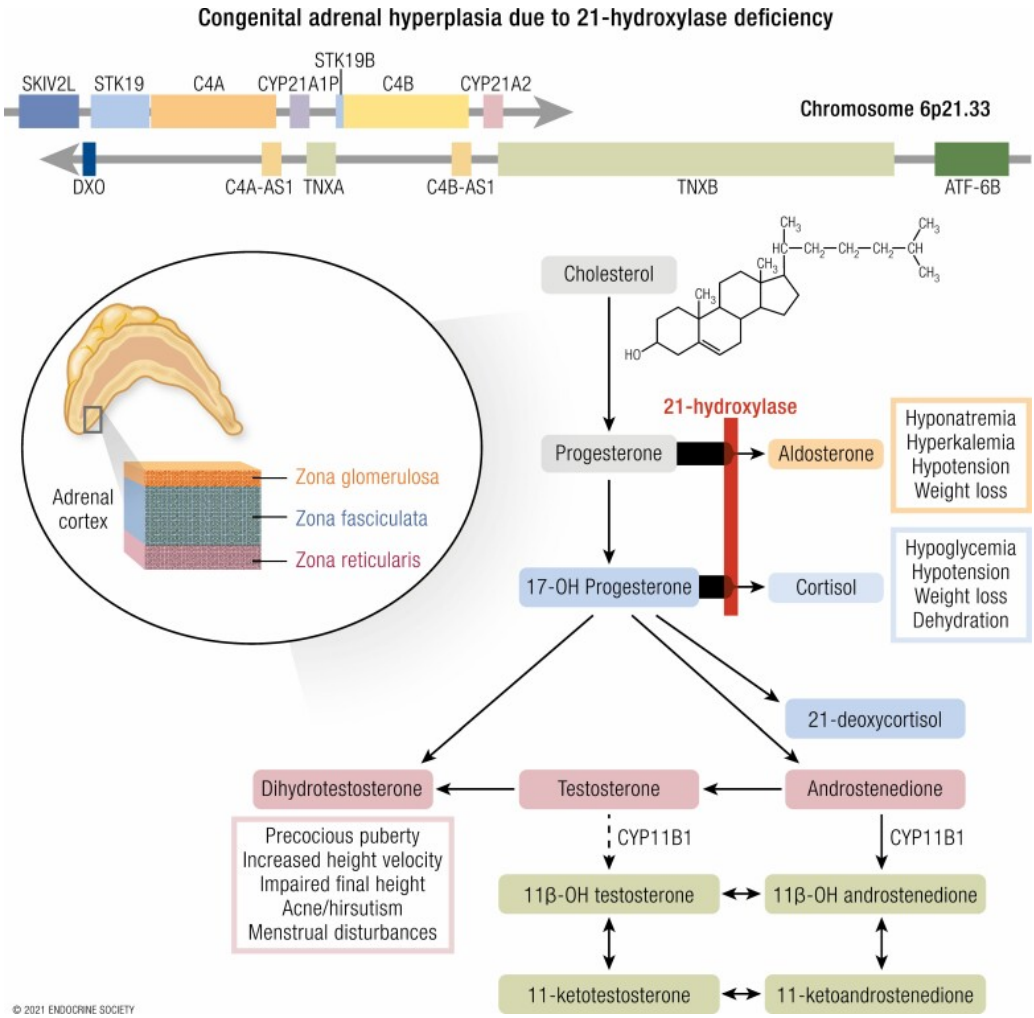
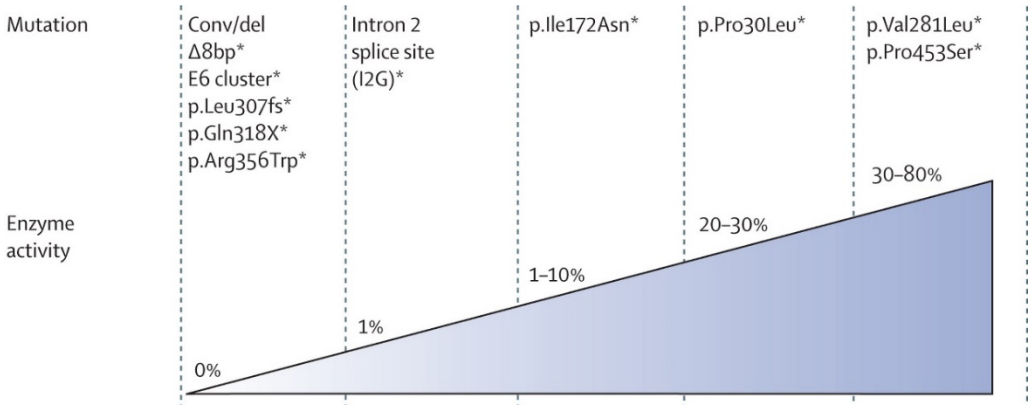


Figure 4. *CAH due to 21-OH deficiency leads to a blockage of the pathways to aldosterone and cortisol production, whereas the precursor 17-OH progesterone gets shunted to the pathway for adrenal androgen production. Reproduced with permission from Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, et al. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocrine reviews. 2022;43(1):91-159. Copyright The Authors 2021 (29).*

In most cases, CAH is caused by a mutation in the *CYP21A2* gene, causing a deficiency in the 21-hydroxylase (21-OH) enzyme needed for the production of cortisol and aldosterone (83, 84). Ten common mutations are responsible for about 95% of cases (figure 5), while the others are caused by rare family-specific mutations (86). Patients specifically lack the production of gluco- and mineralocorticoids. The cortisol deficiency results in disinhibition of the HPA axis, leading to increased levels of ACTH and an accumulation of cortisol precursors, which are then shunted towards the pathway of adrenal androgen production (87, 88, 89). As a result, androgen levels in patients are high, and a

higher dose of GCs than the normal physiologic replacement dose might be needed to suppress these levels. Due to the lack of cortisol prenatally, foetuses with CAH are exposed to high androgen levels that lead to virilisation of the external genitalia in girls, including enlarged clitoris and fusion of the labial folds, which can differ in degree of severity depending on the genotype of CAH. These problems can lead to physiological issues and psychological distress (90, 91).

CAH ranges in severity (figure 5), depending on the specific mutation in the gene coding for the 21-OH enzyme. CAH is classified as salt-wasting (SW), the most severe form, simple virilising (SV) and non-classic (NC) (92, 93). The mildest allele determines the severity of the disease because it determines how much 21-OH enzyme function is left. There usually is a good correlation between the genotype and the phenotype (92, 93, 94). Null mutations result in a complete loss of function, and patients will always have the SW form. SW CAH requires early intervention, as patients suffer a complete lack of cortisol and aldosterone synthesis, which may lead to adrenal crises during the neonatal period. Non-null mutations may also result in SW CAH in some cases or the relatively milder forms of SV and NC CAH.



Cortisol deficiency	+++	+++	++	+/(–)	–/(+)
Baseline cortisol	↓↓↓	↓↓	↓	↔	↔
Stimulated cortisol	Completely insufficient	Completely insufficient	Partly insufficient	Normal or partly insufficient	Normal
Stimulated 17OHP	>300 nmol/L	>300 nmol/L	Variable	30–300 nmol/L	30–300 nmol/L
Mineralocorticoid deficiency	+++	++	(+)	–	–
Aldosterone	↓↓↓	↓↓	↔	↔	↔
Renin	↑↑↑	↑↑	↔↑	↔	↔
Adrenal androgen excess	+++	+++	++	+	+
Androstenedione	↑↑↑	↑↑↑	↑↑	↑	↑↔
Testosterone in female patients and precocious puberty in male patients	↑↑↑	↑↑↑	↑↑	↑	↑↔
46,XX DSD	+	+	+	–/(+)	–
Prader stage	3–5	3–5	2–4	0–3	0

\+ Clinical or laboratory finding is present and multiple + indicate increasing degree of severity
– Clinical or laboratory finding is not present
↑ Laboratory parameter is elevated and the number of ↑ indicates the increase in concentrations compared with established reference ranges
↓ Laboratory parameter is decreased and the number of ↓ indicates the decrease in concentrations compared with established reference ranges
↔ No change in concentration compared with established reference ranges
(+) Clinical or laboratory finding might be present
(–) Clinical or laboratory finding might be absent
+/(–) Clinical or laboratory finding is usually present in mild form, but might also be absent
–/(+) Clinical or laboratory finding is usually absent, but might also be present in mild form
↔↑ Laboratory parameter is usually within reference range or might be mildly elevated
↑↔ Laboratory parameter is usually mildly elevated or might be within reference range

Figure 5. *CAH varies in severity depending on the specific mutation of the 21-OH gene. Common mutations cause most cases. Reproduced with permission from Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2022. Copyright Elsevier 2022. (86).*

1.2.1 Symptoms and diagnosis

In Sweden and more than 50 countries worldwide, newborns are screened for CAH, which usually detects patients with classical CAH, namely SW and SV (85, 95). Consequently, patients are treated from the first or second week of life, preventing early salt-losing crises, hypoglycaemia and neonatal death (96). Screening occurs through a 17OH-progesterone immunoassay (97, 98). Without a neonatal screening programme, SV and SW CAH are detected due to adrenal crises during the neonatal period or genital virilisation in females (29, 96). In contrast, NC CAH may be diagnosed only during early childhood, even in the presence of a screening programme, when precocious pseudo-puberty might be observed along with accelerated growth, or even during adolescence or adulthood, usually as a result of hyperandrogenism and fertility problems in women (92, 99).

1.2.2 Disease management

Treatment of CAH starts at diagnosis and consists of oral replacement of GC and MC with hydrocortisone and fludrocortisone, respectively (86, 100). The dosage and frequency of intake are adapted to the age and size of the person, as well as the severity of the disease and other individual factors. The recommended cortisol replacement dose for adults is 15-30 mg hydrocortisone, divided over three doses a day, or 4-7.5 mg prednisolone, taken twice a day, or a combination of the two, in which case two to three doses of hydrocortisone may be taken in addition to one dose of prednisolone (86). This regimen is considerably higher than the cortisol production rates in healthy adults, which vary from 5-11 mg/m2/day, with an average of 7 mg/m2, which entails for an average sized person of 1.7m2 11.9 mg/day (101). Patients usually take the highest dose in the morning to replicate the morning rise in cortisol and have their last dose in the late afternoon (102). For patients requiring MC replacement, fludrocortisone is given once daily, usually 0.1mg (86).

Strict adherence to treatment is critical to avoid adrenal crises. This adherence is crucial during periods of physical stress, and patients are instructed to take extra doses of GCs (e.g., during illness (fever)) (103). In Sweden, children with CAH receive check-ups every 3 months. Because of the role of cortisol in nearly all tissues, children's development is carefully monitored. For example, patients with CAH

often reach a shorter final height (104), and fertility in girls may be compromised if the androgens are not sufficiently suppressed (105).

In cases of a subsequent pregnancy for a mother who has given birth to a child with classical CAH, the option may be given to treat the mother (and the foetus) with dexamethasone (DEX) to prevent genital virilisation if the foetus should be a girl with CAH (106). However, prenatal DEX treatment is not without controversy as it needs to be started before genotyping for CAH is possible and healthy foetuses are exposed to high levels of GCs during a sensitive period of development. Therefore, this treatment is only offered within research programmes (105) and has been halted in Sweden (107).

1.3 Autoimmune Addison's disease

AAD is a rare disorder with an estimated prevalence of 100-200 per million in Europe (108, 109), although numbers appear to be increasing (110). AAD usually emerges during adulthood, though on rare occasions may have a childhood onset (111, 112, 113). It is also more common in females, but below the age of 30 y, there appears to be no sex difference in prevalence (112, 114).

In AAD, an autoimmune reaction against the adrenal cortex occurs, which destroys the cells and ultimately results in a lack of steroid hormone production (i.e., cortisol, aldosterone and androgens) (115). Only the adrenal cortex is attacked, whereas the catecholamine-producing medulla is spared. In most cases, antibodies against the 21-OH enzyme are found (83% of cases in Sweden) (116). These antibodies, however, are markers of the immune reaction but do not destroy the cells per se. Rather, the destruction of the cortical cells is mediated by CD8+ T-lymphocyte infiltration triggering cytolysis (117). The high heritability of approximately 0.97 suggests a substantial genetic influence (118), where major genetic risk loci include HLA, BACH2 (119) and AIRE (120, 121). The specific pathology is not yet known. For example, it is unclear why the adrenal cells are explicitly attacked. It has been proposed that destruction of the cortex begins in the MC-producing zona glomerulosa, proceeding to the GC-producing zona fasciculate and finally reaching the zona reticularis, which produces androgens (117, 122, 123). It was recently shown that perhaps as many as 30% of patients might have residual GC production, particularly males and those with shorter disease duration (124). However, the amounts left are small and might not affect clinical wellbeing (124).

There is a high co-morbidity with other auto-immune diseases (about 62% in Sweden). AAD is part of the autoimmune polyglandular syndrome (APS) 1, a monogenic disease caused by mutations in AIRE. It includes, in addition to AAD, hypoparathyroidism and/or chronic mucocutaneous candidadis and/or other disorders. AAD may also be part of APS 2, along with thyroid disorder and/or diabetes mellitus type I, or other organ-specific autoimmune diseases. These diseases share a common genetic and/or environmental background, which suggests that AAD may be part of the same underlying disease (116, 125, 126). In addition to these diseases that share an overlapping aetiology, AAD may also have consequences resulting in additional medical and mental health problems. Data suggest that patients have a higher risk of metabolic and psychiatric co-morbidities, including depression, anxiety and hypertension (127, 128, 129). Female patients have an increased risk of ischaemic heart disease, especially with higher GC replacement doses (130). They also have a risk of adverse pregnancy outcomes (131). Increased incidences of cancer have also been reported (132). Noteworthy, patients have also been found to have an increased risk of dementia, particularly Alzheimer's disease, via a potential involvement of androgens and cortisol in amyloid b and tau pathology (133). Overall, patients may suffer from a substantial health burden that significantly impairs their QoL (112, 128, 134, 135, 136, 137, 138, 139).

1.3.1 Symptoms and diagnosis

AAD usually has a long prodromal phase, and diagnosis might not be reached until more than 90% loss of adrenal cortex function (140). Until now, AAD remains a difficult-to-diagnose disease as the symptoms and clinical signs are non-specific. Symptoms and signs may develop over a long period and may include fatigue, anorexia, nausea, dizziness, salt craving, weight loss and a bronze pigmentation of the skin (115, 117, 140). AAD might present with depression as one of its early symptoms (141), and in combination with the loss of weight, is sometimes confused with anorexia nervosa (142, 143, 144), especially in younger people (145, 146). Diagnosis of AAD is ultimately based on low levels of cortisol in combination with high levels of ACTH and low aldosterone but high renin levels, as well as a positive 21-OH autoantibody test to confirm the autoimmune cause of the PAI (147). However, an accurate diagnosis might not be attained until patients enter a life-threatening adrenal crisis (115, 140). No generally accepted definition of an adrenal crisis exists. However, poor clinical status may result in a

medical emergency in which patients experience an acute lack of cortisol and suffer hyponatremia and hypotension, possibly leading to systemic collapse and death. Acute emergency treatment with cortisol and iv fluids is essential to save the patient.

1.3.2 Disease management

Upon diagnosis, life-long replacement therapy for adrenal steroids is started. Compliance with medication is crucial to prevent adrenal crises, which may occur in 10/100 patients annually (148, 149). The therapy usually consists of twice or thrice daily oral intake of immediate-release hydrocortisone (IR-HC), replacing the GC cortisol, and once daily intake of fludrocortisone, replacing the mineralocorticoid aldosterone (6, 7, 150). The recommended dose for hydrocortisone is between 15 and 25 mg/day, divided over two-three doses, and 0.1mg of fludrocortisone taken once a day in the morning (151). Usually, the morning IR-HC dose comprises approximately 50-75% of the total daily intake. IR-HC is absorbed rapidly after intake and reaches a maximum concentration about 1 h after consumption. However, with a half-life of approximately 1.5-1.8 h, IR-HC also declines rapidly (152). AAD patients may take their last dose either around noon or in the afternoon (153). Therapy is usually adjusted according to individual needs, but it is advised to follow the lowest GC dose possible on which the patient feels well. Currently, there is no biomarker to monitor whether the treatment is adequate in the case of AAD, although transcriptional factors have recently been identified that might be candidate biomarkers (154). In adult patients, the doses are not adjusted to the person's size, meaning that smaller people may receive a higher dose than taller people. Taking stress doses is advised (e.g., during illness, surgery or endurance exercise) but not applicable in all situations (155, 156, 157).

GC and MC treatment is similar between males and females. However, because females with AAD lack more than 50% of their total androgen amount, DHEA or testosterone is sometimes given to compensate for this loss (158). The effects of DHEA replacement on health-related QoL (HRQoL) are not yet apparent and might be beneficial only for specific sub-groups of women (159, 160, 161, 162).

1.4 Challenges in the treatment of PAI

Optimal replacement of adrenal hormones remains challenging, and several aspects might negatively affect patients' wellbeing. These aspects include a lack of circadian and ultradian rhythms, reduced flexibility of the HPA axis, difficulties in determining the optimal replacement dose and the need for suppressing androgens in the case of CAH.

Replicating ultradian and circadian rhythms is challenging and may result in specific problems for individuals with PAI, particularly regarding sleep. The replacement schedule is aimed at replicating the circadian rhythm of cortisol secretion to some extent by having patients take the largest dose in the morning and by taking their medication at time points corresponding to natural peaks, with the latest dose in the afternoon (figure 6) (163). Still, several aspects of the circadian cortisol rhythm are affected in PAI. Patients on traditional IR-HC replacement medication lack the early morning part of the cortisol awakening response, as they have to wake up before taking their first dose. Patients may have trouble with this because the CAR has been proposed to contribute to people waking up in the morning as it releases glucose to the brain (41, 42, 43). The deficient cortisol level in the early morning also leads to headaches, nausea and fatigue, which only subsides 1 h after intake of the first GC dose, as cortisol continues to decrease in patients up to half an hour after waking (164). In addition, slow-wave sleep (SWS) and rapid eye movement (REM) may also be affected, given that cortisol facilitates REM (165) and inhibits SWS (47, 166).

In addition to the circadian disruption, individuals with PAI also lack ultradian rhythmicity. Although the significance of these rhythms remains to be elucidated, it may reduce flexibility to respond to stressors and reduce the sensitivity of the GR (34). In individuals with PAI, the HPA axis cannot increase cortisol production in response to internal or external stressors. It is thought that the adrenal medulla in PAI is spared, although this has not been shown. Thus, in times of stress, the SAM is expected to be activated as usual, but no increase in cortisol is produced to help the system return to homeostasis. This lack of HPA axis responsivity is particularly challenging during illness, and patients are advised to increase the GC dose during such times (157).

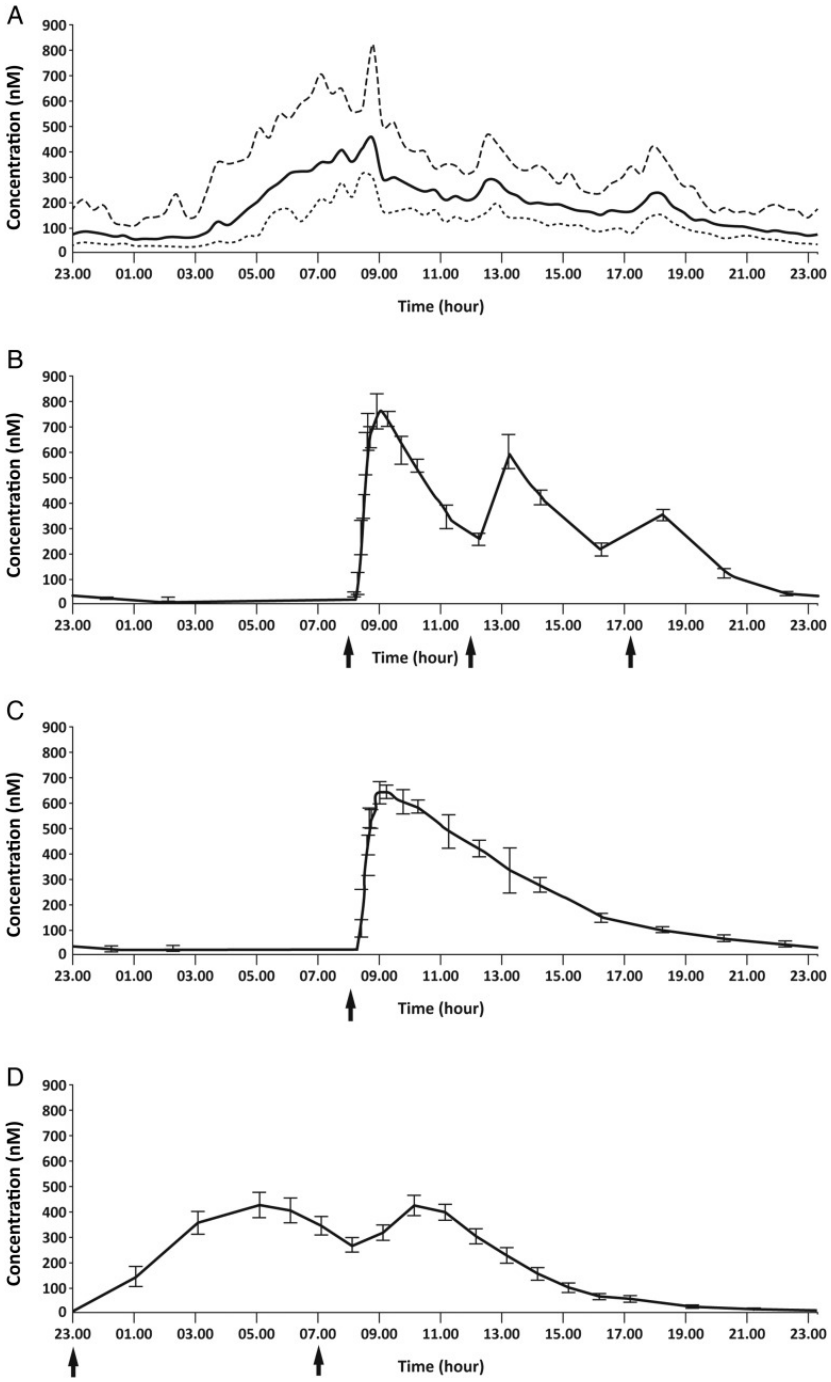


Figure 6. *Diurnal cortisol secretion in A) healthy volunteers, B) individuals with PAI on three times daily IR-HC replacement, C) individuals with PAI on once daily MR-HC and D) individuals with PAI on Chronocort taken at bedtime. This figure was reproduced from Porter J, Blair J, Ross RJ. 2017. Is physiological glucocorticoid replacement important in children? Arch Dis Child. 102:199-205. Open Access. Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license.* (163).

IR-HC leads to supra-physiological cortisol levels about 1 h after intake, but these levels drop relatively sharply (163, 167). Although cortisol is a hormone with slow genomic effects that may last several hours after a peak, basal cortisol may fall below physiological levels before taking the next dose. Individual differences in metabolism further make it hard to determine the optimal treatment schedule and dosing. Over- and under-treatment in AAD is usually determined by the assessment of clinical symptoms by physician expertise (168). Clinical scores do not seem to correlate strongly with GC dose, neither total- nor body-weight adjusted, and serum cortisol does not differ between well-replaced and over- or under-replaced individuals (168). Therefore, patient reports of wellbeing and symptoms are used to estimate the optimal replacement dose. In CAH, symptoms of hyperandrogenism are indicative of under-dosing, and patients with CAH require higher GC doses to suppress adrenal androgens effectively. Thus, they might be periodically exposed to both hypercortisolism and hyperandrogenism.

Too high dosing may lead to overweight and cardiovascular risk, while under-treatment entails the risk of adrenal crises. Patients with PAI develop a bronze colour if undertreated. Nonetheless, patients may request to be put on a low or high dose (e.g., for women who want to avoid gaining weight), while others may request a higher dose if they do not feel well or secure (e.g., in the case of AAD). Overall, the combination of lack of adrenal androgens and periodic too-high cortisol may in particular lead to periods of hypercortisolism in individuals with AAD.

1.4.1 Novel treatment strategies

Figure 6 compares the circadian rhythms of IR-HC, MR-HC and Chronocort® (163). A few years ago, dual-release medication (Plenadren®) was developed for AAD. This medication releases hydrocortisone more slowly, so patients need to take their medicine only once a day and thus avoid sharp fluctuations (169, 170)). Dual-release formulas have both an immediate-release coating and an extended-release core, resulting in improved mimicking of the normal cortisol secretion profile (170, 171). Improved QoL and metabolic profile have been observed in patients on dual-release hydrocortisone (172). However, although avoiding sharp peaks and drops in cortisol, the slow-release medication further abolishes ultradian rhythmicity, which may not necessarily be better. Ideally, the morning rise in cortisol should be mimicked before patients wake up. For this reason, Chronocort® has been developed, which patients can take in the evening before going to bed and which starts to release

cortisol early in the morning, replicating the CAR to some extent (173). This medication is currently available only for CAH and not for AAD. Even more recently, a subcutaneous hydrocortisone pump has been developed that should be able to replicate the natural cortisol rhythm much more closely, including ultradian peaks (174, 175, 176). However, this therapy is principally unavailable, and most patients are on regular oral replacement.

1.5 Brain network organisation

The present thesis will focus primarily on baseline brain organisation regarding the structure and functional connectivity, and outcomes in cognitive function and wellbeing that may be expected due to long-term adrenal gland hormone imbalances. To understand the potential impact of disturbances of the adrenal gland hormone level on the brain in individuals with PAI, the following chapters briefly describe healthy brain network organisation and cognitive functions. The current view is that the human brain is intrinsically organised as a reliable set of networks that give rise to cognition and behaviour. Functional connectivity studies have identified that these networks can be assessed when the participant is at rest, producing networks that can be segregated and are functionally meaningful (177, 178, 179, 180, 181). These resting-state networks are characterised by low-frequency fluctuations (<0.1 hz) of the blood-oxygen-level-dependent (BOLD) signal resulting from synchronised neural activity between and within different brain regions (182, 183, 184). The spontaneous synchronised fluctuations have been proposed to derive from metabolic changes due to neural activity, as similar fluctuations are observed regarding cerebral oxygen consumption (185) and glucose metabolism (186). The degree of functional connectivity appears to be associated with a nonlinear increase in glucose demand, suggesting that connectivity hubs are more energy efficient (187). At the same time, the high metabolic demands of these hubs could make them more sensitive to problems with energy delivery (187, 188).

These resting state networks (RSNs) correspond to the networks employed when engaging in a task and may reflect experience-dependent brain plasticity caused by repeated co-activation (189). Many RSNs have been identified and usually include at least the default mode network (DMN), salience network (SN), central executive network (CEN), which is also referred to as the frontoparietal network, the dorsal

attention (DN), language, cerebellum, subcortical and various primary sensory and motor networks. The DMN involves self-referential processing and is anti-correlated to task-related networks (178).

These networks interact top optimise cognitive functioning, where the brain can switch flexibly between the uses of the networks depending on the demands of the environment. For example, one prominent theory proposes that the hierarchical interaction between the DMN, SN and CEN is critical for cognition (190). An imbalance or deviation in connectivity within and between these three networks, and the ability to switch between them, may underlie many psychiatric and neurological conditions (182, 190). Mental health problems, in particular, have been associated with frontoparietal control (180), and depression specifically is commonly associated with stronger DMN connectivity and reduced suppression of the DMN during tasks (191, 192).

Graph analyses have further shown that the human brain is organised as a small world (193), making the brain effective at both functional segregation and optimal integration relative to other types of networks (194, 195). This dynamic of the human brain to balance integration and segregation is considered important for adapting to environmental insults, including loss of brain volume, impairments in white matter integrity or metabolic challenges (196, 197). For instance, during ageing, the brain becomes less segregated, which has been proposed as a compensation mechanism for loss of brain volume, making it necessary for the brain to recruit a more elaborate network when performing tasks (197). This flexibility is important in disease processes as it is closely related to the brain's ability to compensate for structural changes and maintain optimal functioning for as long as possible (197, 198, 199). Thus, long-term hormonal imbalances might lead to the reorganisation of the brain on a functional level. However, it may be part of an adaptive process and therefore needs to be interpreted in relation to cognitive functioning and wellbeing to understand the nature of the changes.

The functional networks rely on a structural architecture, although the exact relationship is still being clarified, and brain regions can show functional correlations without anatomical connections (200, 201, 202). In addition, long-term brain structure and function alterations can independently affect cognition and emotion regulation (203). Structural networks also co-vary with each other; i.e., there are correlations in cortical thickness between regions of the same network that are also particularly strong for the hubs (204, 205). These correlations may also be activity-dependent, as grey matter has a high

degree of plasticity due to the ability to form new synapses and dendrites or due to the loss of neurons when not used. For example, cortical thickness in the insula has been observed to change even after only 2 months of practicing mindfulness (206). Different brain regions are connected via white matter tracts, and these tracts' integrity and thickness are relevant for cognitive functioning, specifically processing speed and IQ (207).

1.6 Cognitive functioning

Adrenal hormones have a widespread effect on the brain, as described in the following chapters. Still, some cognitive functions might be more vulnerable than others, depending, among other things, on the specific molecular mechanisms involved. Given the limited research in PAI, it is of interest to take a broad and explorative approach to cognitive functioning in these patient groups, especially concerning brain function and structure. According to the American Psychological Association (APA) dictionary, cognitive functioning is defined as "the performance of the mental processes of perception, learning, memory, understanding, awareness, reasoning, judgment, intuition, and language" (https://dictionary.apa.org/cognitive-functioning, accessed 16th February 2023). Although the ecological validity of most standardised cognitive tests has been established, the predictive validity of these tests may be low if the range of outcomes is narrow, i.e., in a relatively well-functioning population (208, 209). In addition, the brain or the patient may employ compensation mechanisms and strategies to perform well during testing. In other words, on the one hand, small reductions in test performance do not necessarily lead to problems in daily life. Conversely, the addition of complexities in life might lead to problems due to impairments in cognitive function that go undetected in a research setting. It is therefore of interest to combine direct cognitive testing with self-reported assessments of experienced difficulties.

1.6.1 Memory

Most psychological and neurobiological models of memory distinguish between short- (STM), long-term (LTM) and working memory (WM) and between the phases of encoding, maintenance and retrieval. The specific mechanisms involved may make these processes differentially susceptible to hormonal disturbances (17, 210). The predominant view is that of a multistore model of memory,

consisting of STM and LTM as separate processes, with STM employing both phonological and visuospatial buffers to keep information online, as well as episodic buffers for multimodal information (maintenance) and a central executive component to manipulate information during WM tasks (211). STM holds information online for a short time (seconds) and has a limited storage capacity (212). It is thought that STM consists of memory traces that depend on neurotransmitter depletion, with forgetting occurring due to decay, interference, or both (212).

In contrast to WM, STM does not manipulate the information; in contrast to LTM, information rapidly decays in STM. Memories may be stored in LTM during encoding and consolidation and retrieved when needed. Consolidation depends on synaptic plasticity called long-term potentiation (LTP), and is very prominent in the hippocampus (213). However, LTMs do not seem to be stored in the hippocampus but, over time, are transferred to the neocortex during sleep in a process termed systems encoding (214). WM differs from STM and LTM because it includes an active working component (211). Because of this working component, WM is often considered an executive function (EF) (215). Models of WM usually include a central executive, an (STM) episodic and semantic buffer, a phonological loop and a visuospatial sketch path (211). WM capacity might potentially be increased by training (216). Of note, memory researchers are still debating whether STM, LTM and WM systems are different processes, as STM is sometimes considered reactivated LTM, and WM to be an EF using STM (see, for example (217)). For this thesis, we shall use the classical distinction. Different brain regions and networks are involved in these functions, with STM depending on primary sensory and sensory integration areas, LTM on the hippocampus and WM on an elaborate network including mostly frontal, in particular superior frontal and parietal regions, especially the intraparietal sulcus (212, 213, 216, 218, 219). In addition, there is a ventral phonological pathway and a dorsal visuospatial pathway employed by STM and WM for object recognition and visuospatial tracking (220).

1.6.2 Executive functions

The APA defines EFs as "higher level cognitive processes of planning, decision making, problem solving, action sequencing, task assignment and organisation, effortful and persistent goal pursuit, inhibition of competing impulses, flexibility in goal selection and goal-conflict resolution." (https://dictionary.apa.org/executive-functions, accessed 16th February 2023). Problems with EFs are

commonly reported in psychiatric disorders and may cause significant impairment in daily life functioning (221). EFs generate goal-directed behaviour and thoughts and are broadly divided into cold and hot functions (222, 223). Cold EFs are purely cognitive, logic-based skills that do not involve emotional arousal or reward-related processing. Examples of cold EFs are inhibition, WM, problem solving and planning (224, 225, 226). By contrast, hot EFs are cognitive processes that involve affective aspects such as emotions, the tension between immediate and delayed reward and motivation (222, 223). In other words, they are cognitive processes "coloured" by these aspects that lead to motivated goal-directed behaviour. Examples of hot EFs are emotion regulation and delay-discounting. Hot EFs seem to develop more slowly than cold EFs during adolescence, which might contribute to impulsive behaviours at this age (223).

Hot and cold EFs use overlapping yet distinguishable neural networks (222, 227, 228). EF is a prefrontal-dependent function involving brain areas that orchestrate activity in other brain areas to result in goal-directed behaviour. Although all EFs use the prefrontal cortex, the regions involved depend on the hotness or coldness of the EF task at hand, which appears to follow a gradient in which the hotter tasks depend more on medial PFC areas, while the colder tasks use more dorsolateral regions (222). For example, cold EF is thought to rely more on the dorsolateral PFC and the dorsal anterior cingulate cortex (ACC) orchestrating activity in parietal areas. Its network largely corresponds to the central executive/frontoparietal network (222, 227). Hot EF is more dependent on ventral-medial PFC, particularly the orbitofrontal cortex (OFC), which is involved in value-based decision making, but also on the DMN, such as the posterior cingulate cortex (PCC), and CEN (227, 229).

1.6.3 Sleep and fatigue

The ability of the brain to maintain optimal cognitive functioning may be negatively affected by sleep disturbances and fatigue, even in the absence of underlying pathology. Sleep directly affects memory, because memory consolidation starts with the repeated reactivation of memories into stable representations during SWS (230). Sleep-dependent memory consolidation is a hippocampal-dependent process during which memories are transferred from the hippocampus to the neocortex (214, 231). During REM, these reactivated memories are integrated with pre-existing knowledge, facilitating LTP (232). In addition, REM sleep seems to be important for effective emotion regulation (233, 234) and is

associated with emotional memory formation (235). All psychiatric problems, including mood disturbances, have been associated with sleep problems, especially altered REM sleep (233, 236, 237).

Fatigue lacks a clear definition and is not always straightforward to measure, but it is usually described as low vitality or perceived lack of energy instead of having the energy to undertake activities (238, 239). It is measured as self-reported descriptions containing mental and physical components (240, 241). Measuring fatigue is challenging because of its subjective nature. However, several psychological scales have been developed to measure fatigue, such as the Multidimensional Fatigue Inventory (MFI), which has good psychometric properties (242, 243). Prolonged periods of demanding cognitive activity may result in mental fatigue (244). Mental fatigue is a descriptive state that includes feeling tired, lacking energy and decreased alertness and motivation (245, 246). The decreased alertness during mental fatigue has been proposed to be related to alteration in sensorimotor gating (247). Mental fatigue specifically is associated with impaired cognitive performance (248, 249), reduced activity (250) and many problems in daily life functioning, including making more errors at work, road accidents, poorer school performance and even poorer physical performance, particularly endurance (244, 251). Unsurprisingly, lack of sleep is one of the strongest predictors of fatigue, in addition to stress (241). People also report affective consequences of fatigue, such as loss of motivation, mood changes and problems with concentration and memory (241).

On a neural level, mental fatigue is characterised by changes in brain activity both at rest and during task performance (252, 253, 254). Brain activity has been found to increase when fatigued, which may be part of a compensation mechanism (255, 256, 257) and may partly be explained by increased motivation (249, 253). However, the change in brain activity probably depends on the extent of exhaustion during task activation (258). Because of these compensation mechanisms, mental fatigue does not necessarily always correlate with worse performance. Mental fatigue may also be a consequence of the inefficient allocation of neural resources, as is found in people with multiple sclerosis (MS), who activate more posterior regions during a task with stronger demands. In contrast, healthy controls recruit more frontal areas (259). Stronger activity and connectivity in the DMN are found during and after cognitively demanding tasks (254, 260) and in fatigued MS patients (261). By comparison, reduced activity/connectivity is observed in frontoparietal networks (254), particularly

during the most exhausting state (258). Fatigue may thus cause a shift in energy expenditure from task-relevant networks towards baseline self-referential processing (260), although this has not been consistently replicated (252). Increased rs-fc in patients with MS has also been suggested to be a compensation mechanism in response to structural atrophy, thereby preventing fatigue (262).

1.7 The role of cortisol and androgens in healthy brain structure and function

1.7.1 Cortisol and androgen effects on the brain

The adrenal gland hormone imbalances may impact these brain networks and cognitive functions because of the wide range of effects these hormones have on the brain. Cortisol is actively transported through the blood-brain barrier (BBB) (263), even though the permeability of the BBB may differ somewhat between endogenous and synthetic forms of GCs (264). In addition to adrenal-derived cortisol, there is some indication, based on the presence of mRNA, that cortisol might be produced *de novo* in the brain. However, the evidence for this claim is limited, and little is known about its relevance to brain function (265, 266, 267). GCs act upon gluco- and mineralocorticoid receptors expressed widely throughout the brain by most cell types, including neurons, oligodendrocytes and microglia, the brain's immune cells (268, 269, 270). Although the GR is found in all brain regions, it is expressed to a greater extent in limbic regions such as the hippocampus, amygdala and prefrontal cortex (271). GRs are expressed by neurons and astrocytes, particularly oligodendrocytes (268, 269, 270). In contrast to the GR, the MR is expressed predominantly in the limbic system (272). Cortisol has a 10 times higher affinity for the MR than the GR, and at rest, most MR receptors in the brain are occupied (273).

Cortisol can therefore be expected to affect a broad range of functions in the brain. Animal studies have shown that GCs affect neurogenesis, cell proliferation and dendritic arborisation. Still, the effects are region- and dose-dependent, with higher GC doses impairing neurogenesis, whereas intermediate doses stimulate neurogenesis, depending on which brain region is being investigated (274, 275). Oligodendrocytes require GCs to develop, so white matter is susceptible to GC alterations and may be impaired as a consequence of such alterations, in particular when cortisol levels are too high (268, 269, 276). Cortisol exerts its effects on the brain through rapid non-genomic and slow genomic effects, the latter occurring more than 1 h after a cortisol peak (34). Non-genomic effects of GCs are needed for

rapid responses to stress and are regulated via receptors in the neuronal membrane, which can affect neurotransmission in the brain within 20 minutes (34, 277, 278). The precise action of GCs depends on the activated receptor type. Rapid non-genomic effects of GCs have been found, among other areas, in the hippocampus, amygdala and paraventricular nucleus and are mediated by changes in glutamatergic and GABAergic neurotransmission (34). For example, in the hippocampus, rapid effects include enhanced frequency of excitatory miniature postsynaptic potentials (279), which seems to be dependent on membrane-bound MRs (280). Slow genomic effects work through gene regulation, as GR and MR are transcription factors, and seem to have timing-dependent effects, with down-regulation of genes occurring within 1 h of a cortisol peak, upregulation of genes after 3 h and expression levels back at baseline after 5 h (281). Many genes are targeted, including those involved in energy metabolism and signal transduction (282). For example, GR increases expression of the glutamatergic NMDA receptors, one of the mechanisms constituting LTP (210, 283). However, the precise effects are region and sub-region dependent (34), and the overall impact of changes in excitatory and inhibitory neurotransmission on brain function that is measurable by functional MRI (fMRI) might be small because the GCs changes are context-specific (18).

In contrast to cortisol, sex hormone effects on the brain are not well understood and are complicated by the fact that they are converted locally to other sex hormones. Considerable attention has been given to the potential neuroprotective role of DHEA, a potent neurosteroid that can also be converted to other neuroactive steroids (284, 285, 286). This hypothesis is mainly based on animal research, which is problematic since DHEA and its increased production as a result from adrenarche is a very human phenomenon. Nonetheless, DHEA and its metabolites have been shown to affect glutamatergic and GABAergic neurotransmission (e.g., through DHEA's negative allosteric modulation of the GABA receptor) (287, 288, 289, 290). Like many other neurosteroids, DHEA is produced *de novo* from cholesterol by neurons and glia throughout the brain, especially in the hippocampus (291, 292, 293). However, it has not yet been established if DHEA synthesis in the brain is independent of that in the adrenal glands, nor what the relative contribution of brain-derived or adrenal-derived DHEA on brain function is (294). DHEA may have neuroprotective effects partly through its antioxidant and its anti-glucocorticoid and anti-inflammatory properties that have been found in rodents (71, 72, 73) and may

stimulate neurogenesis and neuronal survival (73) through inhibiting the suppressive effects of corticosterone (295). The anti-inflammatory properties of DHEA and DHEAS might reduce brain microglia activity (296). DHEA protection from excess GC may be particularly relevant in white matter (297, 298), but it is also abundant in the hippocampus (299). The high density of both cortisol and sex hormone receptors in the hippocampus makes this region particularly vulnerable in women with AAD and CAH (300).

1.7.2 Cognitive functioning

Cognitive function and emotion regulation are affected in the shorter term by fluctuations in the transient levels of cortisol and other hormones required for behavioural and cognitive flexibility, but that impair cognitive function during chronic stress (301) and may even contribute to damage to the nervous system (302) and neurodegeneration (303). Optimal performance on memory tasks has been suggested to depend on a delicate balance between activation of the GRs and MRs (210). STM encoding requires activation of MRs, whereas consolidation and retrieval depend on GR-mediated gene transcription of glutamatergic NMDA receptors (210, 283). Furthermore, the MR is chiefly involved in visuospatial WM and potentially verbal memory (VM) (304, 305). While LTM seems to depend on the slower genomic effects of GC on synapse formation, autobiographical and episodic memory formation, a hippocampus-dependent process, takes place at a larger time scale through systems encoding, i.e., the transfer of memories from the hippocampus to the neocortex (231). This process primarily takes place during sleep, and low cortisol levels at night are thought to mediate the transfer and consolidation of memories (306, 307). At the same time, retrieval of autobiographical memories might be less dependent on cortisol receptors (308). Moreover, cortisol could influence memory performance through its effect on the number of items held in STM by influencing the delay of the visual trace in the occipital cortex (309). These combined effects of receptor function and fluctuating cortisol levels form a U-shaped relationship with cognitive function in general, with cortisol levels impairing cognition when they fall below and rise above the threshold for optimal functioning (310, 311, 312).

Interestingly, a similar U-shaped relationship is found between noradrenaline, dopamine and glutamate concerning WM performance, with too little or too much impairing PFC function (313). In healthy people, this U-shaped relationship of cortisol with cognition is thought to be closely related to the

ultradian rhythm of cortisol secretion. This relationship between cortisol and cognition was recently shown in healthy volunteers in which the ultradian rhythm was artificially suppressed. The volunteers exhibited problems with WM and emotion regulation (54). This finding is fascinating in light of the development of dual-release medication, which, although avoiding supra and infra-physiological cortisol levels, completely abolishes any ultradian rhythmicity. For cognitive function, this might not necessarily be optimal.

Androgens have been found to have an overall beneficial effect on cognitive control, VM and spatial cognition in humans, with most research having been done on DHEA (314, 315, 316). Studies also report a positive impact of DHEA on WM, though potentially at the cost of emotional memory and social understanding (317). However, the relationship between DHEA and cognition is complex and task-dependent, and a consistent beneficial effect of DHEA replacement in older postmenopausal women has not been identified (81, 318). For example, DHEA replacement in older women improved attention but impaired hippocampal-dependent memory after exposure to stress (319). It also enhanced perceptual memory but impaired recognition memory, while estrogens had the opposite effect (320). In addition to the effects on cognition, DHEA is thought to have antidepressant and anti-anxiolytic effects (321, 322). Antidepressant effects of DHEA have been proposed to occur via its metabolism into the neurosteroid androsterone (60). DHEA administration may reduce adverse effects and emotional memory by affecting activity in the limbic system (323), cause a shift from the salience network to the DMN at rest (324) and regulate bottom-up visual attention and WM through the functional connection between the amygdala and hippocampus (325, 326). Conversely, age-related loss of sex hormones accelerated brain ageing, leading to hypometabolism and altered hippocampal activity related to memory functions (327, 328). Because of the anti-GC properties of DHEA, it has been suggested that a specific ratio between cortisol and DHEA may be needed for optimal cognitive function, where DHEA and cortisol assert opposing effects (72, 329), potentially via hippocampal and amygdala connectivity (330). Therefore, the specific changes in cortisol-DHEA ratios in individuals with CAH and AAD may lead to problems with emotion regulation and other cognitive functions, though the specific effects may be difficult to predict in particular on the long term.

1.7.3 Stress adaptation

In healthy people, the effects of cortisol on cognitive functioning are highly timing- and context-dependent through a link with the flexibility of the HPA axis that is needed, especially in stressful situations. Because the flexibility of the HPA axis is sub-optimal in patients with PAI, the neural networks involved in responding to stressful situations are expected to be adversely affected. Stressful situations invoke an adaptive brain mechanism during which a shift occurs from cognitive control networks to the salience network (331), which helps the individual focus on the situation and enhances emotional responses and emotional memory (332, 333, 334, 335, 336, 337). It also improves memory of the situation and context (338, 339) through functional connectivity between the amygdala and hippocampus (340). At the same time, retrieval of autobiographical memory of non-related stimuli might be impaired (338, 341). The system then returns to homeostasis facilitated by an increase in cortisol by the slower response of the HPA axis, which has been proposed to increase WM and emotion regulation abilities such that cognitive control is regained (332, 333, 334, 335). These processes of emotion regulation may be facilitated by the ultradian rhythm of cortisol secretion, since suppressing this rhythm in healthy persons resulted in a bias towards negative stimuli (54). In individuals with PAI, a disrupted cortisol rhythm could reasonably be expected to affect emotion regulation and WM processes, especially under stressful situations. Such problems could potentially contribute to the development of symptoms of anxiety and depression, either due to difficulties with top-down WM and emotion regulation or bottom-up emotion responses (342).

1.7.4 Sleep

In addition to the cortisol awakening response, the circadian rhythm of cortisol secretion is closely linked to other aspects of sleep. Low cortisol levels in the evening and night have been proposed to facilitate sleep, while the first hours of sleep are associated with the inhibition of cortisol secretion (166, 343). Cortisol also plays a crucial role in sleep stage initiation and maintenance and is thought to help consolidate memories at night (307). Lower cortisol levels are associated with more and deeper SWS, notably increased delta sleep, found predominantly at the beginning of the night (166, 343, 344, 345, 346, 347), while higher cortisol is associated with less SWS (47, 166). In contrast, a higher level of cortisol, especially in the last sleep cycle in the early morning, is associated with increases in REM sleep

(165). Accordingly, individuals with PAI may experience disturbances in these sleep cycles that could affect the cognitive functions with which they are associated, and lead to daytime fatigue. Furthermore, the lack of CAR may have effects throughout the day (348), as it influences resting state-functional connectivity (rs-fc) in the afternoon (349) and predicts response inhibition on the same day (350), and affects the brain's preparedness for stress (351).

1.8 Long-term effects of cortisol and androgen dysregulation

Based on the above we may expect that potential problems with cognitive functioning, emotion regulation and sleep in PAI may result from transient fluctuations in the neurochemical environment due to the challenges in optimizing replacement therapy, as well as long-term rewiring of structure and functional networks of the brain. These could involve a multitude of compensatory responses and epigenetic changes. Because AAD and CAH start during different developmental time windows, their brains may be differentially sensitive to hormonal disturbances. For CAH, the entire developmental trajectory is altered. Patients with CAH experience cortisol deficiency and androgen excess *in utero* and are treated with cortisol replacement from week two of life if diagnosed through a neonatal screening programme. Pre- and postnatal hormonal effects might each affect the brain independently, even though it is impossible to disentangle these effects at this stage, especially in the absence of a large cohort of prenatally treated cases. Postnatal, high cortisol doses are used to suppress the adrenal androgen excess, but this may not always be achieved. Hence, women with CAH are still periodically exposed to high androgen levels. Contrarily, no prenatal abnormalities are expected for those with AAD. Nevertheless, they are exposed to a complete lack of cortisol and adrenal androgens postnatal from the time of disease onset, with only GCs being replaced in most cases. They usually have a long prodromal phase of the disease before being diagnosed. These factors may already have contributed to altered brain structure and function development beyond sub-optimal treatment effects.

1.8.1 Prenatal effects of cortisol and androgen dysregulation

Prenatal cortisol and androgen levels are tightly regulated and produced by the adrenal cortex, which develops early in foetal life (before gestational week five) and contains the steroid-producing "foetal zone" (352, 353). Expression of GRs increases in week four (270), and from week eight, cortisol

production in response to ACTH stimulation is observed (354). A surge in cortisol about weeks 7-12 suppresses the androgen levels and ensures female sex development in 46,XX foetuses. Lack of this suppression results in virilised external genitalia in girls with CAH. Cortisol entry in the placenta from the mother is strictly regulated by the HSD11B2 enzyme, which becomes less active only later in pregnancy when more cortisol is needed for organ maturation (355, 356, 357, 358). The fact that CAH cases with null mutations can survive suggests that the lack of cortisol during foetal life is at least not necessarily fatal.

Lack of cortisol and excess androgens during the entire pregnancy might thus affect the structural development of the brain in CAH cases. Structures developing during the first trimester, mostly subcortical, may be especially vulnerable because maternal cortisol entry to the foetus is inhibited during this time (355, 356, 359, 360). Effects on brain structure development may occur either through a direct effect on the developing neurons and astrocytes or through prenatal programming, including possible alterations in DNA methylation of HPA axis regulators (361, 362). To what extent prenatal adrenal gland disturbance affects gene methylation and other epigenetic processes in CAH is unknown, as no neonatal methylation studies have been conducted and postnatal treatment might override these effects. In humans, only research on *excess* prenatal cortisol seems to exist, either in the context of prenatal stress or synthetic GC administration (362, 363, 364). This research has shown, among other long-lasting effects on gene expression in neuronal cells (270), changes in brain structure (365, 366, 367, 368, 369), cognitive functioning and behaviour (370, 371, 372, 373, 374) and methylation of HPA axis genes, including the GC receptor (375, 376). Prenatal cortisol disturbances therefore seem to have long-lasting effects on the developing brain that might be mediated by altered sensitivity of the HPA axis.

The role of DHEA in brain development remains largely unknown in humans. Animal studies have shown that DHEA can increase neurite growth during foetal growth and reduce neuronal death (286). Moreover, it may be involved in developing the organisation of the neocortex by guiding axonal growth (377). Studies on humans are difficult to conduct, but in cells derived from the human foetal cortex, the increased growth rate of neural stem cells was observed in response to DHEA (378). Excess prenatal androgens may be expected to result in masculinisation of the brain. Sex hormones have a complex effect on the brain and behaviour, and sex differences likely depend on the presence of the Y-

chromosome, sex hormone levels and differences in socialisation (379, 380). Prenatal androgens cause sexual differentiation of the brain, in particular nuclei in the hypothalamus, as well as the amygdala, while a second surge in androgens during puberty further induces sex-specific sexual behaviour and phenotypes (299). Androgen excess is usually associated with increased amygdala volumes (381, 382). Both androgens and estradiol are involved in hippocampus development (299). The hippocampus develops early in the second trimester, and rodent studies have found that pre- and postnatal testosterone exposure results in larger CA1 and CA3 volumes because of increased dendritic arborisation (383, 384, 385, 386). Behaviourally, there are some slight but consistent sex differences, especially spatial learning, in favour of males, and verbal learning, in favour of females (379). Animal studies found that females preferred context-dependent hippocampal learning, whereas males preferred proprioceptive-dependent striatum learning, with this preference depending on testosterone (387, 388). This difference was proposed to be related to sex differences in cholinergic release in the hippocampus (388, 389). Thus, differences in neurotransmitter functioning may be related to sex hormone levels. The extent to which prenatal androgens contribute to sex differences in cognition and behaviour has not been adequately studied. Evidence comes mostly from individuals with CAH and complete androgen insensitivity syndrome (CAIS), possibly indicating that androgen exposure prenatally affects mostly personal characteristics (e.g., interests and sexual orientation), but not so much gender identity and cognitive functioning (314, 390, 391). Nonetheless, prenatal hormonal imbalances may affect brain development in individuals with CAH, though neonatal studies would be required to be able to compare these effects to postnatal treatment effects throughout life.

1.8.2 Postnatal effects of cortisol and androgen dysregulation

Children with CAH are treated from birth with high doses of GCs. Nonetheless, even in postnatal life they may still be exposed to high androgen amounts and cortisol periodically when androgens normally should be low. Consequently, children have a risk of entering precocious puberty with poor disease control (392). How this specific combination of factors might affect the developing brain is unknown. Brain structural and functional development is thought to continue into the mid-20s of postnatal life and synaptic pruning mostly during adolescence (393). Because of the slow maturation of the brain, the age of diagnosis may also be relevant for patients with AAD, particularly when diagnosed <18 y of age.

Notably, the brain might be differentially sensitive to the effects of cortisol during different developmental time windows, with greater sensitivity during early years relative to adulthood (394, 395). Thus, the effects of PAI on the brain might be expected to be different between AAD and CAH, as well as between AAD patients who become ill either during adolescence or later in life. Ultimately, their brains may follow alternate developmental trajectories (198).

Most studies on cortisol dysregulation have focused on long-term cortisol excess in adults, such as in stress-related disorders or Cushing's disease (CD). Because individuals with PAI lack cortisol, the effect of these diseases on the brain is likely to differ to some degree from other disorders of cortisol regulation. However, current oral GC replacement therapy results in periods of excess cortisol that may result in effects resembling those of hypercortisolism (396).

1.8.2.1 Cognition and behaviour

Individuals with CD, exposed to prolonged periods of hypercortisolism, have problems in nearly all cognitive domains. Visuospatial and linguistic skills seem to be more affected, as well as memory encoding as opposed to consolidation and retrieval (397, 398, 399). These problems are found in patients with active disease, although some improvement occurs with remission (398). In addition to performing worse on tests in the lab, patients also self-report problems in other life domains (397), including attention problems and irritability (400). Self-reporting complaints about memory, attention and other cognitive issues are substantially higher than detected problems in a research setting, suggesting that experimental tests may not fully capture the difficulties experienced by patients in real life (397). Patients with CD also have increased symptoms of depression and anxiety (401). The cognitive and mood-related problems in CD persist even years after the remission of their disease, with patients continuing to experience difficulties with depression, anxiety, phobia (402) and STM (399).

The effects of long-term cortisol dysregulation seem to be dose-dependent. In individuals treated with GCs for various reasons, depression is a common side effect, as well as problems with declarative memory and WM that may be partially relieved with antidepressant medication or NMDA-receptor antagonists (403). Excessively high GC doses are associated with adversities such as mania, psychosis and even suicide attempts (404). In contrast, subclinical hypercortisolism, as may be found in patients

with adrenal incidentaloma, was associated with *better* performance on VM and other cognitive tests, despite higher incidences of insomnia and perceived stress (405).

1.8.2.2 Brain structure

Problems with cognition may arise from underlying changes in brain structure and function. Studies are beginning to shed light on the relationship between cortisol and human brain structure. For example, in adults, studies with structural magnetic resonance imaging (MRI) have found a link between heightened cortisol levels and widespread brain atrophy in patients with depression (406) and reduced cortical surface area of the left anterior cingulate gyrus, right lateral OFC and right rostral middle frontal gyrus in older people (407). Patients with CD have alterations in both grey and white matter (401, 408), most notably reduced hippocampal volumes (409). Some brain regions and white matter tracts might be more vulnerable than others due to the distribution of GRs in the brain. Accordingly, the hippocampus and other limbic regions are some of the most consistently reported structures affected by cortisol dysregulation. Structural changes generally correlate with cognitive difficulties and symptoms of depression (401, 409). In healthy volunteers, the administration of hydrocortisone for 3 days already resulted in a 1.69% smaller hippocampal volume (410). Reduced volume due to excess cortisol may be caused by glutamate excitotoxicity as it is reversed by a glutamate antagonist (411, 412).

It is not clear whether these structural alterations are reversible. CD shows that some changes in grey matter are reversible, whereas white matter changes are more likely to persist in remitted patients (402, 413, 414). However, another study found that the loss of white matter fibres (seen as diffuse white matter hyperintensities) might also be able to reverse (415). This finding has implications for PAI because adapting GC doses could improve brain health if changes are reversible. Cumulative GC dose is also related to white matter impairments, with the latter being associated with attentional deficits in patients with systemic lupus erythematosus (416). One study on children exposed to GC treatment during childhood to treat rheumatic disease and nephrotic syndrome had changes in white matter microstructure in the left uncinated fasciculus but not the right (417).

1.8.2.3 Brain function

Long-term cortisol imbalances are expected to affect the brain's functional organisation at rest and during task performance. For example, rs-fc was associated with cortisol in patients with depression (418), particularly with enhanced connectivity in the cognitive control network (419). Cortisol imbalances may be expected to affect hubs of those networks with a high density of GR, including the hippocampus and amygdala of the salience network, the middle frontal cortex of the central executive network and the medial frontal cortex of the DMN. In addition, the main hubs of the brain, such as the precuneus of the DMN (420), are high in metabolic demand (421). Because cortisol is involved in glucose metabolism, sub-optimal cortisol levels might affect brain activity, especially during demanding tasks in those areas with the greatest metabolic needs (422, 423). Patients with CD have been found to have altered functional connectivity at rest (424) and during WM performance (425) in networks of the limbic system and the DMN (424, 426, 427). Higher cortisol levels and time since remission were associated with stronger rs-fc in several networks (424, 426, 427).

Moreover, one study reported an association between glucose metabolism and cortisol in several regions of the limbic network (428). In patients with Alzheimer's, higher cortisol levels in parietal regions are associated with hypometabolism (429). Less efficient energy consumption, as seen in problems with processing speed and error rates, might also be related to fatigue (430). However, brain networks are dynamic and compensatory mechanisms may be operative (198). For example, compensatory hyperconnectivity has been found in children with diabetes (431). Hence, changes in functional connectivity might either reflect compensatory or maladaptive activity.

1.9 Brain structure and function in CAH and AAD

Based on the above overview, it may be expected that problems with cognition and brain health are found in individuals with PAI. To understand the effect of PAI on the brain, it is first necessary to determine whether patients display and experience difficulties with cognitive functioning and emotion regulation and, if so, in which specific domains. We then need to ask what are the most important factors contributing to these problems, the underlying brain mechanisms and how we could improve brain health in this patient group in the long term.

1.9.1 Congenital adrenal hyperplasia

1.9.1.1 Cognitive functioning in CAH

Studies on CAH have addressed cognitive functioning, behaviour and, to a smaller extent, brain structure and function at different ages and in the context of prenatal DEX treatment. Inconsistent and contradictory results have been found in cognition, mood and behaviour in CAH, which may depend on differences in the study cohorts such as sex, age, number of experienced SW crises, treatment strategies and, above all, the existence of a prenatal screening programme in the country where the study was conducted.

Children with CAH have been shown to have impairments in WM (432) and STM, with the latter predicting worse spatial and arithmetic performance (433). The authors proposed that problems with higher-order cognitive function in CAH could result from deficits in STM (433). In adults, negative effects on full-scale IQ were seen in some cohorts from countries without a neonatal screening programme, where patients might have been exposed to early hyponatremic or hypoglycemic episodes (434, 435). In addition, patients might have an increased risk of psychiatric diagnoses (436, 437). Difficulties with negative-emotional memory have also been observed in individuals with CAH (438, 439). Otherwise, another study did not find impairments in general intelligence in adults (440).

Results from our research group have shown good overall behavioural adjustment in children with CAH aged 7-17 y (441) and no significant differences in cognitive performance compared to population controls. However, children with SW CAH performed worse on visuospatial WM than those with SV CAH (442). The neonatal screening programme in Sweden might have contributed to the overall good performance. However, as young adults, the patients performed worse on tests assessing EF, including verbal and visuospatial WM, processing speed and inhibition (443). Thus, it seems that a cumulative effect of GCs (and overall disease burden) over time may cause a worsening of cognitive abilities in CAH. Overall, these effects are seen in both men and women.

Because of the pre- and postnatal excess androgens, it was thought that women with CAH might benefit from neural masculinisation in cognitive functioning (444), potentially at the cost of reduced emotion processing (439). However, although girls and women with CAH display more male-stereotyped

behaviour (445) and more male-typical amygdala responses to negative facial cues (446), cognitive masculinisation in females with CAH has not been consistently found. It might be opposed by the negative effect of postnatal cortisol treatment on verbal WM (433). In addition, CAH has reduced, as opposed to increased, amygdala volumes (447), the opposite of what would be expected from excess androgen exposure (381, 382). These findings suggest that prenatal androgen exposure has little effect on cognitive performance, and postnatal treatment efficacy may be more important. The effects of prenatal DEX treatment on cognition and behaviour in girls and boys with CAH are also inconclusive, largely due to the extremely low number of participants, with only eight girls with CAH treated prenatally with DEX in Sweden (448, 449).

1.9.1.2 Brain structure and function in CAH

Initial studies on brain structure in CAH have been conducted on small cohorts without control groups or were case studies. These studies mainly reported increased white matter abnormalities and hippocampal atrophy (450, 451, 452, 453). In an early study, individuals with CAH were found to have smaller amygdalae (447). Recently, Webb and colleagues observed widespread alterations in white matter microstructure (reduced fractional anisotropy (FA) and increased median diffusivity (MD)) in addition to reduced volumes of the bilateral thalami, brainstem, cerebellum and right hippocampus. The authors also reported reduced mesial temporal lobe choline content in adult women with CAH (age 18-49 y) (454). Those on a higher GC replacement dose (doses ranged from 16-25 mg/day) had more impairments of white matter and performed worse on cognitive tasks assessing EFs (454).

Cotter et al., (2021) investigated 23 youth with CAH (range 8-18 years old) and found impairments in white matter microstructure in the fornix and stria terminalis, the tracts connected to the hippocampus and amygdala and which were the specific regions of interest (ROIs) for that study (455). Lower FA in the fornix was associated with smaller hippocampal volumes, while lower FA in the stria terminalis was associated with smaller amygdala volumes. However, they found no association with GC replacement dose or other clinical parameters. The authors propose that the impairments in white matter may be due to inflammatory processes (455). This conclusion was based, among other, on the finding in mice that WM microstructure measured with the same imaging technique they used (NODDI) was associated

with microglia density and activity in the neurite space (456). These studies indicate that white matter and subcortical structures are highly vulnerable in CAH.

Furthermore, the CAH youth, based on the same cohort as (455), also had smaller intracranial volume (ICV) and smaller volumes of prefrontal cortex regions, namely bilateral superior and caudal middle frontal and left lateral OFC (457). The left hippocampus, lateral nucleus of the amygdala and hippocampal subiculum and CA1 sub-regions were also smaller in these CAH youth. Yet, no relationship was seen with any clinical parameters, such as medication dose or markers of androgen excess (457). Although both cohorts indicate altered volumes in regions of the limbic system, the authors did not perform a whole-brain analysis. Thus, they may have missed structural changes in the other brain areas.

Our research group has also found hypermethylation of two CpG sites, FAIM2 and SFI1, involved in neuronal functions (458). The involvement of *FAIM2* in neuroprotection via an anti-apoptotic mechanism (459, 460) suggests that this gene may be involved in changing the brain's developmental trajectory in CAH. Those with a higher GC dose had a higher degree of methylation of this CpG site (458).

In sum, white-matter impairments are a consistent finding in individuals with CAH, as well as whole-brain atrophy and reduced volumes of areas of the limbic system. The relationship with disease-related parameters remains unclear, although a higher GC dose may be associated with worse outcomes regarding white matter microstructure and cognitive functioning (454). These studies were done on youth or women only, and the authors limited their analyses to some areas of interest. Whole-brain analyses that include both sexes and individuals at young adult age are still lacking.

1.9.2 Autoimmune Addison's disease

The link between AAD and psychopathology was made already in the 1950s (461) and even earlier, in 1899, when Kippel proposed "encephalopathy addisonienne"; in other words, noting the co-morbidity of AAD with neuropsychiatric symptoms (462). Later, case studies reported psychiatric co-morbidity or psychosis and other psychiatric symptoms in individual patients (141, 463, 464, 465, 466). More recent cohort studies have shown increased symptoms of anxiety and depression in individuals with

AAD (127, 129, 467), in addition to sleep disturbances and complaints of fatigue (468, 469). Besides a potential direct effect of sub-optimal GC blood levels on cognition and mood, an indirect effect of a disturbance in the sleep/wake cycle might significantly contribute to the impaired QoL of patients with AAD (470).

Studies addressing cognitive performance in AAD have reported mixed results. Differences in findings can be due to differences in test batteries, with some groups employing more elaborate cognitive testing than others. There is also variation in group composition (e.g., combining groups with different causes of PAI, age ranges and sample size). Some studies report specific problems with inhibiting pre-potent responses (Stroop task) (471, 472), certain components of attention, namely vigilance and alertness (in a combined sample of PAI and secondary adrenal insufficiency (SAI)) (473), logical, auditory (verbal) and visual memory tasks. EF (474), verbal learning and declarative memory (475). Problems with episodic memory were found in one study through a telephonic assessment. Longer illness duration correlated with poorer performance across all cognition domains, including episodic memory, attention, executive functioning, reasoning and processing speed (476). This finding suggests that cumulative disease burden or prolonged exposure to GC medication worsens cognitive abilities, similar to what we observed in the CAH cohort (442, 443).

On the other hand, Tiemensma and colleagues found that patients performed *better than controls* on concentration and part of an attention task, which they propose might have resulted from greater motivation to participate than controls (474). The deficits found in (474) were of small effect size. Likewise, in another cohort, although patients did show more depressive symptoms and worse performance on verbal learning, they did not differ from controls in EF, concentration, WM, VM, visuospatial memory and autobiographical memory (477). Thus, even after an average of 18 y of disease duration, the authors found few problems with cognitive functioning in PAI. It must be noted that they decided to include body mass index (BMI), depressive symptoms and systolic blood pressure as covariates in their analyses. These variables correlated with several tests (e.g., BMI was associated with performance on the Stroop test). If these parameters result from having the disease, this may have confounded their findings, and the patient may have more impairments than reported.

The performance of patients on cognitive tasks and their mood may also vary depending on the relative balance of GR and MR occupation, i.e., when they took their hydrocortisone and fludrocortisone medication (478, 479). Verbal learning and WM (digit span) were better in patients when both MR and GR were occupied (478), which is noteworthy in that mostly VM functions seem to be affected in AAD. (479) found that, in addition to VM, current mood was also better during high MR occupation. In real life, all patients of course take their MC medication in the morning, and hydrocortisone binds both GR and MR. However, at times MR occupation in the brain might anyway become low, when cortisol levels have fallen below what is physiologically normal.

Problems with cognition may be mediated by sleep and fatigue. One study directly assessed the effect of sleep on memory in AAD, finding that while sleep improved performance on a declarative memory test in healthy controls, this was not the case for individuals with AAD, suggesting that the low levels of night-time cortisol prevent memory consolidation (475). Severe fatigue is found in approximately 40% of CAH and AAD patients (480), and patients with AAD frequently report sleep problems (468, 470, 475). In one study, 48% of the patients reported feeling abnormally fatigued, with 61% reporting severe fatigue (481). Poor sleep and fatigue may be important factors that could contribute to increased mortality in patients (482). Factors contributing to fatigue in that study were distress, sleep disturbance, physical activity, concentration problems and social functioning (480). These issues are likely part a vicious circle, with sleep problems and fatigue leading to problems with cognition. Most studies have not considered sleep and, in particular, not general and mental fatigue.

Sleep problems may be the result of the lack of cortisol at nighttime. This deficiency in cortisol affects the cortisol awakening response, which is missing before patients wake up, and other aspects of sleep. Evening cortisol levels depend on when patients take their last dose, usually later for CAH than for AAD but at least several hours before bedtime. High cortisol levels at night might reduce SWS, whereas low cortisol levels in the morning may reduce REM sleep (47, 164, 166, 347, 483). The effect on SWS depends on the time of intake of the latest cortisol dose. If evening cortisol levels are already low, SWS in patients might be elevated in addition to reduced REM (347). However, sleep efficiency may be higher than patients report, and daytime fatigue may be present in patients independent of sleepiness (468). Besides sleep problems, low (evening) cortisol levels may directly cause fatigue in patients, and

episodes of nighttime hypoglycaemia have been reported that could have serious adverse effects (484). Administering a higher cortisol dose in the evening in children with CAH did not improve measured sleep activity (485). Moreover, nighttime intravenous HC administration in a small cohort of SAI and PAI patients did not improve sleep either (153).

How the potential problems with cognitive functioning relate to GC replacement dosing, type or scheme, or other disease-related factors remains obscure. Studies on isolated AAD or combined cohorts of PAI usually did not examine this question. However, plasma cortisol levels were not related to performance on cognitive tests in one study (474). Direct testing of the relationship between replacement doses and performance has been done on SAI and cohorts combining PAI and SAI patients. For example, in a study of PAI and SAI that included three patients with AAD, affected individuals on higher replacement doses performed worse on a STM test ($r = -0.55$), with doses ranging between 10-37.5 mg/day (153). In the attention study on PAI and SAI, a higher dose (>24 mg/day) was associated with impaired attention, visual-motoric skills and EF (473). Doses >30 mg of hydrocortisone per day in adult patients have been related to worse outcomes in QoL (137). These findings suggest that higher cortisol doses may cause hypercortisolism and thus lead to non-optimal brain function. However, a higher dose of Plenadren (>20 mg) was associated with better sleep quality, although Plenadren did not improve QoL in a cohort of PAI and SAI patients (486). Patients with SAI on a relatively higher replacement dose were less fatigued and had fewer symptoms of depression and improved motivation but did not differ in cognitive functioning, with low doses defined as 15-20 mg and high doses as 30-40 mg (487). Although these studies include large cohorts of SAI, and these findings therefore not necessarily translate to isolated AAD, they do suggest that higher doses may not be worse for all aspects of functioning.

Some studies have tried improving cognition by controlling glucose levels, but glucose infusion had no beneficial effect on cognitive performance (471). Only high-calorie comfort food may enhance cognitive functioning a little (attention and memory) (472), and a late-night slow-carb release snack was found to improve nighttime glucose levels at least in one patient (484). In fact, Klement et al., (2010) studied patients with AAD under stressful conditions (the Trier social stress test) and found higher

"neuroglycopenic symptoms" in patients in response to the test, with comfort food slightly improving these symptoms (472). At the same time, it did not improve symptoms for controls (472).

Taken together, although some disparate results are found in studies assessing cognitive function in AAD, the most consistent impairments are found for verbal learning and memory and attention, and potentially also other EFs (471, 472, 474, 476, 477), which might partially be mediated by problems with sleep (475). These previously described difficulties point to the vulnerability of hippocampal-dependent learning (verbal and episodic) and prefrontal-dependent tasks such as attention and other EFs. Thus these brain regions may be expected to be affected in individuals with AAD. There is still a major gap in the literature of cognition and the brain in PAI. No neuroimaging studies have been conducted in AAD at all up until recently. Few studies have considered sleep and fatigue as mediating variables despite the frequently reported problems with these domains in AAD. A major challenge in studying AAD and CAH is of course that they are rare disorders. Therefore, obtaining a large sample size may be challenging, resulting in relatively small cohorts and wide age ranges, including PAI and SAI, and other adrenal insufficiencies. Finally, studies on AAD usually include older individuals, while relatively little is known about isolated Addison's in younger individuals.

1.10 Hypothesis

Because of the difficulties in optimising adrenal gland hormones, and the effects these hormones have on the brain, we hypothesize that individuals with CAH and AAD have problems with cognitive functioning, changes in grey and white matter structure and altered functional organisation of the brain at rest. These changes are expected to be associated with GC replacement dose and disease duration. Fatigue is expected to be an important mediator of cognitive and brain functioning in PAI. We also expect that women with AAD will be more affected than men.

2 Research aims

This thesis aims to identify the impact of PAI treated with oral replacement medication on cognitive functions, brain structure and brain function. We aim to determine 1) whether individuals with PAI experience and display problems with cognitive functioning, 2) which factors, such as mood, fatigue and disease-related factors, are associated with these problems, 3) whether there are differences in brain structure and functional activity and 4) whether alterations on the level of the brain are related to cognitive problems and disease-related factors. We also aim to assess the modulating effects of sex. An exploratory whole-brain approach will be applied to evaluate PAI's impact on brain structure and functional activity at rest. This thesis aims to identify brain vulnerabilities in relatively young patients with PAI that might require attention to improve cognitive function and QoL. Ultimately, the knowledge gained in this thesis can be used as a basis for future studies on the effects of novel treatment strategies to improve long-term wellbeing and optimise brain health in individuals with PAI.

3 Materials and methods

3.1 Design

The studies in this thesis use a cross-sectional design comparing individuals with CAH and AAD to healthy controls from the general Swedish population. The study protocol consisted of 1) cognitive testing by a psychologist, 2) self-rating behaviour questionnaires and 3) MRI scanning. The control participants also did a 24-h blood pressure measurement that started after the last part of the study had been completed and left a fasting blood sample at a nearby healthcare centre at their convenience on another day. Most participants completed all parts of the test in 1 day. About half of the participants started with parts 1 and 2, while the other half started with part 3. The order of testing and the time of day when scanned were noted.

3.2 Participants

Figures 7A & 7B present flowcharts of participant inclusion and exclusion. Participants took part in the PREDEX study, which investigates the effects of prenatal dexamethasone and postnatal GC treatment, as well as the disease per se. The PREDEX cohort initially comprised 265 participants, for which data collection was completed in 2016. In 2018, we started recruiting and testing individuals with AAD and additional control subjects to match the sex and age of the AAD patient cohort. We updated the PREDEX study protocol for this newer cohort to include self-reported fatigue, sleep and QoL measures. Hence, half of the population controls in studies II, III and IV tested with the old protocol did not have values for these estimates.

3.2.1 Participant recruitment, inclusion and exclusion criteria

All participants were between 16 and 43 years old. Individuals with CAH were enrolled in the long-term PREDEX study and excluded if they had a history of drug use/abuse, current psychiatric problems, severe depression and treatment with antipsychotic medication and MRI contraindications. Milder previous

depression or mild depression with stable treatment and current ADHD with treatment were accepted only in the CAH group. The positive response rate for CAH was 61.1%.

Individuals with AAD were diagnosed at least 2 y. before study inclusion and recruited through the Swedish Addison Registry (116). The positive response rate for AAD was 71%. Exclusion criteria for the patient group were the presence of autoimmune polyendocrine syndrome type-1, diabetes type 1, epilepsy and a history of severe psychiatric problems (such as schizophrenia) and MRI contraindications. We allowed mild depression, anxiety or ADHD and the use of anti-depressants, anxiolytics or psychostimulants in the patient group because the presence of some of these symptoms was of interest to investigate. Hypothyroidism was also allowed, given the high co-morbidity with AAD. All patients had tested positive for autoantibodies against 21-hydroxylase and were well-characterised and monitored at their clinics.

Control participants were recruited from Stockholm through a population registry and were selected based on sex and approximate age (+- 3 y). The positive response rate for controls was about 20%. Controls were excluded if they responded positively to any of the following criteria: prenatal or chronic postnatal GC treatment, autoimmune disease, psychiatric problems and treatment in the past or present, alcohol or drug abuse, MRI contraindications, abnormal fasting levels of cholesterol, triglycerides and insulin, or abnormal blood pressure (24-h ambulatory blood pressure measurement).

3.2.2 Sub-samples

3.2.2.1 Study I: Brain structure in CAH

Study I included 37 patients with CAH-NODEX (21 females), eight patients with CAH-DEX (2 females), and 43 controls (26 females). Three patients in the CAH-NODEX group had NC CAH, 16 had SV CAH and 18 had SW CAH. From these, 19 patients were on hydrocortisone medication, 14 were on prednisolone and 4 had both. The hydrocortisone equivalent replacement dose ranged from 2.74-25.5 mg/m2/day, with a mean of 13.5. Twenty-three individuals with CAH were on MC medication. The CAH-DEX group consisted of one patient with NC CAH, one with SV CAH and six with SW CAH. All participants were ≥16 y) (range: 16–33 y; mean age = 21.7 y, standard deviation = 4.0 y).

3.2.2.2 Study II: Cognition in AAD

The final cohort of Study II comprised 80 (43 females) controls and 67 (39 females) individuals with AAD, of which 29 (19 females) had hypothyroidism. Fifty-two patients were treated with IR-HC (2 or 3 daily doses) and 15 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 (171). The total GC replacement dose, as HC equivalence dose for all patients ranged from 7.48-21 mg/m2/day, with a mean of 12.8. The range for IR-HC was 7.56-21 mg/m2/day, with a mean of 13.1. The range for those on MR-HC was 7.48-17.2 mg/m2/day (mean 11.8). Eight females received DHEA treatment. All individuals with AAD were on MC replacement. Eighteen patients had been diagnosed with AAD before 18 y of age.

3.2.2.3 Study III: Brain structure in AAD

Study III consisted of 52 (33 females) individuals with AAD and 70 (39 females) controls. Twenty-two patients had co-morbid hypothyroidism. Forty-three patients were treated with IR-HC (two or three daily doses) and nine patients with MR-HC (Plenadren®) once daily. The total GC replacement dose for all patients ranged from 7.48-21 mg/m2/day, with a mean of 13.1. The range for those on IR-HC was 7.56-21 mg/m2/day, with a mean of 13.3. For those on MR-HC, the range was 7.48-17.2 mg/m2/day, with a mean of 12.3. Seven females received DHEA treatment. All individuals with AAD were on MC replacement. Fourteen patients had been diagnosed with AAD before 18 y of age.

3.2.2.4 Study IV: Resting-state functional connectivity in AAD

Study IV included 57 (33 females) individuals with AAD and 69 (39 females) controls. Twenty-two patients had co-morbid hypothyroidism. Forty-five patients were treated with IR-HC (2 or 3 daily doses), and 12 patients with MR-HC (Plenadren®) once daily. The total GC replacement dose for all patients ranged between 7.48 and 21 mg/m2/day, with a mean of 13.2. The range for those on IR-HC was 7.56-21 mg/m2/day, with a mean of 13.3. The range for those on MR-HC was 7.48-17.2 mg/m2/day (mean 12.5). Seven females received DHEA treatment. All individuals with AAD were on MC replacement. Fourteen patients had been diagnosed with AAD before 18 y of age.

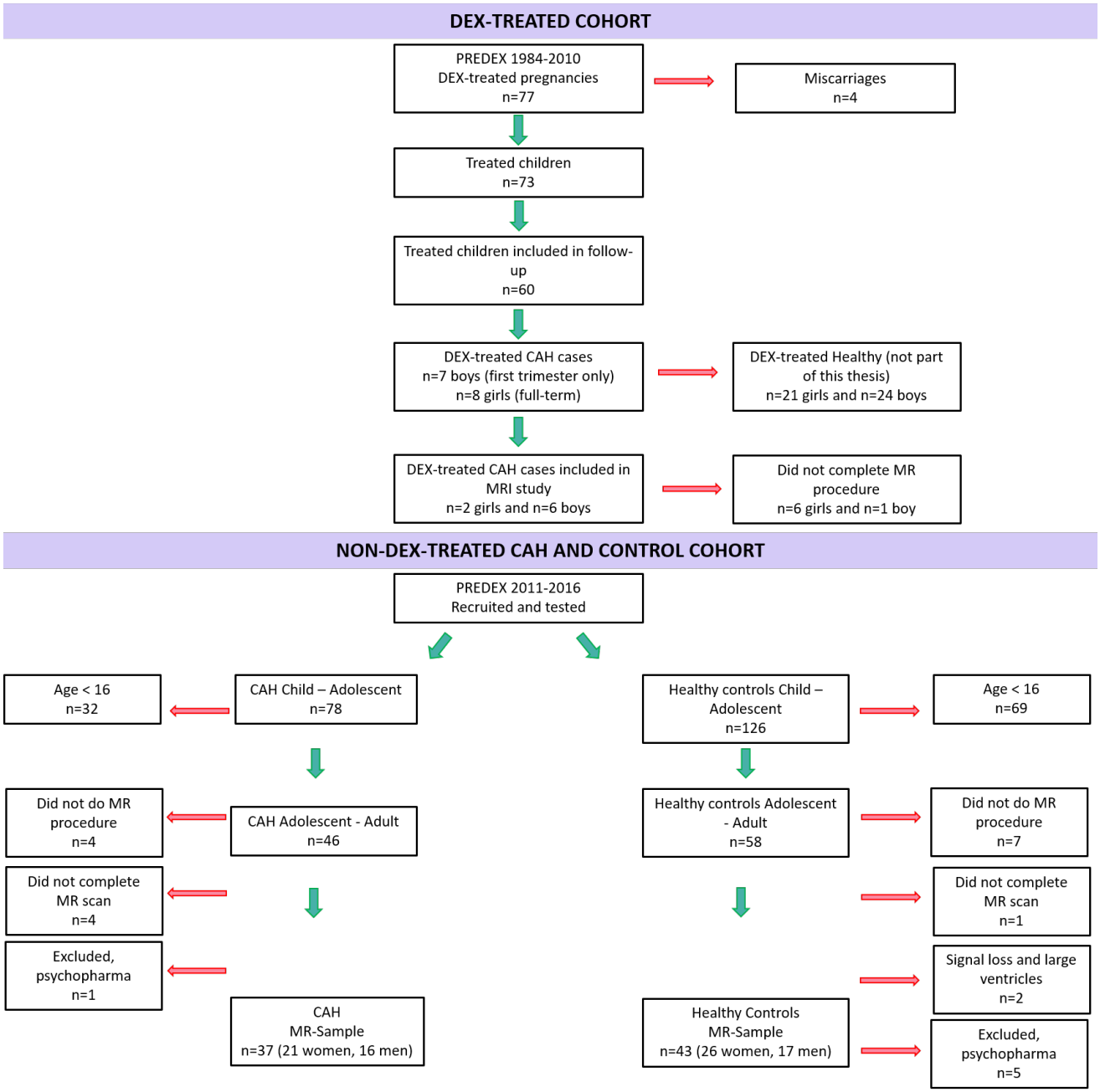


Figure 7A. *Participant flowchart for the PREDEX study, with the DEX-treated cohort (top) and the non-DEX-treated cohorts (bottom). Red arrows = excluded or not part of this study, green arrows = included.*

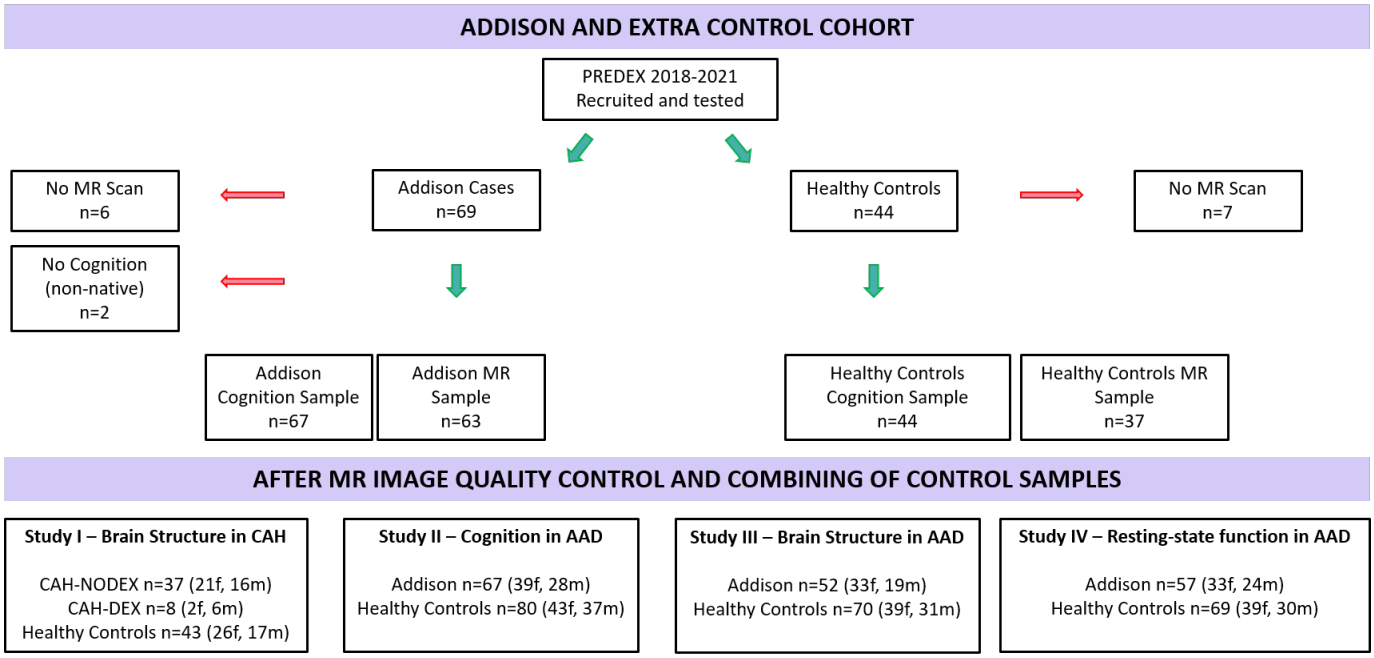


Figure 7B. *Participant flowchart of the Addison and additional control cohort (top), as well as the final samples included in the four studies of this thesis (bottom). Red arrows = excluded or not part of this study, green arrows = included. F= female, m=male.*

3.3 Measures

3.3.1 Descriptives

Descriptive data included participants' biological sex (male or female), age at testing, smoking, drinking and drug habits, medication use (other than GC or MC replacement), employment status and education level of the participant and their parents, measured as whether or not they had completed more than 3 y of university education. Individuals with CAH reported the dose, type and frequency of medication intake. Individuals with AAD reported on dose, type and frequency of medication intake, time of day of medication intake, age at diagnosis and the number of adrenal crises since diagnosis (an episode of adrenal insufficiency requiring immediate hospital treatment).

3.3.2 Cognitive functions

A trained psychologist administered the neuropsychological tests. They included assessments of verbal and non-verbal intellectual ability (Wechsler Adult Intelligence Scale (WAIS)-IV Vocabulary, WAIS-IV Matrices (488)); EFs, including WM performance (WAIS-IV Digit Span (488) and Span Board test (Wechsler Memory Scale (WMS)-III (489)); processing speed and interference control (WAIS-IV Coding (488), and the ability to inhibit pre-potent responses (the Stroop Task (490)); learning and LTM (WMS-III List Learning Test (489) 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).

3.3.3 Self-rated behaviour

Experienced executive functioning problems in the past 2 weeks were assessed with the Barkley Deficits in Executive Functioning Scale-short form (BDEFS-SF) (491)). The BDEFS-SF consists of a 20-item total score and five four-item subscale-scores assessing the "hot" executive functions motivation and emotion regulation and the "cold" executive functions self-management, discipline and self-organization. Age-adjusted cut-off values using American norms were used to determine clinically relevant subscale scores (491). We assessed symptoms of depression and anxiety in the past week (the Hospital Anxiety and Depression Scale (HADS, (492, 493)), with two seven-item subscales (Anxiety and Depression) and symptoms of clinical depression in the past week on the Montgomery-Åsberg Depression Rating Scale (MADRS) (494).

The updated protocol for individuals with AAD and the matched controls additionally included assessments of HRQoL on the Short-Form 36 (SF-36) (495). We also included the Addison disease-specific questionnaire (AddiQoL) for QoL in patients with AAD (135), as well as ratings of sleep quality in the past 6 months using the Karolinska Sleep Questionnaire (KSQ) (496) and fatigue in the past 2 days before testing (the MFI) for all participants (243). The MFI provides five four-item subscales: general fatigue, mental fatigue, physical fatigue, reduced activity and reduced motivation (243).

3.3.4 MRI scanning

MRI scans were acquired on a 3T MR scanner (Discovery MR750, General Electric, Milwaukee, WI, USA) with an 8-channel head coil. During a 70-min session, we acquired anatomical T1-weighted images (T1-weighted BRAVO sequence, TR=7.9 ms, TE=3.1 ms, 176 slices, voxel size: 1.0 x 1.0 x 1.0 mm^3), diffusion-weighted scans (TR=7.4 seconds [s], 62 slices, voxel size: 2.3 x 2.3 x 2.3 mm, 60 directions diffusion-weighted images (b=1500 s/mm^2), eight images with no diffusion sensitisation (b=0 s/mm^2)), two fMRI scans during the execution of a verbal and visuospatial WM task (480 volumes, 16 min each, whole-brain T2*-weighted echo-planar images (TR=2 s, TE=30 ms, voxel-size=3 x 3 x 3 mm, gap-size: 0.5 mm, 41 slices, flip angle 70)), and one resting-state acquisition acquired with a planar echo imaging sequence (TR 2000 ms; TA echo time 30 ms; voxel size 3.0 x 3.0 x 3.0 mm^3; 41 slices; thickness; 3.0 mm; flip angle; 70°). The acquisition time for the resting-state functional magnetic resonance images was 8 min. During this scan, participants were instructed to keep their eyes closed for the entire sequence but not fall asleep.

3.4 Analyses

Statistical analyses were conducted in R version 3.6.1 (497).

3.4.1 Descriptives

For all studies, analyses were conducted to determine group differences between patients and controls in the proportion of males and females, education level (higher education defined as having completed at least 3 y of university studies) (Chi-square tests), illegal drug use (Fisher's exact test) and age and alcohol use (Wilcoxon test for non-parametric data). For AAD patients, sex differences regarding hypothyroidism (Chi-square tests), total hydrocortisone replacement dose (either IR-HC or MR-HC), number of adrenal crises, age of disease onset and disease duration (Wilcoxon test for non-parametric data) were investigated.

3.4.2 Methylation analyses

Methylation analyses were part of another paper from our group, in which methylation of CpG sites was assessed using CD4+ T cells (458). Genome-wide locus-specific DNA methylation levels were measured with the Infinium-HumanMethylation450 BeadChip array. Blood samples for the analyses were collected when participants underwent cognitive testing. This study found two CpG sites (*FAIM2* and *SFI1)* with higher methylation in the CAH group. Given the involvement of *FAIM2* in the brain, we assessed the degree of methylation of the CpG site cg18486102 with brain structure in study I. This analysis was performed on 29 participants (13 CAH without prenatal Dexamethasone treatment (NODEX), and 16 healthy controls).

3.4.3 Preprocessing of MRI data: T1, DTI and resting-state fMRI

3.4.3.1 T1 preprocessing: Surface-based estimates (FreeSurfer)

We estimated cortical thickness, surface area, grey matter volume and volumes of subcortical structures. We also estimated whole brain volume and ICV with a surface-based approach from T1-weighted images using the FreeSurfer pipeline (v6) (http://surfer.nmr.mgh.harvard.edu/). Cortical reconstruction provided estimates of pial surface (cerebral spinal fluid-grey matter boundary), white matter surface (grey-white matter boundary) and segmentation for subcortical volumetric structures. The surfaced-based data were smoothed using a 10-mm full-width at half-maximum smoothing kernel. Technical details of these procedures have been described previously and are documented on the FreeSurfer website (http://surfer.nmr.mgh.harvard.edu/) (Dale et al. 1999; Fischl et al. 1999).

All FreeSurfer surface estimations were visually inspected and manually edited. Because FreeSurfer usually makes some mistakes even in images of participants that lie still, the images of each participant have been edited. Imperfections in the grey-matter pial boundary were removed by editing the pial surface; errors in the grey matter-white matter border were corrected by adding control points to estimate the grey matter-white matter boundaries better.

The surface-based analyses result in a mesh of vertices, triangular-shaped voxels, across the brain's surface. These can be fed in whole brain vertex-wise analyses, or the data can be further analysed using a parcellation approach to estimate average values across regions of an atlas. We used both techniques in our studies for two reasons. First, a vertex-wise approach provides a more locally precise estimate when assessing structural differences. In contrast, a parcellated approach is more amenable for testing associations between brain and cognitive function/WM. Second, for robustness, we can test whether findings are consistent across these two data analysis methods by including two differentially sensitive approaches to noise.

For the parcellation approach, we used two atlases. We used the Destrieux atlas in study I, which segments the cortical surface into 148 bilateral gyri and sulci and 20 subcortical regions (Destrieux et al. 2010). We used the Desikan–Killiany atlas in study III, which segments the brain into 68 bilateral cortical ROIs and 14 subcortical ROIs (498).

3.4.3.2 T1 pre-processing: Voxel-based morphometry (FSL)

Analysis of voxel-based morphology based on anatomical T1-weighted images was analysed with an optimised VBM protocol (Good et al. 2001) implemented in FSL-VBM (Douaud et al. (2007), http://fsl.fmrib.ox.ac. uk/fsl/fslwiki/FSLVBM, part of the FSL tools, Smith et al. (2004)). T1 images were brain-extracted using the brain extraction tool in FSL (BET), visually inspected and then manually edited. The brain-extracted images were segmented to obtain subject-specific GM maps. T1-weighted images were registered into standard space (Montreal Neurological Institute, MNI 152) using nonlinear registration in FNIRT (Andersson et al. 2007a, 2007b). The resulting images were averaged and flipped along the x-axis to create a horizontally symmetric, study-specific GM template. To prevent biases towards one group, an equal number of participants were assigned to each group only for the step of template creation by randomly choosing participants from the larger control group to match the number of the smaller group. The native GM images from all participants were registered to the study-specific template using FNIRT and "modulated" to correct for local expansion or contraction due to the nonlinear component of the spatial transformation. The modulated GM images were smoothed with an isotropic

Gaussian kernel with a sigma of 3 mm. Values for total brain volume were obtained by summing total GM and WM estimates from FSL FAST.

3.4.3.3 DTI pre-processing: TBSS

Voxel-wise whole-brain tract-based spatial statistics (TBSS) analysis was run to obtain estimates of FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) (Smith et al. 2006). We used FSL's eddy correction method without top-up to correct for eddy currents and motion but included the repol option to perform outlier replacement (Andersson et al. 2016). We used rotated bvecs for further steps, brain-extracted Eddy-corrected data using BET (f 0.1 and created FA images by fitting a tensor model to the raw diffusion data using the FMRIB diffusion toolbox (FDT) (Smith 2002). FA data were aligned into a common space (FNIRT, a nonlinear registration tool) using a b-spline representation of the registration warp field (Rueckert et al. 1999). Mean FA images were created and thinned to create a mean FA skeleton representing the centres of all tracts common to the group. Each participant's aligned FA data were projected onto the skeleton and fed into voxel-wise cross-subject statistics. The nonlinear warps and skeleton projection were also applied to the participants' MD, AD and RD images using the tbss_non_FA script.

3.4.3.4 Resting-state functional MRI pre-processing

Resting-state functional MRI data were pre-processed using FMRIB´s Software Libraries version 5.0.11 (FMRIB Laboratory, University of Oxford, England, UK) (Smith et al. 2004). During pre-processing, we applied head motion correction with MCFLIRT (Jenkinson et al. 2002), interleaved slice time correction, brain extraction of the functional image with BET (Smith 2002), spatial smoothing with a Gaussian kernel of 5 mm full width. No high pass filter was applied. The functional images were co-registered to the participant's structural images, which had been brain extracted with the FSL's anat tool using the FMRIBs Linear Image Registration Tool (FLIRT) (Jenkinson and Smith 2001; Jenkinson et al. 2002), and to standard space (MNI152) using the FMRIBs Non-Linear Image Registration Tool (FNIRT) (Andersson et al. 2007), with a 10 mm warp resolution. Next, we applied an independent component analysis (ICA)-based automatic removal of motion artefacts (ICA-AROMA) with the aggressive option to remove motion

artefacts from the data through an ordinary least-squares regression (Pruim, Mennes, Buitelaar, et al. 2015; Pruim, Mennes, van Rooij, et al. 2015). In addition, we applied a custom-made script to remove white matter and CSF from the signal and improve registration. This process resulted in cleaned images further used in the ICA and dual regression analyses.

3.4.4 Statistical power

Statistical power is an issue in studies based on small samples as they concern rare diseases such as CAH and AAD. Hence, these studies do not have the power to detect small effect sizes. As an example, for Study III, brain structure in AAD, based on a linear regression model with three predictors (e.g., group, sex, age) and 122 subjects at alpha 0.05, this study has a power of at least 80% to detect effect sizes of 0.31 (a relatively small effect size) or larger (calculated with R's pwr function).

3.4.5 Co-variate selection and multiple comparison corrections

In all analyses, we included sex and age as covariates, except when assessing scales already adjusted for these variables. We usually presented data with and without correcting for intracranial or total brain volume for the MRI analyses. We opted for this approach because brain volume is the variable of interest. We wanted to understand the relationship between regional differences in brain volume relative to total brain volume and in absolute terms. Put differently, to better understand the relative contribution of brain areas to changes in total brain volume. In addition, brain volume correlates with age at testing, and adding both estimates as covariates may result in multicollinearity.

All studies were exploratory, and we therefore applied multiple comparison corrections in most cases. However, as sub-threshold findings may point at vulnerabilities in the patient group that may be relevant for follow-up studies, we often decided to display results with and without multiple comparison corrections.

3.4.6 Study-specific statistical analyses

3.4.6.1 Study I: Brain structure in CAH

We compared individuals with CAH to healthy controls for cortical thickness, surface area, volume and white matter microstructure, and assessed the relationship between cognitive performance and brain structure using linear models.

We ran a vertex-wise whole-brain analysis using FreeSurfer's Qdec application. Qdec fits a general linear model at each surface vertex to explain the data. Significant clusters were defined with Monte Carlo simulation using pre-run data in Qdec with 10,000 permutations. Talairach coordinates are reported.

For the TBSS analyses, significant clusters were defined using threshold-free cluster enhancement (TFCE) (Smith and Nichols 2009; Winkler et al. 2014) and permutation testing with 10,000 permutations using FSL's randomise tool. TFCE-corrected clusters were localised using the Johns Hopkins University White Matter Tractography Atlas. It was assumed that reduced mean FA but increased mean MD, AD and RD indicate impaired WM microstructure (Beaulieu 2002).

We tested the relationship between cognitive functioning and brain structure using an atlas-based approach. Linear regression models were used to test the association between the degree of methylation and vertex-wise analyses in FreeSurfer, as well as mean estimates of white matter microstructure.

3.4.6.2 Study II: Cognition in AAD

Linear regression models were used unless otherwise specified. We compared individuals 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 was used to test group differences in the number of participants with clinically relevant symptoms of EF (based on American cut-off values).

Within the patient group, we tested whether 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 EF problems. We also tested the relationship between these BDEFS-SF scales and performance on neuropsychological tests of EF (Digit Span and Span Board tests (forward and backward)). Finally, we assessed group differences and interactions with sex for the HADS and MFI scales.

Within the patient cohort, we evaluated the effect of time of testing, order of testing (neuropsychological testing before MR scanning or vice versa) and time since last medication intake in min 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 (n=52), 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.

3.4.6.3 Study III: Brain structure in AAD

Linear regression models were used with sex and age as covariates, unless otherwise specified. Results are reported with and without ICV as a covariate in the FreeSurfer analyses. We compared individuals with AAD to controls on (i) total brain volume (without ventricles) and ICV, (ii) vertex-wise (FreeSurfer QDEC) and ROI (FreeSurfer Desikan–Killiany)-derived cortical thickness, surface area and volume and subcortical volumes (FreeSurfer Desikan–Killiany) and (3) white matter microstructure: FA, MD, AD and RD (FSL-TBSS). Comparisons on these measures were made in 3 steps: (i) whole group comparison, (ii) interaction between AAD and sex and (iii) post hoc analyses dividing by sex for tests where a significant interaction term was found. Results were considered significant with a P- or q-value of <0.05 after correction for multiple comparisons.

To assess whether the relationship between brain structure and cognitive estimates (WM and EF) differs between individuals with AAD and controls, we tested the interaction between groups and brain structure estimates (all Desikan-Killiany atlas ROIs, and whole-brain white matter microstructure FA, MD, AD,

and RD), with tests of WM (WMS Span Board tests forward and backward, WAIS digit span), and self-reported problems with EF (BDEFS-SF total score). For those structural estimates where a significant interaction with group was found, we performed post hoc tests divided by diagnostic group. Linear regression models were used with cognitive estimates as outcome variables and sex and age as covariates. The analyses were repeated with and without correcting for ICV.

Within the patient group, we tested whether GC replacement dose (HC equivalents, mg/m2/day), age at diagnosis, disease duration and the number of adrenal crises (all predictor variables in one model) were associated with brain structure (outcome variables) using linear regression models. Finally, as autoimmune hypothyroidism was common in the AAD cohort (n = 22), we compared individuals with thyroid co-morbidity to 22 healthy controls, matched for age and sex, for all brain structure estimates.

3.4.6.4 Study IV: Resting-state functional connectivity in AAD

Resting-state networks were extracted with spatial ICA on the cleaned data of each subject using MELODIC v 3.15 software (FSL, Oxford, UK) (Beckmann CF 2009). First, ICA was applied for the two groups separately. This analysis aims to visualise/map the average resting-state networks for patients and controls (figure 8). Next, we concatenated the data of all participants and ran the MELODIC ICA on all individuals in our cohort to identify and visualise the networks common to the whole cohort. These networks were fed into the dual regression analyses. The number of components was set to 60 networks. All networks' spatial maps, time courses and power spectra were visually inspected to classify them based on spatial similarity to the functional networks described in healthy people (Smith et al. 2009).

The obtained ICA components were regressed back into individual time series data/space using dual regression (Beckmann CF 2009). Group comparisons were then performed using FSL's randomise tool (Winkler et al. 2014) with 10000 permutations to identify differences in resting-state connectivity between patients with AAD and controls. Sex, age and mean frame-wise displacement were used as covariates. Significant clusters were identified with TFCE with a significance threshold of $P < 0.05$ and a minimum cluster size of 40 voxels (Winkler et al. 2014).

Finally, we tested the association between rs networks and mental fatigue, self-reported EF problems, performance on WM tasks and disease-related factors (i.e., GC replacement dose in mg/m2/day), number of experiences of adrenal crises, age at diagnosis and disease duration in years. We first performed interactions between the diagnostic group and mental fatigue and EF, with rs-fc of all networks as an outcome variable, while correcting for sex, age and mean frame-wise displacement. We performed post hoc tests in the patient and control group separately for the networks where a significant interaction was found. In addition, we assessed the relationship between disease-related factors and rs-fc of the networks where a significant group difference was found in the main analyses within the patient group separately.

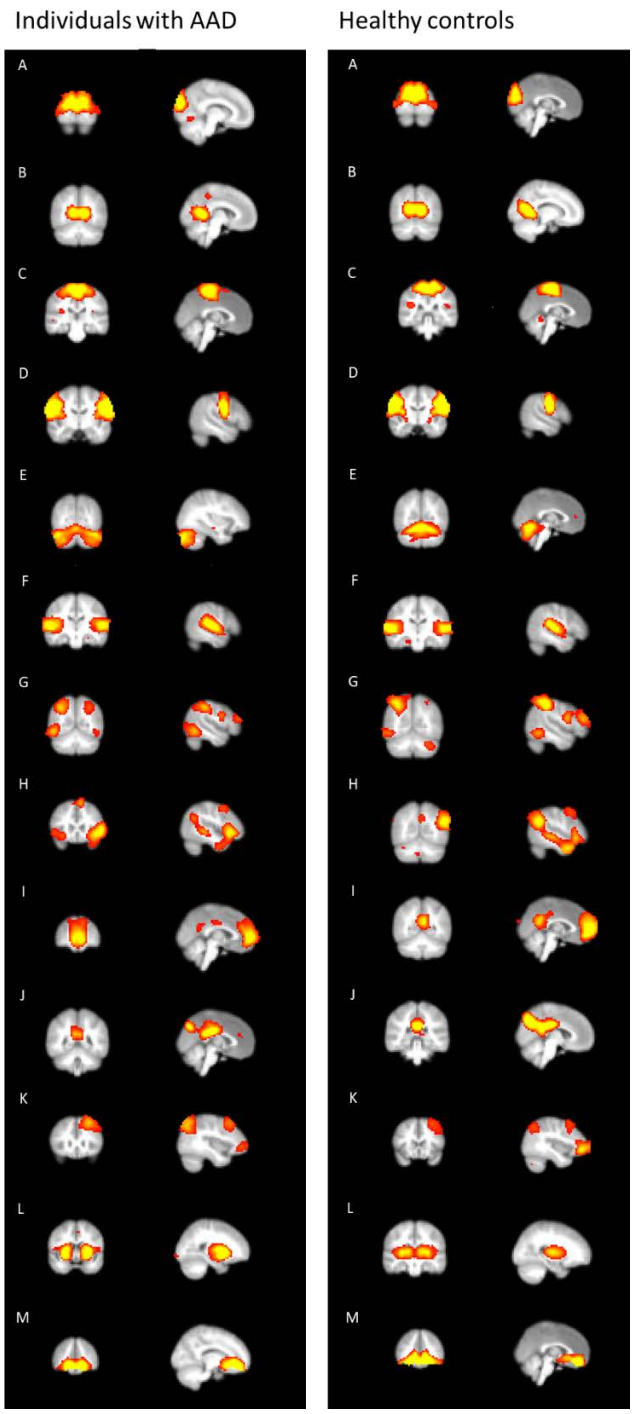


Figure 8. *Resting-state functional connectivity networks in individuals with AAD (left) and healthy controls (right). A: Visual Pole, B: Visual Medial, C: Sensorimotor (motor leg-hand), D: Motor face regions, E: Cerebellum, F: auditory/language, G: Dorsal attention, H: Salience, I: Default Mode Network (anterior), J: Default Mode Network (posterior), K: frontoparietal (CEN), L: basal ganglia (subcortical), M: OFC.*

3.5 Ethical considerations

Ethical considerations in the project encompass several topics. First, participants undergo the procedure voluntarily and can quit at any time without specifying a reason. They give informed consent before the start of the study, in which they agree that they have been informed about the procedure and agree to participate. In addition, all sensitive personal data are stored in a secure environment according to GDPR.

In addition, it is important to keep in mind that we might ask a good deal from the participants. For patients, the whole procedure may be particularly strenuous. The study's outcome should not be at the cost of the physical or mental wellbeing of the participants. Thus, it is crucial to inform the participants how long the tests will take and what will be done so that they precisely know the aim of the study. In particular, MRI scanning might be experienced as challenging. Accordingly, we have been most considerate towards the participants who were concerned by reminding them that they could discontinue participating in the study at any time and are not obligated to participate in both parts of the study (i.e., the cognitive testing and the MRI part). The participants were also given a break and lunch in-between the two test halves.

The project is part of the PREDEX study, which has been approved by the Regional Ethical Committee of Karolinska Institutet and by the Swedish Ethical Review Authority DNR 99-153 (990517); 030619; 2011/1764-32 (111201); 140912; 2017/1658-32 (170831); 2018/1037- 32 (180518); 2020–00564 (200414).

4 Results

4.1 Study I: Brain structure in CAH

Compared to healthy controls, individuals with CAH had widespread alterations in white matter microstructure (figure 9). These alterations were reduced FA, increased MD and increased RD of the major tracts, indicating reduced integrity of the white matter fibers in the patient group. Males with CAH, but not females, also had increased AD in the left forceps minor and left inferior fronto-occipital fasciculus. Within the patient group, a higher GC replacement dose in mg/m2/day correlated with increased mean FA (B = 0.0016, P = 0.002 and reduced mean RD (B = −1.46xe-6, P = 0.037), indicating, on average, less impaired white matter microstructure of those on a higher replacement dose.

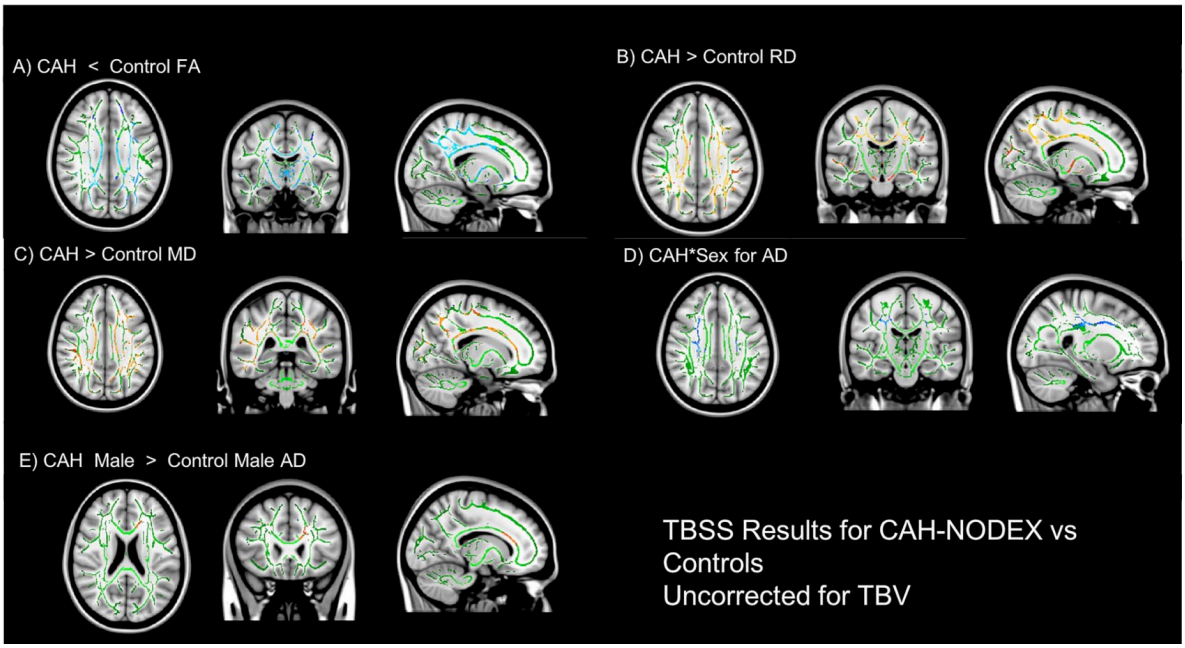


Figure 9. *Alterations in white matter microstructure in individuals with CAH compared to healthy controls, with reduced FA (blue colours in A), increased RD (B) and MD (C), as well as an interaction with sex for AD (D), with males with CAH having increased AD compared to control males (E).*

Individuals with CAH also had 4.23% smaller total brain volume than controls, reduced thickness of the bilateral rostral middle frontal gyrus, left superior parietal cortex and right inferior parietal cortex, increased surface area of the left cuneus and right pericalcarine cortex, and reduced volume of the left precuneus (FSL-VBM) (see figure 10).

Patients with CAH performed worse than controls on visuospatial WM tasks (WMS forward P = 0.016, WMS backward P = 0.007) and displayed more autistic traits on the AQ10 (P = 0.018) (Table 2). Within the patient group, those who performed worse on the backward visuospatial WM task had reduced thickness of the left middle frontal gyrus (B = 7.06, P = 0.046), and those who performed worse on the forward WM task had reduced surface area of the right parietal-occipital gyrus (B = 0.0046, P = 0.029). In controls, no relationship between WM and the middle frontal gyrus was found; however, controls, who performed better on both WM tasks, had greater volume of the left praecuneus (forward: B = 0.0015, P = 0.013; backward: B = 0.0012, P < 0.001), and those who did better on the backward WM task had greater thickness of the left superior parietal cortex (B = 0.032, P = 0.029).

We also assessed the effect of prenatal DEX treatment by comparing DEX-treated to untreated patients. Those who had received DEX had reduced surface area of the bilateral pericalcarine cortex and reduced volume in the left pericalcarine and right superior parietal cortex.

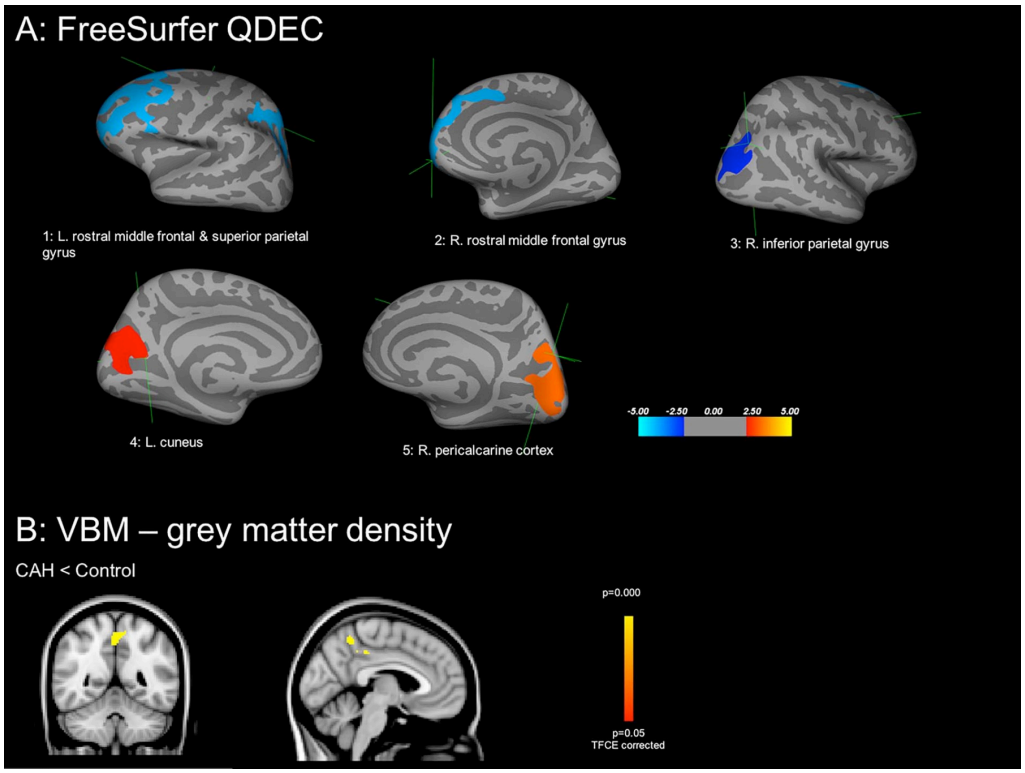


***Figure 10**. Alterations in cortical thickness, surface area and volume in individuals with CAH compared to healthy controls. Blue shades indicate reduced cortical thickness (A1-3), red-orange shades indicate increased surface area (A4&5) in individuals with CAH compared to controls. Yellow (B) indicates reduced grey matter volume in individuals with CAH compared to controls.*

4.2 Study II: Cognition in AAD

In general, we found only a few differences between patients with AAD and controls in cognitive functioning. Patients scored somewhat lower on verbal intellectual ability (B= − 0.75, p = 0042, Cohen's d= − 0.34) and visuospatial WM (Span Board forward) (B= − 1.09, p = 0.020, Cohen's d= − 0.41) and reported more problems with EFs on the total BDEFS-SF scale (B= 2.84, p = 0.030, Cohen's d= 0.25) and on the subscales self-organisation (B= 1.05, p = 0.005, Cohen's d= 0.45) and emotion regulation (B= 1.09, p = 0.017, Cohen's d= 0.28). The self-reported EF problems were specific to female patients for the full scale (B= 5.53, p = 0.001, Cohen's d= 0.49) and the self-organisation subscale (B= 1.97, p < 0.001, Cohen's d= 0.74)) (figure 11). Thirteen patients (11 females) had clinically significant symptoms of emotion regulation according to the BDEFS-SF (American norms) as opposed to only two controls (p = 0.002).

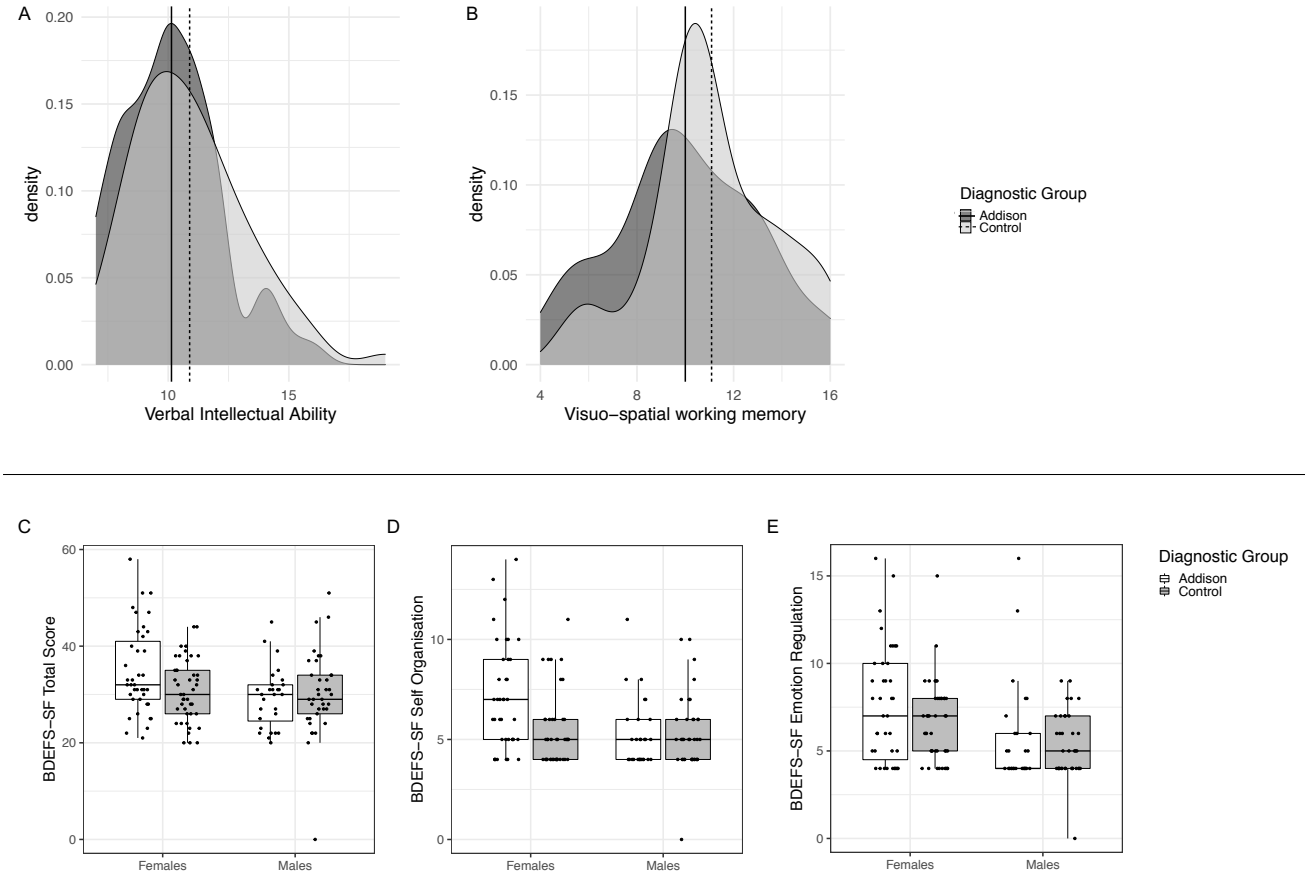


Figure 11. *Individuals with AAD scored somewhat lower on verbal intellectual ability (A) and visuospatial WM (B). They also self-reported more problems with executive functions (C), especially self-organisation (D) and emotion regulation (E).*

Several factors predicted self-reported EF problems within the patient group (figure 12). Symptoms of anxiety (B=0.59, p = 0.019) and depression (B=0.86, p = 0.012) were associated with a higher total BDEFS-SF score. Self-organisation problems were explicitly associated with symptoms of depression (B=0.24, p = 0.032), whereas emotion regulation problems were associated expressly with anxiety symptoms (B=0.24, p = 0.025). Furthermore, mental tiredness, but not general tiredness, was associated with higher scores on all three EF scales: total scores (B=1.21, p < 0.001), self-organisation (B=0.34, p < 0.001) and emotion regulation (B=0.30, p = 0.020). Only female patients reported more mental tiredness compared to controls (B=2.65, p = 0.002). Regarding disease-related factors, there was only a significant association for GC replacement dose in mg/m2/day, with patients on a lower dose experiencing more subjective problems with emotion regulation (B=− 0.30, p = 0.013).

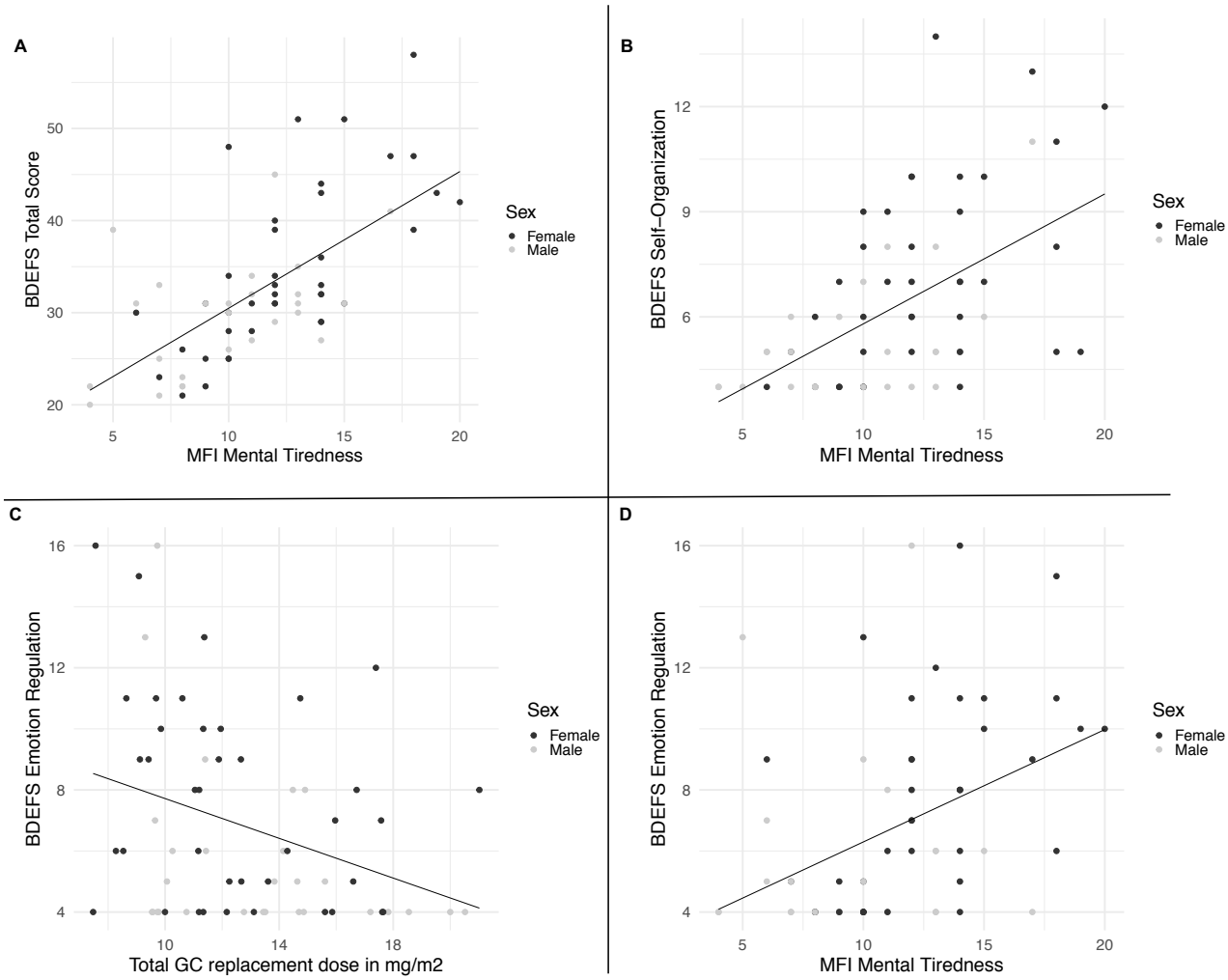


Figure 12. *In individuals with AAD, self-reported problems with executive functions on the BDEFS total (A) and self-organisation (B) scales were associated with mental tiredness. Self-reported difficulties with emotion regulation were associated with a lower GC replacement dose (C) and mental tiredness (D).*

We then determined the unique contribution of these factors to the three subscales by combining them in one model per outcome scale. Mental tiredness remained the only significant predictive factor for BDEFS total (B=1.19, $p < 0.001$) and self-organisation scores (B=0.36, $p < 0.001$). 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) remained as significant predictors.

Patients who performed worse on the verbal and visuospatial WM tasks reported more problems on the BDEFS-SF total scale. Worse performance on the verbal WM task was related explicitly to more problems with self-organisation.

4.3 Study III: Brain structure in AAD

No group differences were found in white matter microstructure between individuals with AAD and controls. AAD Patients did have 4.3% smaller total brain volumes (B= −35,772, P = 0.026), 4.1% smaller ICVs (B= −46134.6, P = 0.042), a smaller surface area of the left supramarginal gyrus and right inferior parietal cortex and smaller volume of the right lateral OFC, but not when including ICV as a covariate. Only male patients with AAD had smaller volume and surface area of the right superior parietal cortex than male controls, even when correcting for ICV.

AAD patients on a higher GC replacement dose in mg/m2/day had a smaller volume of the left lingual (B= −106.28, q = 0.045), rostral anterior cingulate (B= −59.45, q = 0.033) and right supramarginal gyrus (B= −177.30, q = 0.045), as well as smaller total brain volume (B= −8383, P = 0.027) (see figure 13). The latter entails a reduction of 0.73% TBV (8,383/1,144,326 ∗ 100) for every mg/m2/day increase in GC dose. Given that medication doses in our patient group ranged between 7.5 and 21 mg/m2/day, we may expect an approximate difference of 9.9% (13.5 ∗ 0.73) in total brain volume related to GC medication dosing. GC replacement dose was not associated with the number of experienced adrenal crises in the total patient group (B= −0.07, P = 0.450), but individuals with AAD who had experienced more adrenal crises were more likely to be on MR-HC (B= 0.13, P = 0.040).

Because the medication dose is estimated in mg/m2/day, the person's size may confound the relationship between GC dose and brain volume because shorter individuals could have a relatively higher medication dose and relatively smaller brains. Height in cm was significantly associated with total brain

volume (B= −7124, P = 0.045) but not with GC dose (mg/m2/day) (B= −0.08, P = 0.382). Moreover, BMI did not correlate with brain volume or GC dose (mg/m2/day). Including height as a covariate, the relationship between total brain volume and medication dose remained significant (B= −7124, P = 0.045), entailing a 0.62% brain volume reduction with every increase in mg/m2/day and a maximum expected difference in TBV related to medication use of 8.4% (13.5 ∗ 0.62).

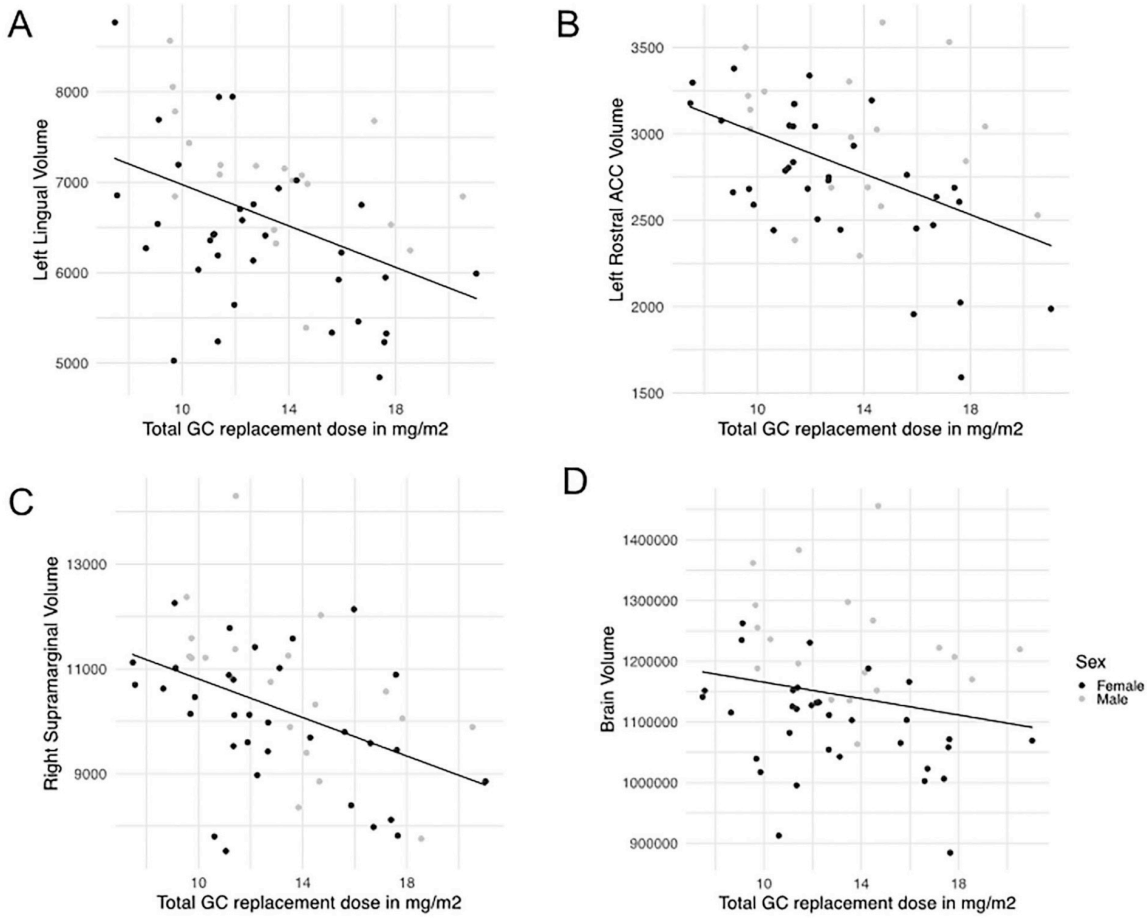


Figure 13. *The relationship between GC replacement dose (mg/m2/day) and volume of the left lingual gyrus, left rostral anterior cingulate cortex, right supramarginal gyrus and total brain volume.*

4.4 Study IV: Resting-state functional connectivity in AAD

Patients with AAD had increased rs-fc compared to healthy controls in three main clusters, belonging to three networks: the bilateral medial OFC (Orbitofrontal Network), the left precuneus and lingual gyrus (Posterior DMN) and left intracalcarine cortex/part of the lingual cortex (Medial Visual Network) (figure 14). These findings did not change by excluding patients on SSRI treatment (n=7), correcting for IQ or correcting for the time of the day when scanned.

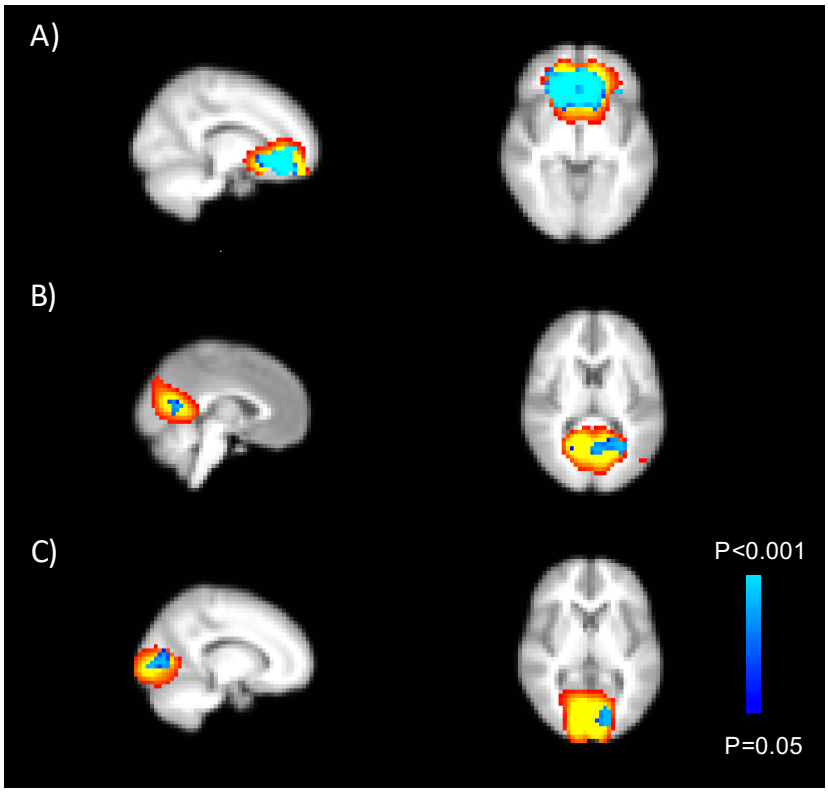


Figure 14. *Individuals with AAD had increased rs-fc in three networks: A) the orbitofrontal cortex (OFC), B) the posterior DMN and C) the medial visual network.*

GC replacement dose (mg/m2/day) was associated with stronger rs-fc in a small part of the left OFC (figure 15). An interaction was revealed between the diagnostic group and mental fatigue for rs-fc within the left inferior lateral OFC (Lateral Visual Network), right lingual gyrus (Lateral Visual Network) and left intracalcarine cortex (Medial Visual Network). General fatigue was also differentially associated with rs-fc within the left lateral inferior OCC (Lateral Visual Network) and the left intracalcarine cortex (Medial Visual Network) between patients and controls. However, post hoc analyses did not reveal

significant associations between mental or general fatigue and rs-fc in these regions in patients or controls separately.

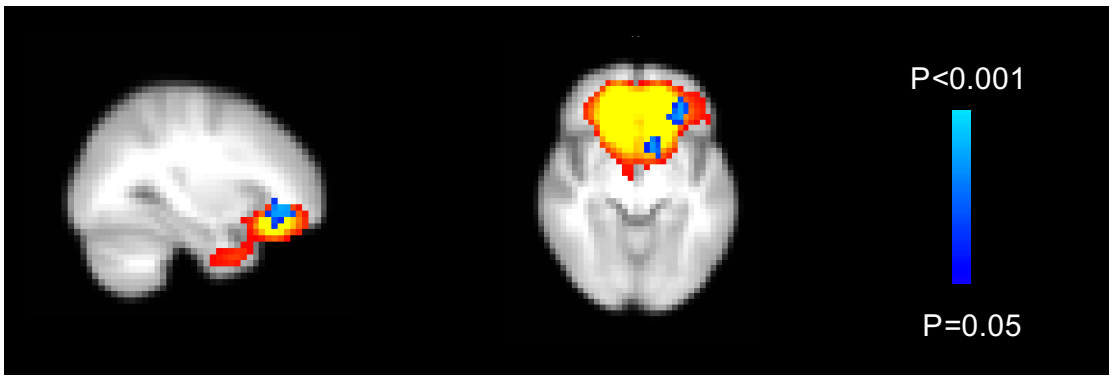


Figure 15. *A higher GC replacement dose in mg/m2/day was associated with stronger rs-fc in a small part of the left OFC.*

5 Discussion

5.1 Brain structure and function in CAH

These studies show that PAI affects cognitive functioning, brain structure and brain function in young adults (16-43y). In study I, we have shown that young adults with CAH have impaired white matter microstructure in the major fiber tracts and alterations in grey matter structure, particularly in the frontoparietal network. White matter microstructure impairments align with most other brain imaging studies in CAH and point to the vulnerability of oligodendrocytes to cortisol disturbances (454, 455). White matter changes were widely distributed and not limited to any specific region or tract, both in our study and in the only other quantitative study that took a whole-brain approach to white matter assessment in adult women with CAH (454). In a younger cohort aged 8-18 y, focusing on the fornix and stria terminalis, the authors also found uniform impairments of white matter across the whole tract (455). The outcome of white matter changes may result from many factors, including prenatal programming effects, as individuals with CAH lack cortisol and have increased androgen levels prenatally. Oligodendrocytes also need cortisol to develop (268, 269) and are sensitive to DHEA (499). Hence, sub-optimal cortisol levels, a sub-optimal DHEA/cortisol ratio or epigenetic changes in the expression of GR on oligodendrocytes could all affect their development (500). Inflammatory processes are another possible explanation for white matter impairments in CAH, as cortisol affects the immune system and increased microglia activity was found in mice with impairments in neurite dispersion (a white matter integrity estimate) (456).

How to improve white matter integrity in CAH is a challenge. In our cohort, a relatively higher GC replacement dose, though within therapeutic ranges, was, on average, associated with *less* impaired white matter microstructure. This finding contrasts with other studies, that show more white matter impairments on higher replacement doses in CAH (454), but also concerning hypercortisolism in such diseases as Cushing's (276, 408, 501). Based on these observations, our finding warrants replication and more detailed analyses.

In healthy people, estimates of white matter microstructure (e.g., FA) correlate with the cortical thickness of their connecting regions (502). In the child and adolescent cohort from the US, the impaired white matter of the fornix and stria terminalis was seen to correlate with reduced volume of the hippocampus and amygdala, respectively (455). We did not test the association between grey and white matter, but multimodal imaging analyses may be conducted in the future. The white matter change in the fronto-occipital and superior and inferior longitudinal fasciculi, which connect the frontal with the occipital and parietal cortexes, correspond to changes in grey matter that we also found predominantly in the fronto-parietal and occipital cortexes, and not in subcortical or more limbic frontal regions. Potentially, the white matter impairments affect grey matter activity in the connecting regions, which could contribute to the problems with WM that the patients displayed. However, white matter estimates did not correlate with cognitive functioning in our cohort. At the same time, reduced cortical thickness of the middle frontal gyrus *was* associated with worse performance on WM in the CAH group, which partly supports this hypothesis.

Individuals with CAH performed worse on WM tasks compared to healthy controls, which we previously also reported in a slightly larger cohort (443). In that group, we also found that individuals with CAH had reduced performance on cognitive inhibition and a male-specific reduction in non-verbal IQ (443). The present results suggest that these problems with EFs may be partly related to cortical thinning of the frontoparietal network. Interestingly, at a younger age, during childhood and adolescence, our CAH cohort did not show the same problems with EFs (442), suggesting that the patient's cognitive functioning declines with time. Other studies did find problems with cognitive functioning in children with CAH. Thus, the findings may be specific to our cohort or indicate that children in Sweden with CAH are well-managed as they are all diagnosed through the neonatal screening programme (432, 433). Unfortunately, we did not scan participants at a younger age, so we have no information about longitudinal brain changes that may have taken place.

Other studies on individuals with CAH have found reductions in grey matter volume in areas of the limbic system (457). Because of the known vulnerability of fronto-limbic regions to cortisol, particularly the hippocampus, many studies have limited their research to these regions. They might thereby miss other vulnerabilities in the brain. Our whole-brain exploratory approach confirmed

vulnerability of the prefrontal cortex, particularly the middle frontal gyrus in the CAH group, but also found differences in grey matter structure in the parietal and occipital cortex. Surprisingly, neither CAH nor AAD patients in our studies had changes in hippocampal or subcortical volumes. The studies that did find subcortical and hippocampal volume reductions were from cohorts containing patients that had not been screened in the neonatal screening programme (454, 457) and some patients that were on Dexamethasone treatment, which is a very potent synthetic GC agonist (454). Early-life salt-wasting crises and remarkably high GC doses may have negatively impacted the subcortical regions of their brains. Therefore, our results suggest that early detection and careful management may spare the brain to some extent. GC replacement dose was not associated with grey matter structure in our sample, which confirms this hypothesis.

We found an association between hypermethylation of the *FAIM2* gene and the surface area of the medial occipitotemporal and lingual sulcus. *FAIM2* is a neuroprotective membrane-bound protein (459, 460). A higher GC dose was associated with hypermethylation of this site (458). However, as we do not know whether this results in more or less protein products, we cannot determine whether this genetic alteration is maladaptive. CAH patients had increased surface area of the left cuneus and right pericalcarine cortex but not in the areas where an association with *FAIM2* methylation was found. Further research is needed to understand this relationship.

5.2 Brain structure and function in AAD

A different pattern of brain structure and function alterations was observed in the AAD group as opposed to what we found in CAH. Overall, individuals with AAD did quite well on the cognitive tests assessed during the lab visit. Accordingly, we found few differences in the grey matter structure of the brain, apart from reduced total brain volume along the same 4% as found in the CAH group. However, individuals with AAD had stronger resting-state functional connectivity, especially in networks of the DMN and primary visual areas. Both reduced brain volume and stronger rs-fc in part of the OFC were associated with a higher GC replacement dose. This finding suggests that excess GC may be related to mild brain atrophy and reorganisation of network connectivity. However, due to the cross-sectional

nature of our study, we cannot determine causality. Those on a higher dose may have been more ill in the past.

Individuals with AAD reported problems with hot and cold EF, and altered rs-fc and reduced cortical volume were found in the OFC, a region mostly related to hot EF (222, 229). Although EF networks strongly overlap, this alteration may suggest that patients are vulnerable to problems with emotion regulation or other even hotter functions, such as motivation and reward processing. If patients are more susceptible to hot EF problems, this could explain why we did not find many differences in the tasks that were assessing only cold EFs. Meanwhile, there was no correlation between rs-fc of the OFC and self-reported hot or cold EF, and patients also reported experiencing cold EF problems related to self-organization. It seems therefore that EFs in general may be affected in AAD.

Patients had somewhat lower verbal IQ and reduced visuospatial WM, which might indicate a specific vulnerability for these functions in AAD, while LTM was not affected. There was a correlation between worse performance on WM and self-reported EFs. The slight reduction in performance on the cognitive tests potentially contributes to real-life problems for these patients. This discrepancy between experimental testing and real-life patient experience has also been observed in Cushing's disease, with many patients experiencing problems with cognitive functioning while cognitive tests in the lab reproduce only a part of that. This discrepancy was even 80% vs 30% for memory problems (397, 400).

Regrettably, we did not precisely match our participants' education level and may have underestimated their problems. Another confounding factor is that patients may be more motivated to participate, as indicated by the much higher positive response rate. In one study, individuals with PAI were even found to perform better on a concentration task, which the authors attributed to increased motivation (474). Compared to previous studies on AAD, we have a unique cohort of young individuals with isolated AAD, apart from co-morbid hypothyroidism. This may also explain why they are performing relatively well, as cumulative disease burden may increase problems for other patient groups. Although one group also reported few differences in cognition in AAD, except verbal learning problems, these authors included BMI and depressive symptoms as covariates (477). In our view, this may mask the effects of the disease, as these symptoms are correlated with each other.

Previous research has shown that sleep might be an important mediator of cognitive problems in AAD (475), which is in line with the findings from Study II where we found mental fatigue to be the strongest predictor of experience EF problems. Reducing fatigue and improving sleep quality should therefore be a major focus of developing future medication for these patients (e.g., with treatments such as Chronocort® that aim at replicating the natural cortisol awakening response). Mental fatigue was only significantly different from controls in women with AAD, and most patients with clinically significant emotion regulation problems were also females. Because the main sex-difference in AAD is related to the lack of testosterone in females, this finding raises the question whether DHEA replacement could improve fatigue in women. DHEA supplementation was found to improve both mood (503) and fatigue (504) in some studies, while others did not replicate the improvement of fatigue (158). Other patient groups did not benefit from DHEA as to fatigue either (505) and further research is therefore needed to understand the relationship between androgens, fatigue and brain function. Of note, brain-derived DHEA may be intact in AAD, which could explain the lack of DHEA supplementation effects on cognitive functioning (294). Patients may further be fatigued without being sleepy, and daytime fatigue may be independent of sleep problems (468). Previous studies found that fatigue was more often reported on higher GC replacement doses (468), whereas a study on SAI found the exact opposite; those on a higher dose were less fatigued (487). Additional analyses of our data showed that within the female group, those on a higher GC dose were less fatigued (data not shown). We also found a small correlation between a higher GC dose and fewer reported EF problems (Study II). However, a few women in our cohort had unusually low GC replacement doses. This observation may explain these results because we performed a within-group linear regression, where "higher" does not necessarily mean higher than any specific cut-off value. In other words, too low GC doses may also lead to fatigue and cognitive problems and the relationship between these variables, particularly in females, needs further investigation.

5.3 Sex differences

In contrast to our hypothesis, we found few sex differences in CAH and AAD. Although this lack of differences could potentially be related to the innate ability of the brain to produce DHEA (294), it may be more likely that the cortisol dysregulation, which is similar between sexes, had a more significant

impact on cognitive functioning and the brain in individuals with PAI. Our findings suggest that DHEA loss in women with AAD is not detrimental to the brain at this age. While the mental fatigue was specific to women with AAD, some brain structure alterations in the parietal lobe were found only in men with AAD and CAH (Study III and I). Moreover, men with CAH performed worse than male controls on non-verbal IQ (443). The brain may require an optimum ratio between DHEA and cortisol during development (330), complicating the effects of hormonal disturbances in men and women with CAH and AAD. Our findings need replication in other, larger cohorts. One factor to consider when assessing self-report measures is that there might be sex differences in self-perception and reporting that may exaggerate observed sex differences. In sum, we find no evidence of sex-specificity of outcomes on cognition, brain structure, and function in patients with PAI, or androgenising effects, other than mental fatigue in women with AAD.

6 Conclusions

Our findings suggest that brain structure and function are altered in individuals with CAH and AAD. Problems with cognitive functioning were found to some extent in both groups, with fatigue being an important predictive factor for experienced EF problems in individuals with AAD. Changes in the brain were also noted in both cohorts, although in different modalities: mostly grey and white matter in CAH, and mostly rs-fc in AAD. The relationship with cognitive functioning is not straightforward. Cortical thinning seems to be associated with cognitive problems in CAH, but we found no clear relationship between the structure or rs-fc of the brain with cognition and fatigue in individuals with AAD. Although we did not directly compare the two groups, patients with CAH seem to have more cognitive problems and brain structure alterations. Those with AAD appear at first sight to do relatively well but show reorganisation of functional brain networks. The reasons for these differences may be manifold but could be related to the different developmental time windows of the disease onset, the difference in disease duration, which was on average two decades for CAH, and one decade for AAD, the differences in DHEA levels and GC replacement doses, or the timing when the doses are taken. We can speculate that because structural networks develop before functional ones, structure may be altered more in CAH. On the contrary, individuals with AAD had normal brain development until disease onset, which may have led to a change in functional organisation in response to that impact. Cognitive reserve could also be greater in those with AAD. Direct comparisons between the two groups is of interest here, especially in longitudinal follow-up studies and studies including older and younger cohorts.

In conclusion, cognition and the brain are affected in PAI, but the extent and nature of the changes seem to differ between CAH and AAD. Although our study is not designed to make recommendations about treatment improvement, it does suggest that treatment optimisation may be needed to sustain brain health in PAI.

7 Points of perspective

Our ultimate goal is to improve patient wellbeing and QoL by considering brain health throughout their lifespan. Future studies should incorporate longitudinal designs where patients are followed and tested at numerous time points. It will also be worthwhile to test a wider age span on a much larger sample so that the groups can be split into age bins. Age of onset (in AAD) and disease duration likely interact to impact brain structure and function. However, because people were of different ages in this cross-sectional study, these effects could not be disentangled. Even healthy people display a characteristic age-related cognitive decline (506), and those with PAI might be expected to have a steeper age-related cognitive decline. This phenomenon is worth investigating, particularly in improving medication that might normalise this process.

When developing new medication, brain health should be considered. For instance, even though slow-release medication may better replicate some aspects of circadian secretion, it abolishes ultradian rhythmicity, which may not necessarily be better for the brain. More extensive studies are needed to replicate our findings, with a special focus on sex differences and the effects of GC dosing, as there was little variation in medication doses for AAD cases. For this, international collaboration is recommended due to the relatively low prevalence of AAD.

Defining brain health is a challenge, given the compensatory capacity of the brain. Therefore, interpreting structural and functional changes in relation to cognitive functioning and wellbeing needs to be investigated using a longitudinal multimodal design. Some patients may also be more vulnerable to cognitive problems, which is a question that was not addressed in the present study, but could be looked at in the future. It will further be relevant to investigate whether the observed changes, such as mild atrophy in AAD and white matter changes in CAH, can be reversed with improved treatment.

We further propose conducting qualitative research to study which executive functioning problems individuals are experiencing daily and to what extent fatigue is mediating these issues. Such an approach will give insight into areas where individuals with PAI may require more support. The present thesis indicates that the most critical area would be to improve fatigue in women with AAD. This suggestion is consistent with patients' self-reports, who experience physical and mental fatigue daily (507). In

addition, individuals with PAI must deal with a potentially life-threatening disease. These individuals may also have many co-morbid diseases that could cause anxiety and stress. Such disorders, as well as the induced anxiety and stress itself could contribute to problems with executive functioning in everyday life that are not caused by some biological mechanism directly related to PAI. Considering the patient's unmet needs and their perspectives (e.g., in the case of an adrenal crisis) are essential to address in future studies (508, 509). Living with a chronic illness requires a great deal of patient responsibility to seek timely care, which may be modulated by educational and socio-economic background and sex. Individuals with AAD need to learn how to deal with their disease and manage medication, which may cause uncertainty (507). They experience a lack of health care providers' awareness about their condition. They also need to learn when to increase their medication doses. This understanding of own disease-management is complicated because individual differences in stress sensitivity exist, and stress dosing may be required more frequently and in different situations than prescribed by health care providers (507). These factors also need to be considered when investigating these illnesses' effects on brain health, mainly if the aim is to improve medication schemes to preserve the brain.

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9 References

1. Betterle C, Morlin L. Autoimmune Addison's disease. Endocrine development. 2011;20:161-72.
2. Addison T. On the constitutional and local effects of disease of the supura-renal capsules. Highley, London. 1855.
3. Delle Piane L, Rinaudo PF, Miller WL. 150 years of congenital adrenal hyperplasia: translation and commentary of De Crecchio's classic paper from 1865. Endocrinology. 2015;156(4):1210-7.
4. De_Crecchio L. Sopra un caso di apparenze virili in una donna: Stab. tip. di F. Vitale; 1865.
5. Kendall EC. Cortisone. Ann Intern Med. 1950;33(4):787-96.
6. Arlt W, Allolio B. Adrenal insufficiency. Lancet (London, England). 2003;361(9372):1881-93.
7. Quinkler M, Oelkers W, Remde H, Allolio B. Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. Best practice & research Clinical endocrinology & metabolism. 2015;29(1):17-24.
8. MacKenzie SM, van Kralingen JC, Davies E. Regulation of Aldosterone Secretion. Vitamins and hormones. 2019;109:241-63.
9. Bollag WB. Regulation of aldosterone synthesis and secretion. Comprehensive Physiology. 2014;4(3):1017-55.
10. Bae YJ, Kratzsch J. Corticosteroid-binding globulin: modulating mechanisms of bioavailability of cortisol and its clinical implications. Best practice & research Clinical endocrinology & metabolism. 2015;29(5):761-72.
11. Lewis JG, Bagley CJ, Elder PA, Bachmann AW, Torpy DJ. Plasma free cortisol fraction reflects levels of functioning corticosteroid-binding globulin. Clinica chimica acta; international journal of clinical chemistry. 2005;359(1-2):189-94.
12. Mendel CM. The free hormone hypothesis: a physiologically based mathematical model. Endocrine reviews. 1989;10(3):232-74.
13. Nicolaides NC. The Human Glucocorticoid Receptor Beta: From Molecular Mechanisms to Clinical Implications. Endocrinology. 2022;163(11).
14. Vandevyver S, Dejager L, Libert C. Comprehensive overview of the structure and regulation of the glucocorticoid receptor. Endocr Rev. 2014;35(4):671-93.
15. Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology. 2009;34 Suppl 1:S186-95.
16. Funder JW. Glucocorticoid receptors. The Journal of steroid biochemistry and molecular biology. 1992;43(5):389-94.
17. de Kloet ER, Reul JM, Sutanto W. Corticosteroids and the brain. The Journal of steroid biochemistry and molecular biology. 1990;37(3):387-94.
18. Jaszczyk A, Juszczak GR. Glucocorticoids, metabolism and brain activity. Neurosci Biobehav Rev. 2021;126:113-45.
19. Song IH, Buttgereit F. Non-genomic glucocorticoid effects to provide the basis for new drug developments. Mol Cell Endocrinol. 2006;246(1-2):142-6.
20. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of general psychiatry. 2000;57(10):925-35.
21. Picard M, McEwen BS, Epel ES, Sandi C. An energetic view of stress: Focus on mitochondria. Front Neuroendocrinol. 2018;49:72-85.
22. Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. Frontiers in behavioral neuroscience. 2018;12:127.

23. Kuo T, McQueen A, Chen TC, Wang JC. Regulation of Glucose Homeostasis by Glucocorticoids. Advances in experimental medicine and biology. 2015;872:99-126.
24. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. Endocrinology and metabolism clinics of North America. 2014;43(1):75-102.
25. Meier CA. Mechanisms of immunosuppression by glucocorticoids. Eur J Endocrinol. 1996;134(1):50.
26. Whitworth JA, Brown MA, Kelly JJ, Williamson PM. Mechanisms of cortisol-induced hypertension in humans. Steroids. 1995;60(1):76-80.
27. Buehring B, Viswanathan R, Binkley N, Busse W. Glucocorticoid-induced osteoporosis: an update on effects and management. The Journal of allergy and clinical immunology. 2013;132(5):1019-30.
28. Mazziotti G, Giustina A. Glucocorticoids and the regulation of growth hormone secretion. Nature reviews Endocrinology. 2013;9(5):265-76.
29. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, et al. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocrine reviews. 2022;43(1):91-159.
30. Miller WL. The Hypothalamic-Pituitary-Adrenal Axis: A Brief History. Horm Res Paediatr. 2018;89(4):212-23.
31. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocrine reviews. 2020;41(3):470-90.
32. Sarabdjitsingh RA, Conway-Campbell BL, Leggett JD, Waite EJ, Meijer OC, de Kloet ER, et al. Stress responsiveness varies over the ultradian glucocorticoid cycle in a brain-region-specific manner. Endocrinology. 2010;151(11):5369-79.
33. Sarabdjitsingh RA, Isenia S, Polman A, Mijalkovic J, Lachize S, Datson N, et al. Disrupted corticosterone pulsatile patterns attenuate responsiveness to glucocorticoid signaling in rat brain. Endocrinology. 2010;151(3):1177-86.
34. Joëls M, Sarabdjitsingh RA, Karst H. Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. Pharmacol Rev. 2012;64(4):901-38.
35. Kalafatakis K, Russell GM, Zarros A, Lightman SL. Temporal control of glucocorticoid neurodynamics and its relevance for brain homeostasis, neuropathology and glucocorticoid-based therapeutics. Neurosci Biobehav Rev. 2016;61:12-25.
36. Focke CMB, Iremonger KJ. Rhythmicity matters: Circadian and ultradian patterns of HPA axis activity. Mol Cell Endocrinol. 2020;501:110652.
37. Kalafatakis K, Russell G, Lightman S. MECHANISMS IN ENDOCRINOLOGY: Does circadian and ultradian glucocorticoid exposure affect the brain? Eur J Endocrinol. 2018.
38. Rosenwasser AM, Turek FW. Neurobiology of Circadian Rhythm Regulation. Sleep Med Clin. 2015;10(4):403-12.
39. Angelousi A, Kassi E, Nasiri-Ansari N, Weickert MO, Randeva H, Kaltsas G. Clock genes alterations and endocrine disorders. Eur J Clin Invest. 2018;48(6):e12927.
40. Chan S, Debono M. Replication of cortisol circadian rhythm: new advances in hydrocortisone replacement therapy. Ther Adv Endocrinol Metab. 2010;1(3):129-38.
41. Chang FC, Opp MR. Corticotropin-releasing hormone (CRH) as a regulator of waking. Neurosci Biobehav Rev. 2001;25(5):445-53.
42. Benedict C, Kern W, Schmid SM, Schultes B, Born J, Hallschmid M. Early morning rise in hypothalamic-pituitary-adrenal activity: a role for maintaining the brain's energy balance. Psychoneuroendocrinology. 2009;34(3):455-62.
43. Späth-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psychiatry. 1991;29(6):575-84.

44. Smyth N, Thorn L, Hucklebridge F, Evans P, Clow A. Detailed time course of the cortisol awakening response in healthy participants. Psychoneuroendocrinology. 2015;62:200-3.
45. Linkowski P, Van Onderbergen A, Kerkhofs M, Bosson D, Mendlewicz J, Van Cauter E. Twin study of the 24-h cortisol profile: evidence for genetic control of the human circadian clock. The American journal of physiology. 1993;264(2 Pt 1):E173-81.
46. Krieger DT. Rhythms of ACTH and corticosteroid secretion in health and disease, and their experimental modification. Journal of steroid biochemistry. 1975;6(5):785-91.
47. Steiger A. Sleep and endocrine regulation. Front Biosci. 2003;8:s358-76.
48. Godsil BP, Kiss JP, Spedding M, Jay TM. The hippocampal-prefrontal pathway: the weak link in psychiatric disorders? Eur Neuropsychopharmacol. 2013;23(10):1165-81.
49. Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocrine reviews. 1991;12(2):118-34.
50. Herman JP, Prewitt CM, Cullinan WE. Neuronal circuit regulation of the hypothalamo-pituitary-adrenocortical stress axis. Crit Rev Neurobiol. 1996;10(3-4):371-94.
51. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, et al. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol. 2003;24(3):151-80.
52. Gaillet S, Lachuer J, Malaval F, Assenmacher I, Szafarczyk A. The involvement of noradrenergic ascending pathways in the stress-induced activation of ACTH and corticosterone secretions is dependent on the nature of stressors. Exp Brain Res. 1991;87(1):173-80.
53. Ritter S, Watts AG, Dinh TT, Sanchez-Watts G, Pedrow C. Immunotoxin lesion of hypothalamically projecting norepinephrine and epinephrine neurons differentially affects circadian and stressor-stimulated corticosterone secretion. Endocrinology. 2003;144(4):1357-67.
54. Kalafatakis K, Russell GM, Harmer CJ, Munafo MR, Marchant N, Wilson A, et al. Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. Proc Natl Acad Sci U S A. 2018;115(17):E4091-e100.
55. Endoh A, Kristiansen SB, Casson PR, Buster JE, Hornsby PJ. The zona reticularis is the site of biosynthesis of dehydroepiandrosterone and dehydroepiandrosterone sulfate in the adult human adrenal cortex resulting from its low expression of 3 beta-hydroxysteroid dehydrogenase. J Clin Endocrinol Metab. 1996;81(10):3558-65.
56. Oostdijk W, Idkowiak J, Mueller JW, House PJ, Taylor AE, O'Reilly MW, et al. PAPSS2 deficiency causes androgen excess via impaired DHEA sulfation--in vitro and in vivo studies in a family harboring two novel PAPSS2 mutations. J Clin Endocrinol Metab. 2015;100(4):E672-80.
57. Klinge CM, Clark BJ, Prough RA. Dehydroepiandrosterone Research: Past, Current, and Future. Vitamins and hormones. 2018;108:1-28.
58. Wang T, Cook I, Falany CN, Leyh TS. Paradigms of sulfotransferase catalysis: the mechanism of SULT2A1. J Biol Chem. 2014;289(38):26474-80.
59. Nakamura Y, Hornsby PJ, Casson P, Morimoto R, Satoh F, Xing Y, et al. Type 5 17beta-hydroxysteroid dehydrogenase (AKR1C3) contributes to testosterone production in the adrenal reticularis. J Clin Endocrinol Metab. 2009;94(6):2192-8.
60. Ben Dor R, Marx CE, Shampine LJ, Rubinow DR, Schmidt PJ. DHEA metabolism to the neurosteroid androsterone: a possible mechanism of DHEA's antidepressant action. Psychopharmacology. 2015;232(18):3375-83.

61. Mueller JW, Gilligan LC, Idkowiak J, Arlt W, Foster PA. The Regulation of Steroid Action by Sulfation and Desulfation. Endocrine reviews. 2015;36(5):526-63.
62. Rege J, Nakamura Y, Satoh F, Morimoto R, Kennedy MR, Layman LC, et al. Liquid chromatography-tandem mass spectrometry analysis of human adrenal vein 19-carbon steroids before and after ACTH stimulation. J Clin Endocrinol Metab. 2013;98(3):1182-8.
63. Webb SJ, Geoghegan TE, Prough RA, Michael Miller KK. The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev. 2006;38(1-2):89-116.
64. Arlt W. Androgen replacement therapy in women. Curr Opin Investig Drugs. 2005;6(10):1028-36.
65. Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, et al. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005;187(2):169-96.
66. Labrie F, Martel C, Bélanger A, Pelletier G. Androgens in women are essentially made from DHEA in each peripheral tissue according to intracrinology. The Journal of steroid biochemistry and molecular biology. 2017;168:9-18.
67. Migeon CJ, Keller AR, Lawrence B, Shepard TH, 2nd. Dehydroepiandrosterone and androsterone levels in human plasma: effect of age and sex; day-to-day and diurnal variations. J Clin Endocrinol Metab. 1957;17(9):1051-62.
68. Longcope C. Dehydroepiandrosterone metabolism. J Endocrinol. 1996;150 Suppl:S125-7.
69. Clark BJ, Prough RA, Klinge CM. Mechanisms of Action of Dehydroepiandrosterone. Vitamins and hormones. 2018;108:29-73.
70. Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A, Rutkowski R. Dehydroepiandrosterone (DHEA): hypes and hopes. Drugs. 2014;74(11):1195-207.
71. Vieira-Marques C, Arbo BD, Cozer AG, Hoefel AL, Cecconello AL, Zanini P, et al. Sex-specific effects of dehydroepiandrosterone (DHEA) on glucose metabolism in the CNS. The Journal of steroid biochemistry and molecular biology. 2017;171:1-10.
72. Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). Molecular and cellular biochemistry. 1994;131(2):99-104.
73. Maggio M, De Vita F, Fisichella A, Colizzi E, Provenzano S, Lauretani F, et al. DHEA and cognitive function in the elderly. The Journal of steroid biochemistry and molecular biology. 2015;145:281-92.
74. Reiter EO, Fuldauer VG, Root AW. Secretion of the adrenal androgen, dehydroepiandrosterone sulfate, during normal infancy, childhood, and adolescence, in sick infants, and in children with endocrinologic abnormalities. J Pediatr. 1977;90(5):766-70.
75. Parker CR, Jr. Dehydroepiandrosterone and dehydroepiandrosterone sulfate production in the human adrenal during development and aging. Steroids. 1999;64(9):640-7.
76. Bornstein SR, Ehrhart-Bornstein M. Basic and clinical aspects of intraadrenal regulation of steroidogenesis. Z Rheumatol. 2000;59 Suppl 2:Ii/12-7.
77. Dong Y, Zheng P. Dehydroepiandrosterone sulphate: action and mechanism in the brain. J Neuroendocrinol. 2012;24(1):215-24.
78. Rosenfeld RS, Rosenberg BJ, Fukushima DK, Hellman L. 24-Hour secretory pattern of dehydroisoandrosterone and dehydroisoandrosterone sulfate. J Clin Endocrinol Metab. 1975;40(5):850-5.
79. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab. 1984;59(3):551-5.

80. Elraiyah T, Sonbol MB, Wang Z, Khairalseed T, Asi N, Undavalli C, et al. Clinical review: The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2014;99(10):3536-42.
81. Wierman ME, Kiseljak-Vassiliades K. Should Dehydroepiandrosterone Be Administered to Women? J Clin Endocrinol Metab. 2022;107(6):1679-85.
82. Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A, New MI. High frequency of nonclassical steroid 21-hydroxylase deficiency. American journal of human genetics. 1985;37(4):650.
83. Wedell A. Molecular genetics of 21-hydroxylase deficiency. Pediatric Adrenal Diseases. 20: Karger Publishers; 2011. p. 80-7.
84. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocrine reviews. 2000;21(3):245-91.
85. Zetterström RH, Karlsson L, Falhammar H, Lajic S, Nordenström A. Update on the Swedish Newborn Screening for Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. Int J Neonatal Screen. 2020;6(3).
86. Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2022.
87. Jones CM, Mallappa A, Reisch N, Nikolaou N, Krone N, Hughes BA, et al. Modified-Release and Conventional Glucocorticoids and Diurnal Androgen Excretion in Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2017;102(6):1797-806.
88. Xing Y, Edwards MA, Ahlem C, Kennedy M, Cohen A, Gomez-Sanchez CE, et al. The effects of ACTH on steroid metabolomic profiles in human adrenal cells. J Endocrinol. 2011;209(3):327-35.
89. Fukami M, Homma K, Hasegawa T, Ogata T. Backdoor pathway for dihydrotestosterone biosynthesis: implications for normal and abnormal human sex development. Dev Dyn. 2013;242(4):320-9.
90. Tschaidse L, Quinkler M, Claahsen-van der Grinten H, Nordenström A, De Brac de la Perriere A, Auer MK, et al. Body Image and Quality of Life in Women with Congenital Adrenal Hyperplasia. J Clin Med. 2022;11(15).
91. Meyer-Bahlburg HFL, Khuri J, Reyes-Portillo J, Ehrhardt AA, New MI. Stigma Associated with Classical Congenital Adrenal Hyperplasia in Women's Sexual Lives. Arch Sex Behav. 2018;47(4):943-51.
92. Krone N, Rose IT, Willis DS, Hodson J, Wild SH, Doherty EJ, et al. Genotype-phenotype correlation in 153 adult patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: analysis of the United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) cohort. The Journal of Clinical Endocrinology & Metabolism. 2013;98(2):E346-E54.
93. New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, et al. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Proc Natl Acad Sci U S A. 2013;110(7):2611-6.
94. Wedell A, Ritzén EM, Haglund-Stengler B, Luthman H. Steroid 21-hydroxylase deficiency: three additional mutated alleles and establishment of phenotype-genotype relationships of common mutations. Proc Natl Acad Sci U S A. 1992;89(15):7232-6.
95. White PC. Neonatal screening for congenital adrenal hyperplasia. Nature reviews Endocrinology. 2009;5(9):490-8.
96. Gidlöf S, Wedell A, Guthenberg C, von Döbeln U, Nordenström A. Nationwide neonatal screening for congenital adrenal hyperplasia in sweden: a 26-year longitudinal prospective population-based study. JAMA pediatrics. 2014;168(6):567-74.

97. Thil'en A, Nordenström A, Hagenfeldt L, von Döbeln U, Guthenberg C, Larsson A. Benefits of neonatal screening for congenital adrenal hyperplasia (21-hydroxylase deficiency) in Sweden. Pediatrics. 1998;101(4):E11.
98. Larsson A, Hagenfeldt L, von Döbeln U, Curstedt T, Gustafsson J, Svensson E. Neonatal screening for congenital adrenal hyperplasia using 17-hydroxyprogesterone assay in filter paper blood spots. Horm Res. 1988;30(6):235-40.
99. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2010;95(9):4133-60.
100. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(11):4043-88.
101. Oprea A, Bonnet NCG, Polle O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther Adv Endocrinol Metab. 2019;10:2042018818821294.
102. Schröder MAM, van Herwaarden AE, Span PN, van den Akker ELT, Bocca G, Hannema SE, et al. Optimizing the Timing of Highest Hydrocortisone Dose in Children and Adolescents With 21-Hydroxylase Deficiency. J Clin Endocrinol Metab. 2022;107(4):e1661-e72.
103. El-Maouche D, Hargreaves CJ, Sinaii N, Mallappa A, Veeraraghavan P, Merke DP. Longitudinal Assessment of Illnesses, Stress Dosing, and Illness Sequelae in Patients With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2018;103(6):2336-45.
104. Muthusamy K, Elamin MB, Smushkin G, Murad MH, Lampropulos JF, Elamin KB, et al. Clinical review: Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. J Clin Endocrinol Metab. 2010;95(9):4161-72.
105. Claahsen-van der Grinten HL, Stikkelbroeck NM, Sweep CG, Hermus AR, Otten BJ. Fertility in patients with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 2006;19(5):677-85.
106. David M, Forest MG. Prenatal treatment of congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency. J Pediatr. 1984;105(5):799-803.
107. Hirvikoski T, Nordenström A, Wedell A, Ritzen M, Lajic S. Prenatal dexamethasone treatment of children at risk for congenital adrenal hyperplasia: the Swedish experience and standpoint. The Journal of Clinical Endocrinology & Metabolism. 2012;97(6):1881-3.
108. Bjornsdottir S, Sundstrom A, Ludvigsson JF, Blomqvist P, Kampe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. J Clin Endocrinol Metab. 2013;98(5):2009-18.
109. Erichsen MM, Løvås K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab. 2009;94(12):4882-90.
110. Olafsson AS, Sigurjonsdottir HA. INCREASING PREVALENCE OF ADDISON DISEASE: RESULTS FROM A NATIONWIDE STUDY. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(1):30-5.
111. Amano N, Narumi S, Hayashi M, Takagi M, Imai K, Nakamura T, et al. Genetic defects in pediatric-onset adrenal insufficiency in Japan. Eur J Endocrinol. 2017;177(2):187-94.

112. Bensing S, Hulting AL, Husebye ES, Kämpe O, Løvås K. MANAGEMENT OF ENDOCRINE DISEASE: Epidemiology, quality of life and complications of primary adrenal insufficiency: a review. Eur J Endocrinol. 2016;175(3):R107-16.
113. Mourinho Bala N, Gonçalves RS, Serra Caetano J, Cardoso R, Dinis I, Mirante A. Autoimmune Primary Adrenal Insufficiency in Children. J Clin Res Pediatr Endocrinol. 2022;14(3):308-12.
114. Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clinica chimica acta; international journal of clinical chemistry. 2020;505:78-91.
115. Barthel A, Benker G, Berens K, Diederich S, Manfras B, Gruber M, et al. An Update on Addison's Disease. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2019;127(2-03):165-75.
116. Dalin F, Nordling Eriksson G, Dahlqvist P, Hallgren Å, Wahlberg J, Ekwall O, et al. Clinical and Immunological Characteristics of Autoimmune Addison Disease: A Nationwide Swedish Multicenter Study. J Clin Endocrinol Metab. 2017;102(2):379-89.
117. Betterle C, Presotto F, Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. Journal of endocrinological investigation. 2019.
118. Skov J, Höijer J, Magnusson PKE, Ludvigsson JF, Kämpe O, Bensing S. Heritability of Addison's disease and prevalence of associated autoimmunity in a cohort of 112,100 Swedish twins. Endocrine. 2017;58(3):521-7.
119. Eriksson D, Bianchi M, Landegren N, Nordin J, Dalin F, Mathioudaki A, et al. Extended exome sequencing identifies BACH2 as a novel major risk locus for Addison's disease. Journal of internal medicine. 2016;280(6):595-608.
120. Eriksson D, Bianchi M, Landegren N, Dalin F, Skov J, Hultin-Rosenberg L, et al. Common genetic variation in the autoimmune regulator (AIRE) locus is associated with autoimmune Addison's disease in Sweden. Sci Rep. 2018;8(1):8395.
121. Eriksson D, Røyrvik EC, Aranda-Guillén M, Berger AH, Landegren N, Artaza H, et al. GWAS for autoimmune Addison's disease identifies multiple risk loci and highlights AIRE in disease susceptibility. Nature communications. 2021;12(1):959.
122. Betterle C, Scalici C, Presotto F, Pedini B, Moro L, Rigon F, et al. The natural history of adrenal function in autoimmune patients with adrenal autoantibodies. J Endocrinol. 1988;117(3):467-75.
123. Naletto L, Frigo AC, Ceccato F, Sabbadin C, Scarpa R, Presotto F, et al. The natural history of autoimmune Addison's disease from the detection of autoantibodies to development of the disease: a long-term follow-up study on 143 patients. Eur J Endocrinol. 2019;180(3):223-34.
124. Sævik Å B, Åkerman AK, Methlie P, Quinkler M, Jørgensen AP, Höybye C, et al. Residual Corticosteroid Production in Autoimmune Addison Disease. J Clin Endocrinol Metab. 2020;105(7):2430-41.
125. Skov J, Eriksson D, Kuja-Halkola R, Höijer J, Gudbjörnsdottir S, Svensson AM, et al. Co-aggregation and heritability of organ-specific autoimmunity: a population-based twin study. Eur J Endocrinol. 2020;182(5):473-80.
126. Eriksson D, Dalin F, Eriksson GN, Landegren N, Bianchi M, Hallgren Å, et al. Cytokine Autoantibody Screening in the Swedish Addison Registry Identifies Patients With Undiagnosed APS1. J Clin Endocrinol Metab. 2018;103(1):179-86.
127. Stewart PM, Biller BM, Marelli C, Gunnarsson C, Ryan MP, Johannsson G. Exploring Inpatient Hospitalizations and Morbidity in Patients With Adrenal Insufficiency. J Clin Endocrinol Metab. 2016;101(12):4843-50.
128. Tiemensma J, Andela CD, Kaptein AA, Romijn JA, van der Mast RC, Biermasz NR, et al. 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. 2014;171(2):171-82.
129. Thomsen AF, Kvist TK, Andersen PK, Kessing LV. The risk of affective disorders in patients with adrenocortical insufficiency. Psychoneuroendocrinology. 2006;31(5):614-22.
130. Skov J, Sundström A, Ludvigsson JF, Kämpe O, Bensing S. Sex-Specific Risk of Cardiovascular Disease in Autoimmune Addison Disease-A Population-Based Cohort Study. J Clin Endocrinol Metab. 2019;104(6):2031-40.
131. Björnsdottir S, Cnattingius S, Brandt L, Nordenström A, Ekbom A, Kämpe O, et al. Addison's disease in women is a risk factor for an adverse pregnancy outcome. J Clin Endocrinol Metab. 2010;95(12):5249-57.
132. Bensing S, Brandt L, Tabaroj F, Sjöberg O, Nilsson B, Ekbom A, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clinical endocrinology. 2008;69(5):697-704.
133. Wotton CJ, Goldacre MJ. Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. Journal of epidemiology and community health. 2017;71(6):576-83.
134. Løvås K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. Clinical endocrinology. 2002;56(5):581-8.
135. Løvås K, Curran S, Oksnes M, Husebye ES, Huppert FA, Chatterjee VK. Development of a disease-specific quality of life questionnaire in Addison's disease. J Clin Endocrinol Metab. 2010;95(2):545-51.
136. Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. J Clin Endocrinol Metab. 2007;92(10):3912-22.
137. Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B, et al. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. Clinical endocrinology. 2010;72(3):297-304.
138. De Bucy C, Guignat L, Niati T, Bertherat J, Coste J. Health-related quality of life of patients with hypothalamic-pituitary-adrenal axis dysregulations: a cohort study. Eur J Endocrinol. 2017;177(1):1-8.
139. Didriksen NM, Sævik Å B, Sortland LS, Øksnes M, Husebye ES. Sex-Specific Limitations in Physical Health in Primary Adrenal Insufficiency. Front Endocrinol (Lausanne). 2021;12:718660.
140. Joersjö P, Block L. A Challenging diagnosis that eventually results in a life-threatening condition: Addison's disease and adrenal crisis. BMJ case reports. 2019;12(12).
141. Kaushik ML, Sharma RC. Addison's disease presenting as depression. Indian journal of medical sciences. 2003;57(6):249-51.
142. Steiner J, Zajontz H, Reiss S, Bogerts B. [Differential diagnosis of anorexia nervosa and depression. A case report of Addison's disease in a female patient]. Der Nervenarzt. 2006;77(3):338-42.
143. Lazare K. Addison's Disease and Possible Cannabis Withdrawal Syndrome Presenting as an Eating Disorder in a Thirty-Year-Old Female. Case reports in endocrinology. 2017;2017:4096021.
144. Feeney C, Buell K. A Case of Addison's Disease Nearly Mistaken for Anorexia Nervosa. The American journal of medicine. 2018;131(11):e457-e8.
145. Wass J, Newell-Price J, Arlt W. Consider Addison's disease in differential diagnosis of eating disorders in children and young people. BMJ (Clinical research ed). 2018;360:k277.

146. Nicholls K, Boggis N, Pandya N. Anorexia nervosa: a mistaken diagnosis. BMJ case reports. 2016;2016.
147. Løvås K, Husebye ES. Addison's disease. Lancet (London, England). 2005;365(9476):2058-61.
148. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol. 2010;162(1):115-20.
149. Meyer G, Koch M, Herrmann E, Bojunga J, Badenhoop K. Longitudinal AddiQoL scores may identify higher risk for adrenal crises in Addison's disease. Endocrine. 2018;60(2):355-61.
150. Groves RW, Toms GC, Houghton BJ, Monson JP. Corticosteroid replacement therapy: twice or thrice daily? Journal of the Royal Society of Medicine. 1988;81(9):514-6.
151. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(2):364-89.
152. Elder CJ, Dimitri P. Hydrocortisone for adrenal insufficiency. Arch Dis Child Educ Pract Ed. 2015;100(5):272-6.
153. Harbeck B, Kropp P, Monig H. Effects of short-term nocturnal cortisol replacement on cognitive function and quality of life in patients with primary or secondary adrenal insufficiency: a pilot study. Applied psychophysiology and biofeedback. 2009;34(2):113-9.
154. Sævik Å B, Wolff AB, Björnsdottir S, Simunkova K, Hynne MS, Dolan DWP, et al. Potential Transcriptional Biomarkers to Guide Glucocorticoid Replacement in Autoimmune Addison's Disease. J Endocr Soc. 2021;5(3):bvaa202.
155. Simunkova K, Jovanovic N, Rostrup E, Methlie P, Oksnes M, Nilsen RM, et al. Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure. Eur J Endocrinol. 2016;174(1):97-105.
156. Bonnecaze AK, Reynolds P, Burns CA. Stress-Dosed Glucocorticoids and Mineralocorticoids Before Intensive Endurance Exercise in Primary Adrenal Insufficiency. Clin J Sport Med. 2019;29(6):e73-e5.
157. Michels A, Michels N. Addison disease: early detection and treatment principles. Am Fam Physician. 2014;89(7):563-8.
158. Gurnell EM, Hunt PJ, Curran SE, Conway CL, Pullenayegum EM, Huppert FA, et al. Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. J Clin Endocrinol Metab. 2008;93(2):400-9.
159. Lovas K, Husebye ES. Replacement therapy for Addison's disease: recent developments. Expert opinion on investigational drugs. 2008;17(4):497-509.
160. Pluchino N, Carmignani A, Cubeddu A, Santoro A, Cela V, Errasti T. Androgen therapy in women: for whom and when. Archives of gynecology and obstetrics. 2013;288(4):731-7.
161. Allolio B, Arlt W, Hahner S. DHEA: why, when, and how much--DHEA replacement in adrenal insufficiency. Annales d'endocrinologie. 2007;68(4):268-73.
162. Løvås K, Gebre-Medhin G, Trovik TS, Fougner KJ, Uhlving S, Nedrebø BG, et al. Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. J Clin Endocrinol Metab. 2003;88(3):1112-8.
163. Porter J, Blair J, Ross RJ. Is physiological glucocorticoid replacement important in children? Arch Dis Child. 2017;102(2):199-205.
164. Henry M, Ross IL, Thomas KGF. Reduced Slow-Wave Sleep and Altered Diurnal Cortisol Rhythms in Patients with Addison's Disease. Eur J Endocrinol. 2018;179(5):319-30.
165. Vgontzas AN, Bixler EO, Papanicolaou DA, Kales A, Stratakis CA, Vela-Bueno A, et al. Rapid eye movement sleep correlates with the overall activities of the

hypothalamic-pituitary-adrenal axis and sympathetic system in healthy humans. J Clin Endocrinol Metab. 1997;82(10):3278-80.
166. Born J, Späth-Schwalbe E, Schwakenhofer H, Kern W, Fehm HL. Influences of corticotropin-releasing hormone, adrenocorticotropin, and cortisol on sleep in normal man. J Clin Endocrinol Metab. 1989;68(5):904-11.
167. Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, et al. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clinical endocrinology. 2004;61(3):367-75.
168. Arlt W, Rosenthal C, Hahner S, Allolio B. Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. Clinical endocrinology. 2006;64(4):384-9.
169. Whitaker M, Debono M, Huatan H, Merke D, Arlt W, Ross RJ. An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure. Clinical endocrinology. 2014;80(4):554-61.
170. Stewart PM. Modified-Release Hydrocortisone: Is It Time to Change Clinical Practice? J Endocr Soc. 2019;3(6):1150-3.
171. Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab. 2012;97(2):473-81.
172. Giordano R, Guaraldi F, Marinazzo E, Fumarola F, Rampino A, Berardelli R, et al. Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. Endocrine. 2016;51(2):360-8.
173. Mallappa A, Sinaii N, Kumar P, Whitaker MJ, Daley LA, Digweed D, et al. A phase 2 study of Chronocort, a modified-release formulation of hydrocortisone, in the treatment of adults with classic congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2015;100(3):1137-45.
174. Björnsdottir S, Øksnes M, Isaksson M, Methlie P, Nilsen RM, Hustad S, et al. Circadian hormone profiles and insulin sensitivity in patients with Addison's disease: a comparison of continuous subcutaneous hydrocortisone infusion with conventional glucocorticoid replacement therapy. Clinical endocrinology. 2015;83(1):28-35.
175. Oksnes M, Bjornsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM, et al. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial. J Clin Endocrinol Metab. 2014;99(5):1665-74.
176. Russell GM, Lightman SL. Can side effects of steroid treatments be minimized by the temporal aspects of delivery method? Expert opinion on drug safety. 2014;13(11):1501-13.
177. Shaw EE, Schultz AP, Sperling RA, Hedden T. Functional Connectivity in Multiple Cortical Networks Is Associated with Performance Across Cognitive Domains in Older Adults. Brain Connect. 2015;5(8):505-16.
178. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005;102(27):9673-8.
179. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700-11.
180. Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE. Intrinsic and task-evoked network architectures of the human brain. Neuron. 2014;83(1):238-51.

181. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A. 2009;106(31):13040-5.
182. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506.
183. Raichle ME. The restless brain: how intrinsic activity organizes brain function. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2015;370(1668).
184. Raichle ME. The brain's default mode network. Annual review of neuroscience. 2015;38:433-47.
185. Wu CW, Gu H, Lu H, Stein EA, Chen JH, Yang Y. Mapping functional connectivity based on synchronized CMRO2 fluctuations during the resting state. Neuroimage. 2009;45(3):694-701.
186. Riedl V, Bienkowska K, Strobel C, Tahmasian M, Grimmer T, Förster S, et al. Local activity determines functional connectivity in the resting human brain: a simultaneous FDG-PET/fMRI study. J Neurosci. 2014;34(18):6260-6.
187. Tomasi D, Wang GJ, Volkow ND. Energetic cost of brain functional connectivity. Proc Natl Acad Sci U S A. 2013;110(33):13642-7.
188. Passow S, Specht K, Adamsen TC, Biermann M, Brekke N, Craven AR, et al. Default-mode network functional connectivity is closely related to metabolic activity. Hum Brain Mapp. 2015;36(6):2027-38.
189. Guerra-Carrillo B, Mackey AP, Bunge SA. Resting-state fMRI: a window into human brain plasticity. Neuroscientist. 2014;20(5):522-33.
190. Zhou Y, Friston KJ, Zeidman P, Chen J, Li S, Razi A. The Hierarchical Organization of the Default, Dorsal Attention and Salience Networks in Adolescents and Young Adults. Cereb Cortex. 2018;28(2):726-37.
191. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. Proc Natl Acad Sci U S A. 2009;106(6):1942-7.
192. Bartova L, Meyer BM, Diers K, Rabl U, Scharinger C, Popovic A, et al. Reduced default mode network suppression during a working memory task in remitted major depression. J Psychiatr Res. 2015;64:9-18.
193. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature. 1998;393(6684):440-2.
194. Bassett DS, Bullmore ET. Small-World Brain Networks Revisited. Neuroscientist. 2017;23(5):499-516.
195. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010;52(3):1059-69.
196. Alderson TH, Bokde ALW, Kelso JAS, Maguire L, Coyle D. Metastable neural dynamics underlies cognitive performance across multiple behavioural paradigms. Hum Brain Mapp. 2020;41(12):3212-34.
197. Naik S, Banerjee A, Bapi RS, Deco G, Roy D. Metastability in Senescence. Trends Cogn Sci. 2017;21(7):509-21.
198. Johnson MH, Jones EJ, Gliga T. Brain adaptation and alternative developmental trajectories. Development and psychopathology. 2015;27(2):425-42.
199. Stern Y, Gazes Y, Razlighi Q, Steffener J, Habeck C. A task-invariant cognitive reserve network. Neuroimage. 2018;178:36-45.
200. Abdelnour F, Dayan M, Devinsky O, Thesen T, Raj A. Functional brain connectivity is predictable from anatomic network's Laplacian eigen-structure. Neuroimage. 2018;172:728-39.
201. van den Heuvel MP, Sporns O. An anatomical substrate for integration among functional networks in human cortex. J Neurosci. 2013;33(36):14489-500.

202. Gordon EM, Laumann TO, Adeyemo B, Huckins JF, Kelley WM, Petersen SE. Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. Cerebral cortex (New York, NY : 1991). 2016;26(1):288-303.
203. Evangelista ND, O'Shea A, Kraft JN, Hausman HK, Boutzoukas EM, Nissim NR, et al. Independent Contributions of Dorsolateral Prefrontal Structure and Function to Working Memory in Healthy Older Adults. Cerebral cortex (New York, NY : 1991). 2020.
204. Vijayakumar N, Ball G, Seal ML, Mundy L, Whittle S, Silk T. The development of structural covariance networks during the transition from childhood to adolescence. Sci Rep. 2021;11(1):9451.
205. DuPre E, Spreng RN. Structural covariance networks across the life span, from 6 to 94 years of age. Netw Neurosci. 2017;1(3):302-23.
206. Santarnecchi E, D'Arista S, Egiziano E, Gardi C, Petrosino R, Vatti G, et al. Interaction between neuroanatomical and psychological changes after mindfulness-based training. PLoS One. 2014;9(10):e108359.
207. Yokota S, Takeuchi H, Asano K, Asano M, Sassa Y, Taki Y, et al. Sex interaction of white matter microstructure and verbal IQ in corpus callosum in typically developing children and adolescents. Brain Dev. 2022;44(8):531-9.
208. Weber E, Goverover Y, DeLuca J. Beyond cognitive dysfunction: Relevance of ecological validity of neuropsychological tests in multiple sclerosis. Mult Scler. 2019;25(10):1412-9.
209. Ghawami H, Homaei Shoaa J, Moazenzadeh M, Sorkhavandi M, Okhovvat A, Hadizadeh N, et al. Ecological validity of executive function tests in predicting driving performance. Appl Neuropsychol Adult. 2022:1-13.
210. Oitzl MS, de Kloet ER. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. Behavioral neuroscience. 1992;106(1):62-71.
211. Baddeley A. Working memory: theories, models, and controversies. Annu Rev Psychol. 2012;63:1-29.
212. Jonides J, Lewis RL, Nee DE, Lustig CA, Berman MG, Moore KS. The mind and brain of short-term memory. Annu Rev Psychol. 2008;59:193-224.
213. Dringenberg HC. The history of long-term potentiation as a memory mechanism: Controversies, confirmation, and some lessons to remember. Hippocampus. 2020;30(9):987-1012.
214. Takehara-Nishiuchi K. Neurobiology of systems memory consolidation. Eur J Neurosci. 2020.
215. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68.
216. Constantinidis C, Klingberg T. The neuroscience of working memory capacity and training. Nat Rev Neurosci. 2016;17(7):438-49.
217. Norris D. Short-term memory and long-term memory are still different. Psychol Bull. 2017;143(9):992-1009.
218. Eriksson J, Vogel EK, Lansner A, Bergstrom F, Nyberg L. Neurocognitive Architecture of Working Memory. Neuron. 2015;88(1):33-46.
219. Machizawa MG, Driver J, Watanabe T. Gray Matter Volume in Different Cortical Structures Dissociably Relates to Individual Differences in Capacity and Precision of Visual Working Memory. Cerebral cortex (New York, NY : 1991). 2020;30(9):4759-70.
220. Valyear KF, Culham JC, Sharif N, Westwood D, Goodale MA. A double dissociation between sensitivity to changes in object identity and object orientation in the ventral and dorsal visual streams: a human fMRI study. Neuropsychologia. 2006;44(2):218-28.
221. Schwörer MC, Reinelt T, Petermann F, Petermann U. Influence of executive functions on the self-reported health-related quality of life of children with ADHD. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2020;29(5):1183-92.

222. Nejati V, Salehinejad MA, Nitsche MA. Interaction of the Left Dorsolateral Prefrontal Cortex (l-DLPFC) and Right Orbitofrontal Cortex (OFC) in Hot and Cold Executive Functions: Evidence from Transcranial Direct Current Stimulation (tDCS). Neuroscience. 2018;369:109-23.
223. Prencipe A, Kesek A, Cohen J, Lamm C, Lewis MD, Zelazo PD. Development of hot and cool executive function during the transition to adolescence. J Exp Child Psychol. 2011;108(3):621-37.
224. Chan RC, Shum D, Toulopoulou T, Chen EY. Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol. 2008;23(2):201-16.
225. Poland SE, Monks CP, Tsermentseli S. Cool and hot executive function as predictors of aggression in early childhood: Differentiating between the function and form of aggression. Br J Dev Psychol. 2016;34(2):181-97.
226. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41(1):49-100.
227. Salehinejad MA, Ghanavati E, Rashid MHA, Nitsche MA. Hot and cold executive functions in the brain: A prefrontal-cingular network. Brain Neurosci Adv. 2021;5:23982128211007769.
228. Zaehringer J, Falquez R, Schubert AL, Nees F, Barnow S. Neural correlates of reappraisal considering working memory capacity and cognitive flexibility. Brain Imaging Behav. 2018;12(6):1529-43.
229. Padoa-Schioppa C, Conen KE. Orbitofrontal Cortex: A Neural Circuit for Economic Decisions. Neuron. 2017;96(4):736-54.
230. Born J, Rasch B, Gais S. Sleep to remember. Neuroscientist. 2006;12(5):410-24.
231. Yonelinas AP, Ranganath C, Ekstrom AD, Wiltgen BJ. A contextual binding theory of episodic memory: systems consolidation reconsidered. Nat Rev Neurosci. 2019;20(6):364-75.
232. Walker MP, Stickgold R. Overnight alchemy: sleep-dependent memory evolution. Nat Rev Neurosci. 2010;11(3):218; author reply
233. Walker MP. The role of sleep in cognition and emotion. Annals of the New York Academy of Sciences. 2009;1156:168-97.
234. Wagner U, Hallschmid M, Rasch B, Born J. Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry. 2006;60(7):788-90.
235. Kim SY, Kark SM, Daley RT, Alger SE, Rebouças D, Kensinger EA, et al. Interactive effects of stress reactivity and rapid eye movement sleep theta activity on emotional memory formation. Hippocampus. 2020;30(8):829-41.
236. Cartwright R, Baehr E, Kirkby J, Pandi-Perumal SR, Kabat J. REM sleep reduction, mood regulation and remission in untreated depression. Psychiatry Res. 2003;121(2):159-67.
237. Palmer CA, Alfano CA. Sleep and emotion regulation: An organizing, integrative review. Sleep medicine reviews. 2017;31:6-16.
238. Ryan RM, Frederick C. On energy, personality, and health: subjective vitality as a dynamic reflection of well-being. J Pers. 1997;65(3):529-65.
239. Aouizerat BE, Gay CL, Lerdal A, Portillo CJ, Lee KA. Lack of energy: an important and distinct component of HIV-related fatigue and daytime function. J Pain Symptom Manage. 2013;45(2):191-201.
240. van Steenbergen E, van Dongen JM, Wendel-Vos GC, Hildebrandt VH, Strijk JE. Insights into the concept of vitality: associations with participation and societal costs. Eur J Public Health. 2016;26(2):354-9.

241. Gledhill J. A qualitative study of the characteristics and representation of fatigue in a French speaking population of cancer patients and healthy subjects. Eur J Oncol Nurs. 2005;9(4):294-312; discussion 3-4.
242. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.
243. Hagelin CL, Wengström Y, Runesdotter S, Fürst CJ. The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. Acta oncologica (Stockholm, Sweden). 2007;46(1):97-104.
244. Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B. The Effects of Mental Fatigue on Physical Performance: A Systematic Review. Sports Med. 2017;47(8):1569-88.
245. Boksem MA, Tops M. Mental fatigue: costs and benefits. Brain Res Rev. 2008;59(1):125-39.
246. Boksem MA, Meijman TF, Lorist MM. Mental fatigue, motivation and action monitoring. Biol Psychol. 2006;72(2):123-32.
247. van der Linden D, Massar SA, Schellekens AF, Ellenbroek BA, Verkes RJ. Disrupted sensorimotor gating due to mental fatigue: preliminary evidence. Int J Psychophysiol. 2006;62(1):168-74.
248. Wascher E, Rasch B, Sänger J, Hoffmann S, Schneider D, Rinkenauer G, et al. Frontal theta activity reflects distinct aspects of mental fatigue. Biol Psychol. 2014;96:57-65.
249. Möckel T, Beste C, Wascher E. The Effects of Time on Task in Response Selection--An ERP Study of Mental Fatigue. Sci Rep. 2015;5:10113.
250. Engberg I, Segerstedt J, Waller G, Wennberg P, Eliasson M. Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. BMC Public Health. 2017;17(1):654.
251. Tardy AL, Pouteau E, Marquez D, Yilmaz C, Scholey A. Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence. Nutrients. 2020;12(1).
252. Josev EK, Malpas CB, Seal ML, Scheinberg A, Lubitz L, Rowe K, et al. Resting-state functional connectivity, cognition, and fatigue in response to cognitive exertion: a novel study in adolescents with chronic fatigue syndrome. Brain Imaging Behav. 2020;14(5):1815-30.
253. Hopstaken JF, van der Linden D, Bakker AB, Kompier MA. A multifaceted investigation of the link between mental fatigue and task disengagement. Psychophysiology. 2015;52(3):305-15.
254. Gergelyfi M, Sanz-Arigita EJ, Solopchuk O, Dricot L, Jacob B, Zénon A. Mental fatigue correlates with depression of task-related network and augmented DMN activity but spares the reward circuit. Neuroimage. 2021;243:118532.
255. Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage. 2007;36(1):108-22.
256. Brownsberger J, Edwards A, Crowther R, Cottrell D. Impact of mental fatigue on self-paced exercise. International journal of sports medicine. 2013;34(12):1029-36.
257. Tran Y, Craig A, Craig R, Chai R, Nguyen H. The influence of mental fatigue on brain activity: Evidence from a systematic review with meta-analyses. Psychophysiology. 2020;57(5):e13554.
258. Esposito F, Otto T, Zijlstra FR, Goebel R. Spatially distributed effects of mental exhaustion on resting-state FMRI networks. PLoS One. 2014;9(4):e94222.

259. Chen MH, Wylie GR, Sandroff BM, Dacosta-Aguayo R, DeLuca J, Genova HM. Neural mechanisms underlying state mental fatigue in multiple sclerosis: a pilot study. J Neurol. 2020;267(8):2372-82.
260. Pyka M, Beckmann CF, Schöning S, Hauke S, Heider D, Kugel H, et al. Impact of working memory load on FMRI resting state pattern in subsequent resting phases. PLoS One. 2009;4(9):e7198.
261. Bisecco A, Nardo FD, Docimo R, Caiazzo G, d'Ambrosio A, Bonavita S, et al. Fatigue in multiple sclerosis: The contribution of resting-state functional connectivity reorganization. Mult Scler. 2018;24(13):1696-705.
262. Cruz Gómez Á J, Ventura Campos N, Belenguer A, Ávila C, Forn C. Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis. PLoS One. 2013;8(10):e77914.
263. Mason BL, Pariante CM, Jamel S, Thomas SA. Central nervous system (CNS) delivery of glucocorticoids is fine-tuned by saturable transporters at the blood-CNS barriers and nonbarrier regions. Endocrinology. 2010;151(11):5294-305.
264. Karssen AM, Meijer OC, van der Sandt IC, Lucassen PJ, de Lange EC, de Boer AG, et al. Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and human brain. Endocrinology. 2001;142(6):2686-94.
265. Beyenburg S, Watzka M, Clusmann H, Blümcke I, Bidlingmaier F, Elger CE, et al. Messenger RNA of steroid 21-hydroxylase (CYP21) is expressed in the human hippocampus. Neuroscience letters. 2001;308(2):111-4.
266. Yu L, Romero DG, Gomez-Sanchez CE, Gomez-Sanchez EP. Steroidogenic enzyme gene expression in the human brain. Mol Cell Endocrinol. 2002;190(1-2):9-17.
267. Taves MD, Gomez-Sanchez CE, Soma KK. Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. American journal of physiology Endocrinology and metabolism. 2011;301(1):E11-24.
268. Matsusue Y, Horii-Hayashi N, Kirita T, Nishi M. Distribution of corticosteroid receptors in mature oligodendrocytes and oligodendrocyte progenitors of the adult mouse brain. Journal of Histochemistry & Cytochemistry. 2014;62(3):211-26.
269. Barres B, Lazar M, Raff M. A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte development. Development. 1994;120(5):1097-108.
270. Cruceanu C, Dony L, Krontira AC, Fischer DS, Roeh S, Di Giaimo R, et al. Cell-Type-Specific Impact of Glucocorticoid Receptor Activation on the Developing Brain: A Cerebral Organoid Study. The American journal of psychiatry. 2021:appiajp202121010095.
271. de Kloet ER. Functional profile of the binary brain corticosteroid receptor system: mediating, multitasking, coordinating, integrating. European journal of pharmacology. 2013;719(1-3):53-62.
272. de Kloet ER, Otte C, Kumsta R, Kok L, Hillegers MH, Hasselmann H, et al. Stress and Depression: a Crucial Role of the Mineralocorticoid Receptor. J Neuroendocrinol. 2016;28(8).
273. de Kloet ER, Meijer OC, de Nicola AF, de Rijk RH, Joels M. Importance of the brain corticosteroid receptor balance in metaplasticity, cognitive performance and neuro-inflammation. Front Neuroendocrinol. 2018;49:124-45.
274. Shirazi SN, Friedman AR, Kaufer D, Sakhai SA. Glucocorticoids and the Brain: Neural Mechanisms Regulating the Stress Response. Advances in experimental medicine and biology. 2015;872:235-52.
275. Morsi A, DeFranco D, Witchel SF. The Hypothalamic-Pituitary-Adrenal Axis and the Fetus. Horm Res Paediatr. 2018;89(5):380-7.

276. Sheikh HI, Joanisse MF, Mackrell SM, Kryski KR, Smith HJ, Singh SM, et al. Links between white matter microstructure and cortisol reactivity to stress in early childhood: Evidence for moderation by parenting. NeuroImage: Clinical. 2014;6:77-85.
277. Groeneweg FL, Karst H, de Kloet ER, Joëls M. Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. Mol Cell Endocrinol. 2012;350(2):299-309.
278. Pfaff DW, Silva MT, Weiss JM. Telemetered recording of hormone effects on hippocampal neurons. Science. 1971;172(3981):394-5.
279. Karst H, Joëls M. Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. J Neurophysiol. 2005;94(5):3479-86.
280. Qiu S, Champagne DL, Peters M, Catania EH, Weeber EJ, Levitt P, et al. Loss of limbic system-associated membrane protein leads to reduced hippocampal mineralocorticoid receptor expression, impaired synaptic plasticity, and spatial memory deficit. Biol Psychiatry. 2010;68(2):197-204.
281. Morsink MC, Steenbergen PJ, Vos JB, Karst H, Joëls M, De Kloet ER, et al. Acute activation of hippocampal glucocorticoid receptors results in different waves of gene expression throughout time. J Neuroendocrinol. 2006;18(4):239-52.
282. Datson NA, Morsink MC, Meijer OC, de Kloet ER. Central corticosteroid actions: Search for gene targets. European journal of pharmacology. 2008;583(2-3):272-89.
283. de Kloet ER, Joels M. Brain mineralocorticoid receptor function in control of salt balance and stress-adaptation. Physiology & behavior. 2017;178:13-20.
284. Mellon SH, Griffin LD. Neurosteroids: biochemistry and clinical significance. Trends Endocrinol Metab. 2002;13(1):35-43.
285. Spivak CE. Desensitization and noncompetitive blockade of GABAA receptors in ventral midbrain neurons by a neurosteroid dehydroepiandrosterone sulfate. Synapse. 1994;16(2):113-22.
286. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. Front Neuroendocrinol. 2000;21(1):1-56.
287. Gartside SE, Griffith NC, Kaura V, Ingram CD. The neurosteroid dehydroepiandrosterone (DHEA) and its metabolites alter 5-HT neuronal activity via modulation of GABAA receptors. J Psychopharmacol. 2010;24(11):1717-24.
288. Lhullier FL, Nicolaidis R, Riera NG, Cipriani F, Junqueira D, Dahm KC, et al. Dehydroepiandrosterone increases synaptosomal glutamate release and improves the performance in inhibitory avoidance task. Pharmacol Biochem Behav. 2004;77(3):601-6.
289. Genud R, Merenlender A, Gispan-Herman I, Maayan R, Weizman A, Yadid G. DHEA lessens depressive-like behavior via GABA-ergic modulation of the mesolimbic system. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2009;34(3):577-84.
290. Demirgören S, Majewska MD, Spivak CE, London ED. Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the GABAA receptor. Neuroscience. 1991;45(1):127-35.
291. He XY, Dobkin C, Yang SY. 17β-Hydroxysteroid dehydrogenases and neurosteroid metabolism in the central nervous system. Mol Cell Endocrinol. 2019;489:92-7.
292. Zwain IH, Yen SS. Dehydroepiandrosterone: biosynthesis and metabolism in the brain. Endocrinology. 1999;140(2):880-7.
293. Rossetti MF, Cambiasso MJ, Holschbach MA, Cabrera R. Oestrogens and Progestagens: Synthesis and Action in the Brain. J Neuroendocrinol. 2016;28(7).
294. Quinn T, Greaves R, Badoer E, Walker D. DHEA in Prenatal and Postnatal Life: Implications for Brain and Behavior. Vitamins and hormones. 2018;108:145-74.

295. Karishma KK, Herbert J. Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression. Eur J Neurosci. 2002;16(3):445-53.
296. Alexaki VI, Fodelianaki G, Neuwirth A, Mund C, Kourgiantaki A, Ieronimaki E, et al. DHEA inhibits acute microglia-mediated inflammation through activation of the TrkA-Akt1/2-CREB-Jmjd3 pathway. Mol Psychiatry. 2018;23(6):1410-20.
297. Fiore C, Inman DM, Hirose S, Noble LJ, Igarashi T, Compagnone NA. Treatment with the neurosteroid dehydroepiandrosterone promotes recovery of motor behavior after moderate contusive spinal cord injury in the mouse. J Neurosci Res. 2004;75(3):391-400.
298. Muntwyler R, Bologa L. In vitro hormonal regulation of astrocyte proliferation. Schweiz Arch Neurol Psychiatr (1985). 1989;140(1):29-33.
299. Kight KE, McCarthy MM. Androgens and the developing hippocampus. Biology of sex differences. 2020;11(1):30.
300. Atwi S, McMahon D, Scharfman H, MacLusky NJ. Androgen Modulation of Hippocampal Structure and Function. Neuroscientist. 2016;22(1):46-60.
301. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6(6):463-75.
302. Sapolsky RM. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. Stress. 1996;1(1):1-19.
303. Vyas S, Rodrigues AJ, Silva JM, Tronche F, Almeida OF, Sousa N, et al. Chronic Stress and Glucocorticoids: From Neuronal Plasticity to Neurodegeneration. Neural Plast. 2016;2016:6391686.
304. Hinkelmann K, Wingenfeld K, Kuehl LK, Fleischer J, Heuser I, Wiedemann K, et al. Stimulation of the mineralocorticoid receptor improves memory in young and elderly healthy individuals. Neurobiol Aging. 2015;36(2):919-24.
305. Wingenfeld K, Otte C. Mineralocorticoid receptor function and cognition in health and disease. Psychoneuroendocrinology. 2019;105:25-35.
306. Feld GB, Born J. Neurochemical mechanisms for memory processing during sleep: basic findings in humans and neuropsychiatric implications. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2020;45(1):31-44.
307. Bennion KA, Mickley Steinmetz KR, Kensinger EA, Payne JD. Sleep and cortisol interact to support memory consolidation. Cerebral cortex (New York, NY : 1991). 2015;25(3):646-57.
308. Fleischer J, Wingenfeld K, Kuehl LK, Hinkelmann K, Roepke S, Otte C. Does fludrocortisone influence autobiographical memory retrieval? A study in patients with major depression, patients with borderline personality disorder and healthy controls. Stress. 2015;18(6):718-22.
309. Miller R, Weckesser LJ, Smolka MN, Kirschbaum C, Plessow F. Hydrocortisone accelerates the decay of iconic memory traces: on the modulation of executive and stimulus-driven constituents of sensory information maintenance. Psychoneuroendocrinology. 2015;53:148-58.
310. Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology. 2005;30(8):771-84.
311. Lupien SJ, McEwen BS. The acute effects of corticosteroids on cognition: integration of animal and human model studies. Brain research Brain research reviews. 1997;24(1):1-27.
312. Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. Neurosci Biobehav Rev. 2016;68:651-68.

313. Arnsten AF, Raskind MA, Taylor FB, Connor DF. The Effects of Stress Exposure on Prefrontal Cortex: Translating Basic Research into Successful Treatments for Post-Traumatic Stress Disorder. Neurobiol Stress. 2015;1:89-99.
314. Berenbaum SA, Beltz AM. Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. Front Neuroendocrinol. 2011;32(2):183-200.
315. Janowsky JS. Thinking with your gonads: testosterone and cognition. Trends Cogn Sci. 2006;10(2):77-82.
316. Vázquez-Pereyra F, Rivas-Arancibia S, Loaeza-Del Castillo A, Schneider-Rivas S. Modulation of short term and long term memory by steroid sexual hormones. Life sciences. 1995;56(14):Pl255-60.
317. do Vale S, Escera C. Dehydroepiandrosterone and Dehydroepiandrosterone-Sulfate and Emotional Processing. Vitamins and hormones. 2018;108:413-41.
318. Grimley Evans J, Malouf R, Huppert F, van Niekerk JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Cochrane Database Syst Rev. 2006;2006(4):Cd006221.
319. Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C. Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. Psychoneuroendocrinology. 1998;23(6):617-29.
320. Hirshman E, Wells E, Wierman ME, Anderson B, Butler A, Senholzi M, et al. The effect of dehydroepiandrosterone (DHEA) on recognition memory decision processes and discrimination in postmenopausal women. Psychon Bull Rev. 2003;10(1):125-34.
321. Kische H, Gross S, Wallaschofski H, Grabe HJ, Völzke H, Nauck M, et al. Associations of androgens with depressive symptoms and cognitive status in the general population. PLoS One. 2017;12(5):e0177272.
322. Hough CM, Lindqvist D, Epel ES, Denis MS, Reus VI, Bersani FS, et al. Higher serum DHEA concentrations before and after SSRI treatment are associated with remission of major depression. Psychoneuroendocrinology. 2017;77:122-30.
323. Sripada RK, Marx CE, King AP, Rajaram N, Garfinkel SN, Abelson JL, et al. DHEA enhances emotion regulation neurocircuits and modulates memory for emotional stimuli. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2013;38(9):1798-807.
324. Sripada RK, Welsh RC, Marx CE, Liberzon I. The neurosteroids allopregnanolone and dehydroepiandrosterone modulate resting-state amygdala connectivity. Hum Brain Mapp. 2014;35(7):3249-61.
325. Nguyen TV, Gower P, Albaugh MD, Botteron KN, Hudziak JJ, Fonov VS, et al. The developmental relationship between DHEA and visual attention is mediated by structural plasticity of cortico-amygdalar networks. Psychoneuroendocrinology. 2016;70:122-33.
326. Nguyen TV, Wu M, Lew J, Albaugh MD, Botteron KN, Hudziak JJ, et al. Dehydroepiandrosterone impacts working memory by shaping cortico-hippocampal structural covariance during development. Psychoneuroendocrinology. 2017;86:110-21.
327. Zarate S, Stevnsner T, Gredilla R. Role of Estrogen and Other Sex Hormones in Brain Aging. Neuroprotection and DNA Repair. Frontiers in aging neuroscience. 2017;9:430.
328. Konishi K, Cherkerzian S, Jacobs EG, Richards C, Remington A, Aizley H, et al. Impact of adrenal hormones, reproductive aging, and major depression on memory circuitry decline in early midlife. Brain research. 2019;1721:146303.
329. do Vale S, Selinger L, Martins JM, Gomes AC, Bicho M, do Carmo I, et al. The relationship between dehydroepiandrosterone (DHEA), working memory and distraction--a behavioral and electrophysiological approach. PLoS One. 2014;9(8):e104869.

330. Farooqi NAI, Scotti M, Yu A, Lew J, Monnier P, Botteron KN, et al. Sex-specific contribution of DHEA-cortisol ratio to prefrontal-hippocampal structural development, cognitive abilities and personality traits. J Neuroendocrinol. 2018:e12682.
331. Vogel S, Klumpers F, Schröder TN, Oplaat KT, Krugers HJ, Oitzl MS, et al. Stress Induces a Shift Towards Striatum-Dependent Stimulus-Response Learning via the Mineralocorticoid Receptor. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017;42(6):1262-71.
332. Jentsch VL, Merz CJ, Wolf OT. Restoring emotional stability: Cortisol effects on the neural network of cognitive emotion regulation. Behavioural brain research. 2019;374:111880.
333. Henckens MJ, van Wingen GA, Joels M, Fernandez G. Time-dependent corticosteroid modulation of prefrontal working memory processing. Proc Natl Acad Sci U S A. 2011;108(14):5801-6.
334. Henckens MJ, van Wingen GA, Joels M, Fernandez G. Corticosteroid induced decoupling of the amygdala in men. Cerebral cortex (New York, NY : 1991). 2012;22(10):2336-45.
335. Henckens MJ, van Wingen GA, Joels M, Fernandez G. Time-dependent effects of corticosteroids on human amygdala processing. J Neurosci. 2010;30(38):12725-32.
336. Hermans EJ, Henckens MJ, Joels M, Fernandez G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends in neurosciences. 2014;37(6):304-14.
337. Henckens MJ, Pu Z, Hermans EJ, van Wingen GA, Joels M, Fernandez G. Dynamically changing effects of corticosteroids on human hippocampal and prefrontal processing. Hum Brain Mapp. 2012;33(12):2885-97.
338. Vogel S, Schwabe L. Stress in the zoo: Tracking the impact of stress on memory formation over time. Psychoneuroendocrinology. 2016;71:64-72.
339. Sazma MA, McCullough AM, Shields GS, Yonelinas AP. Using acute stress to improve episodic memory: The critical role of contextual binding. Neurobiology of learning and memory. 2019;158:1-8.
340. de Voogd LD, Klumpers F, Fernández G, Hermans EJ. Intrinsic functional connectivity between amygdala and hippocampus during rest predicts enhanced memory under stress. Psychoneuroendocrinology. 2017;75:192-202.
341. Fleischer J, Metz S, Dusenberg M, Grimm S, Golde S, Roepke S, et al. Neural correlates of glucocorticoids effects on autobiographical memory retrieval in healthy women. Behavioural brain research. 2019;359:895-902.
342. Pico-Perez M, Radua J, Steward T, Menchon JM, Soriano-Mas C. Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in neuro-psychopharmacology & biological psychiatry. 2017;79(Pt B):96-104.
343. Balbo M, Leproult R, Van Cauter E. Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. Int J Endocrinol. 2010;2010:759234.
344. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Sci. 2015;8(3):143-52.
345. Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. Sleep. 1992;15(1):21-7.
346. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C, et al. Delta sleep response to metyrapone in post-traumatic stress disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2003;28(9):1666-76.

347. Gillin JC, Jacobs LS, Snyder F, Henkin RI. Effects of decreased adrenal corticosteroids: changes in sleep in normal subjects and patients with adrenal cortical insufficiency. Electroencephalography and clinical neurophysiology. 1974;36(3):283-9.
348. Shi X, Wu J, Smyth N. An inverted U-shaped relationship between cortisol awakening response and same-day error monitoring function in healthy males. Biol Psychol. 2021;160:108052.
349. Wu J, Zhang S, Li W, Qin S, He Y, Yang Z, et al. Cortisol awakening response predicts intrinsic functional connectivity of the medial prefrontal cortex in the afternoon of the same day. Neuroimage. 2015;122:158-65.
350. Shi X, Sun X, Yao Z, Yuan Y, Wu J, Clow A. The cortisol awakening response predicts response inhibition in the afternoon of the same day. Psychoneuroendocrinology. 2018;89:23-9.
351. Xiong B, Chen C, Tian Y, Zhang S, Liu C, Evans TM, et al. Brain preparedness: The proactive role of the cortisol awakening response in hippocampal-prefrontal functional interactions. Prog Neurobiol. 2021;205:102127.
352. Barwick TD, Malhotra A, Webb JA, Savage MO, Reznek RH. Embryology of the adrenal glands and its relevance to diagnostic imaging. Clinical radiology. 2005;60(9):953-9.
353. Ishimoto H, Jaffe RB. Development and function of the human fetal adrenal cortex: a key component in the feto-placental unit. Endocrine reviews. 2011;32(3):317-55.
354. Goto M, Piper Hanley K, Marcos J, Wood PJ, Wright S, Postle AD, et al. In humans, early cortisol biosynthesis provides a mechanism to safeguard female sexual development. The Journal of clinical investigation. 2006;116(4):953-60.
355. Chapman K, Holmes M, Seckl J. 11beta-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev. 2013;93(3):1139-206.
356. Stewart PM, Whorwood CB, Mason JI. Type 2 11 beta-hydroxysteroid dehydrogenase in foetal and adult life. The Journal of steroid biochemistry and molecular biology. 1995;55(5-6):465-71.
357. Bonanno C, Wapner RJ. Antenatal corticosteroids in the management of preterm birth: are we back where we started? Obstetrics and gynecology clinics of North America. 2012;39(1):47-63.
358. Busada JT, Cidlowski JA. Mechanisms of Glucocorticoid Action During Development. Current topics in developmental biology. 2017;125:147-70.
359. Humphrey T. The development of the human amygdala during early embryonic life. Journal of Comparative Neurology. 1968;132(1):135-65.
360. Nikolić I, Kostović I. Development of the lateral amygdaloid nucleus in the human fetus: transient presence of discrete cytoarchitectonic units. Anatomy and embryology. 1986;174(3):355-60.
361. Seckl JR. Prenatal glucocorticoids and long-term programming. Eur J Endocrinol. 2004;151 Suppl 3:U49-62.
362. Krontira AC, Cruceanu C, Binder EB. Glucocorticoids as Mediators of Adverse Outcomes of Prenatal Stress. Trends in neurosciences. 2020;43(6):394-405.
363. Cartier J, Zeng Y, Drake AJ. Glucocorticoids and the prenatal programming of neurodevelopmental disorders. Current Opinion in Behavioral Sciences. 2016;7:1-7.
364. Monk C, Lugo-Candelas C, Trumpff C. Prenatal Developmental Origins of Future Psychopathology: Mechanisms and Pathways. Annual review of clinical psychology. 2019;15:317-44.
365. Cheong JL, Burnett AC, Lee KJ, Roberts G, Thompson DK, Wood SJ, et al. Association between postnatal dexamethasone for treatment of bronchopulmonary dysplasia and brain volumes at adolescence in infants born very preterm. The Journal of pediatrics. 2014;164(4):737-43. e1.

366. Davis EP, Sandman CA, Buss C, Wing DA, Head K. Fetal glucocorticoid exposure is associated with preadolescent brain development. Biol Psychiatry. 2013;74(9):647-55.
367. Zou R, Tiemeier H, van der Ende J, Verhulst FC, Muetzel RL, White T, et al. Exposure to Maternal Depressive Symptoms in Fetal Life or Childhood and Offspring Brain Development: A Population-Based Imaging Study. The American journal of psychiatry. 2019;176(9):702-10.
368. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proceedings of the National Academy of Sciences. 2012:201201295.
369. Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M, et al. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. Biological psychiatry. 2018;83(2):109-19.
370. Räikkönen K, Gissler M, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children. Jama. 2020;323(19):1924-33.
371. Melamed N, Asztalos E, Murphy K, Zaltz A, Redelmeier D, Shah BR, et al. Neurodevelopmental disorders among term infants exposed to antenatal corticosteroids during pregnancy: a population-based study. BMJ open. 2019;9(9):e031197.
372. Rakers F, Schleußner E, Muth I, Hoyer D, Rupprecht S, Schiecke K, et al. Association between antenatal glucocorticoid exposure and the activity of the stress system, cognition, and behavior in 8- to 9-year-old children: A prospective observational study. Acta Obstet Gynecol Scand. 2022;101(9):996-1006.
373. Laplante DP, Brunet A, Schmitz N, Ciampi A, King S. Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. Journal of the American Academy of Child & Adolescent Psychiatry. 2008;47(9):1063-72.
374. Green CG, Babineau V, Jolicoeur-Martineau A, Bouvette-Turcot AA, Minde K, Sassi R, et al. Prenatal maternal depression and child serotonin transporter linked polymorphic region (5-HTTLPR) and dopamine receptor D4 (DRD4) genotype predict negative emotionality from 3 to 36 months. Development and psychopathology. 2017;29(3):901-17.
375. Braithwaite EC, Kundakovic M, Ramchandani PG, Murphy SE, Champagne FA. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. Epigenetics. 2015;10(5):408-17.
376. Stonawski V, Frey S, Golub Y, Rohleder N, Kriebel J, Goecke TW, et al. Associations of prenatal depressive symptoms with DNA methylation of HPA axis-related genes and diurnal cortisol profiles in primary school-aged children. Development and psychopathology. 2019;31(2):419-31.
377. Compagnone NA, Mellon SH. Dehydroepiandrosterone: a potential signalling molecule for neocortical organization during development. Proc Natl Acad Sci U S A. 1998;95(8):4678-83.
378. Suzuki M, Wright LS, Marwah P, Lardy HA, Svendsen CN. Mitotic and neurogenic effects of dehydroepiandrosterone (DHEA) on human neural stem cell cultures derived from the fetal cortex. Proc Natl Acad Sci U S A. 2004;101(9):3202-7.
379. Bakker J. The role of steroid hormones in the sexual differentiation of the human brain. J Neuroendocrinol. 2021:e13050.
380. McCarthy MM, Arnold AP. Reframing sexual differentiation of the brain. Nat Neurosci. 2011;14(6):677-83.

381. Kaufman MJ, Janes AC, Hudson JI, Brennan BP, Kanayama G, Kerrigan AR, et al. Brain and cognition abnormalities in long-term anabolic-androgenic steroid users. Drug and alcohol dependence. 2015;152:47-56.
382. Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS, Jr., et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cerebral cortex (New York, NY : 1991). 2001;11(6):490-7.
383. Isgor C, Sengelaub DR. Effects of neonatal gonadal steroids on adult CA3 pyramidal neuron dendritic morphology and spatial memory in rats. J Neurobiol. 2003;55(2):179-90.
384. Isgor C, Sengelaub DR. Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. Horm Behav. 1998;34(2):183-98.
385. Zhang JM, Tonelli L, Regenold WT, McCarthy MM. Effects of neonatal flutamide treatment on hippocampal neurogenesis and synaptogenesis correlate with depression-like behaviors in preadolescent male rats. Neuroscience. 2010;169(1):544-54.
386. Pallarés ME, Adrover E, Imsen M, González D, Fabre B, Mesch V, et al. Maternal administration of flutamide during late gestation affects the brain and reproductive organs development in the rat male offspring. Neuroscience. 2014;278:122-35.
387. Williams CL, Barnett AM, Meck WH. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. Behavioral neuroscience. 1990;104(1):84-97.
388. Grissom EM, Hawley WR, Hodges KS, Fawcett-Patel JM, Dohanich GP. Biological sex influences learning strategy preference and muscarinic receptor binding in specific brain regions of prepubertal rats. Hippocampus. 2013;23(4):313-22.
389. Mitsushima D, Takase K, Takahashi T, Kimura F. Activational and organisational effects of gonadal steroids on sex-specific acetylcholine release in the dorsal hippocampus. J Neuroendocrinol. 2009;21(4):400-5.
390. Beltz AM, Demidenko MI, Wilson SJ, Berenbaum SA. Prenatal androgen influences on the brain: A review, critique, and illustration of research on congenital adrenal hyperplasia. J Neurosci Res. 2021.
391. Berenbaum SA, Meyer-Bahlburg HF. Gender development and sexuality in disorders of sex development. Horm Metab Res. 2015;47(5):361-6.
392. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. Nat Rev Endocrinol. 2022;18(6):337-52.
393. Stiles J, Jernigan TL. The basics of brain development. Neuropsychology review. 2010;20(4):327-48.
394. Romeo RD. The impact of stress on the structure of the adolescent brain: Implications for adolescent mental health. Brain research. 2017;1654(Pt B):185-91.
395. Eiland L, Romeo RD. Stress and the developing adolescent brain. Neuroscience. 2013;249:162-71.
396. Staufenbiel SM, Andela CD, Manenschijn L, Pereira AM, van Rossum EF, Biermasz NR. Increased Hair Cortisol Concentrations and BMI in Patients With Pituitary-Adrenal Disease on Hydrocortisone Replacement. J Clin Endocrinol Metab. 2015;100(6):2456-62.
397. Dekkers AJ, Amaya JM, van der Meulen M, Biermasz NR, Meijer OC, Pereira AM. Long-term effects of glucocorticoid excess on the brain. J Neuroendocrinol. 2022;34(8):e13142.
398. Siegel S, Kirstein CF, Grzywotz A, Hütter BO, Wrede KH, Kuhna V, et al. Neuropsychological Functioning in Patients with Cushing's Disease and Cushing's Syndrome. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2021;129(3):194-202.

399. Forget H, Lacroix A, Bourdeau I, Cohen H. Long-term cognitive effects of glucocorticoid excess in Cushing's syndrome. Psychoneuroendocrinology. 2015;65:26-33.
400. Na S, Fernandes MA, Ioachimescu AG, Penna S. Neuropsychological and Emotional Functioning in Patients with Cushing's Syndrome. Behav Neurol. 2020;2020:4064370.
401. Pires P, Santos A, Vives-Gilabert Y, Webb SM, Sainz-Ruiz A, Resmini E, et al. White matter involvement on DTI-MRI in Cushing's syndrome relates to mood disturbances and processing speed: a case-control study. Pituitary. 2017;20(3):340-8.
402. Andela CD, van der Werff SJ, Pannekoek JN, van den Berg SM, Meijer OC, van Buchem MA, et al. Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case-control study. Eur J Endocrinol. 2013;169(6):811-9.
403. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Annals of the New York Academy of Sciences. 2009;1179:41-55.
404. Judd LL, Schettler PJ, Brown ES, Wolkowitz OM, Sternberg EM, Bender BG, et al. Adverse consequences of glucocorticoid medication: psychological, cognitive, and behavioral effects. The American journal of psychiatry. 2014;171(10):1045-51.
405. Morelli V, Ghielmetti A, Caldiroli A, Grassi S, Siri FM, Caletti E, et al. Mental Health in Patients With Adrenal Incidentalomas: Is There a Relation With Different Degrees of Cortisol Secretion? J Clin Endocrinol Metab. 2021;106(1):e130-e9.
406. Lebedeva A, Sundström A, Lindgren L, Stomby A, Aarsland D, Westman E, et al. Longitudinal relationships among depressive symptoms, cortisol, and brain atrophy in the neocortex and the hippocampus. Acta psychiatrica Scandinavica. 2018;137(6):491-502.
407. Stomby A, Boraxbekk CJ, Lundquist A, Nordin A, Nilsson LG, Adolfsson R, et al. Higher diurnal salivary cortisol levels are related to smaller prefrontal cortex surface area in elderly men and women. Eur J Endocrinol. 2016;175(2):117-26.
408. Jiang H, He NY, Sun YH, Jian FF, Bian LG, Shen JK, et al. Altered gray and white matter microstructure in Cushing's disease: A diffusional kurtosis imaging study. Brain research. 2017;1665:80-7.
409. Andela CD, van Haalen FM, Ragnarsson O, Papakokkinou E, Johannsson G, Santos A, et al. MECHANISMS IN ENDOCRINOLOGY: Cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies. Eur J Endocrinol. 2015;173(1):R1-14.
410. Brown ES, Jeon-Slaughter H, Lu H, Jamadar R, Issac S, Shad M, et al. Hippocampal volume in healthy controls given 3-day stress doses of hydrocortisone. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2015;40(5):1216-21.
411. Brown ES, Woolston DJ, Frol AB. Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry. 2008;63(7):705-9.
412. Desai S, Khanani S, Shad MU, Brown ES. Attenuation of amygdala atrophy with lamotrigine in patients receiving corticosteroid therapy. J Clin Psychopharmacol. 2009;29(3):284-7.
413. Jiang H, Ren J, He NY, Liu C, Sun YH, Jian FF, et al. Volumetric magnetic resonance imaging analysis in patients with short-term remission of Cushing's disease. Clinical endocrinology. 2017;87(4):367-74.
414. Jiang H, Liu C, Pan SJ, Ren J, He NY, Sun YH, et al. Reversible and the irreversible structural alterations on brain after resolution of hypercortisolism in Cushing's disease. Steroids. 2019;151:108457.
415. Chen Y, Zhang J, Tan H, Li J, Yu Y. Detrimental effects of hypercortisolism on brain structure and related risk factors. Sci Rep. 2020;10(1):12708.

416. Qian X, Ji F, Ng KK, Koh AJ, Loo BRY, Townsend MC, et al. Brain white matter extracellular free-water increases are related to reduced neurocognitive function in systemic lupus erythematosus. Rheumatology (Oxford). 2022;61(3):1166-74.
417. Vestergaard M, Baaré WFC, Holm SK, Madsen CG, Paulson OB, Born AP, et al. Glucocorticoid treatment for non-cerebral diseases in children and adolescents is associated with differences in uncinate fasciculus microstructure. Pediatr Res. 2022;91(4):879-87.
418. Wang Y, Chen G, Zhong S, Jia Y, Xia L, Lai S, et al. Association between resting-state brain functional connectivity and cortisol levels in unmedicated major depressive disorder. J Psychiatr Res. 2018;105:55-62.
419. Peters AT, Jenkins LM, Stange JP, Bessette KL, Skerrett KA, Kling LR, et al. Pre-scan cortisol is differentially associated with enhanced connectivity to the cognitive control network in young adults with a history of depression. Psychoneuroendocrinology. 2019;104:219-27.
420. Utevsky AV, Smith DV, Huettel SA. Precuneus is a functional core of the default-mode network. J Neurosci. 2014;34(3):932-40.
421. Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME. Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. Cell metabolism. 2014;19(1):49-57.
422. Kern S, Oakes TR, Stone CK, McAuliff EM, Kirschbaum C, Davidson RJ. Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor. Psychoneuroendocrinology. 2008;33(4):517-29.
423. Liu S, Wang Y, Xu K, Ping F, Li F, Wang R, et al. Voxel-based comparison of brain glucose metabolism between patients with Cushing's disease and healthy subjects. NeuroImage Clinical. 2018;17:354-8.
424. Stomby A, Salami A, Dahlqvist P, Evang JA, Ryberg M, Bollerslev J, et al. Elevated resting-state connectivity in the medial temporal lobe and the prefrontal cortex among patients with Cushing's syndrome in remission. Eur J Endocrinol. 2019;180(5):329-38.
425. Ragnarsson O, Stomby A, Dahlqvist P, Evang JA, Ryberg M, Olsson T, et al. Decreased prefrontal functional brain response during memory testing in women with Cushing's syndrome in remission. Psychoneuroendocrinology. 2017;82:117-25.
426. van der Werff SJ, Pannekoek JN, Andela CD, Meijer OC, van Buchem MA, Rombouts SA, et al. Resting-State Functional Connectivity in Patients with Long-Term Remission of Cushing's Disease. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2015;40(8):1888-98.
427. Jiang H, He NY, Sun YH, Jian FF, Bian LG, Shen JK, et al. Altered spontaneous brain activity in Cushing's disease: a resting-state functional MRI study. Clinical endocrinology. 2017;86(3):367-76.
428. Liu S, Wang Y, Xu K, Ping F, Wang R, Li F, et al. Brain glucose metabolism is associated with hormone level in Cushing's disease: A voxel-based study using FDG-PET. NeuroImage Clinical. 2016;12:415-9.
429. Wirth M, Lange C, Huijbers W. Plasma cortisol is associated with cerebral hypometabolism across the Alzheimer's disease spectrum. Neurobiol Aging. 2019;84:80-9.
430. Piasecka M, Papakokkinou E, Valassi E, Santos A, Webb SM, de Vries F, et al. Psychiatric and neurocognitive consequences of endogenous hypercortisolism. Journal of internal medicine. 2020;288(2):168-82.
431. Saggar M, Tsalikian E, Mauras N, Mazaika P, White NH, Weinzimer S, et al. Compensatory Hyperconnectivity in Developing Brains of Young Children With Type 1 Diabetes. Diabetes. 2017;66(3):754-62.

432. Browne WV, Hindmarsh PC, Pasterski V, Hughes IA, Acerini CL, Spencer D, et al. Working memory performance is reduced in children with congenital adrenal hyperplasia. Horm Behav. 2015;67:83-8.
433. Collaer ML, Hindmarsh PC, Pasterski V, Fane BA, Hines M. Reduced short term memory in congenital adrenal hyperplasia (CAH) and its relationship to spatial and quantitative performance. Psychoneuroendocrinology. 2016;64:164-73.
434. Johannsen TH, Ripa CP, Reinisch JM, Schwartz M, Mortensen EL, Main KM. Impaired cognitive function in women with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2006;91(4):1376-81.
435. Helleday J, Bartfai A, Ritzen EM, Forsman M. General intelligence and cognitive profile in women with congenital adrenal hyperplasia (CAH). Psychoneuroendocrinology. 1994;19(4):343-56.
436. Engberg H, Butwicka A, Nordenstrom A, Hirschberg AL, Falhammar H, Lichtenstein P, et al. Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study. Psychoneuroendocrinology. 2015;60:195-205.
437. Falhammar H, Butwicka A, Landén M, Lichtenstein P, Nordenskjöld A, Nordenström A, et al. Increased psychiatric morbidity in men with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2014;99(3):E554-60.
438. Maheu FS, Merke DP, Schroth EA, Keil MF, Hardin J, Poeth K, et al. Steroid abnormalities and the developing brain: declarative memory for emotionally arousing and neutral material in children with congenital adrenal hyperplasia. Psychoneuroendocrinology. 2008;33(2):238-45.
439. Mazzone L, Mueller SC, Maheu F, VanRyzin C, Merke DP, Ernst M. Emotional memory in early steroid abnormalities: an FMRI study of adolescents with congenital adrenal hyperplasia. Developmental neuropsychology. 2011;36(4):473-92.
440. Berenbaum SA, Bryk KK, Duck SC. Normal intelligence in female and male patients with congenital adrenal hyperplasia. Int J Pediatr Endocrinol. 2010;2010:853103.
441. Messina V, Hirvikoski T, Karlsson L, Vissani S, Wallensteen L, Ortolano R, et al. Good overall behavioural adjustment in children and adolescents with classic congenital adrenal hyperplasia. Endocrine. 2020;68(2):427-37.
442. Messina V, Karlsson L, Hirvikoski T, Nordenström A, Lajic S. Cognitive Function of Children and Adolescents With Congenital Adrenal Hyperplasia: Importance of Early Diagnosis. J Clin Endocrinol Metab. 2020;105(3):e683-91.
443. Karlsson L, Gezelius A, Nordenstrom A, Hirvikoski T, Lajic S. Cognitive impairment in adolescents and adults with congenital adrenal hyperplasia. Clinical endocrinology. 2017;87(6):651-9.
444. Mueller SC, Temple V, Oh E, VanRyzin C, Williams A, Cornwell B, et al. Early androgen exposure modulates spatial cognition in congenital adrenal hyperplasia (CAH). Psychoneuroendocrinology. 2008;33(7):973-80.
445. Nordenstrom A, Servin A, Bohlin G, Larsson A, Wedell A. Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2002;87(11):5119-24.
446. Ernst M, Maheu FS, Schroth E, Hardin J, Golan LG, Cameron J, et al. Amygdala function in adolescents with congenital adrenal hyperplasia: a model for the study of early steroid abnormalities. Neuropsychologia. 2007;45(9):2104-13.
447. Merke DP, Fields JD, Keil MF, Vaituzis AC, Chrousos GP, Giedd JN. Children with classic congenital adrenal hyperplasia have decreased amygdala volume: potential prenatal and postnatal hormonal effects. J Clin Endocrinol Metab. 2003;88(4):1760-5.

448. Lajic S, Karlsson L, Nordenstrom A. Prenatal Treatment of Congenital Adrenal Hyperplasia: Long-Term Effects of Excess Glucocorticoid Exposure. Horm Res Paediatr. 2018;89(5):362-71.
449. Lajic S, Wedell A, Bui T-H, Ritzén EM, Holst M. Long-term somatic follow-up of prenatally treated children with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology & Metabolism. 1998;83(11):3872-80.
450. Nass R, Heier L, Moshang T, Oberfield S, George A, New MI, et al. Magnetic resonance imaging in the congenital adrenal hyperplasia population: increased frequency of white-matter abnormalities and temporal lobe atrophy. J Child Neurol. 1997;12(3):181-6.
451. Bergamaschi R, Livieri C, Uggetti C, Candeloro E, Egitto MG, Pichiecchio A, et al. Brain white matter impairment in congenital adrenal hyperplasia. Arch Neurol. 2006;63(3):413-6.
452. Samia YM, Mahdi K, Baha Z, Saida JO, Tahar SM, Habib SM. Congenital adrenal hyperplasia and brain magnetic resonance imaging abnormalities. Clin Pediatr Endocrinol. 2010;19(4):109-13.
453. Mnif MF, Kamoun M, Mnif F, Charfi N, Kallel N, Rekik N, et al. Brain magnetic resonance imaging findings in adult patients with congenital adrenal hyperplasia: Increased frequency of white matter impairment and temporal lobe structures dysgenesis. Indian J Endocrinol Metab. 2013;17(1):121-7.
454. Webb EA, Elliott L, Carlin D, Wilson M, Hall K, Netherton J, et al. Quantitative Brain MRI in Congenital Adrenal Hyperplasia: In Vivo Assessment of the Cognitive and Structural Impact of Steroid Hormones. J Clin Endocrinol Metab. 2018;103(4):1330-41.
455. Cotter DL, Azad A, Cabeen RP, Kim MS, Geffner ME, Sepehrband F, et al. White Matter Microstructural Differences in Youth With Classical Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2021;106(11):3196-212.
456. Yi SY, Barnett BR, Torres-Velázquez M, Zhang Y, Hurley SA, Rowley PA, et al. Detecting Microglial Density With Quantitative Multi-Compartment Diffusion MRI. Front Neurosci. 2019;13:81.
457. Herting MM, Azad A, Kim R, Tyszka JM, Geffner ME, Kim MS. Brain Differences in the Prefrontal Cortex, Amygdala, and Hippocampus in Youth with Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2020;105(4):1098-111.
458. Karlsson L, Barbaro M, Ewing E, Gomez-Cabrero D, Lajic S. Genome-wide investigation of DNA methylation in congenital adrenal hyperplasia. The Journal of steroid biochemistry and molecular biology. 2020;201:105699.
459. Beier CP, Wischhusen J, Gleichmann M, Gerhardt E, Pekanovic A, Krueger A, et al. FasL (CD95L/APO-1L) resistance of neurons mediated by phosphatidylinositol 3-kinase-Akt/protein kinase B-dependent expression of lifeguard/neuronal membrane protein 35. J Neurosci. 2005;25(29):6765-74.
460. Fernandez M, Segura MF, Sole C, Colino A, Comella JX, Cena V. Lifeguard/neuronal membrane protein 35 regulates Fas ligand-mediated apoptosis in neurons via microdomain recruitment. Journal of neurochemistry. 2007;103(1):190-203.
461. Bleuler M. [Psychopathology of the Cushing syndrome and Addison's disease; comparative study]. Schweizerische medizinische Wochenschrift. 1951;81(22):512-3.
462. Bertorini TE, Perez A. Neurologic complications of disorders of the adrenal glands. Handbook of clinical neurology. 2014;120:749-71.
463. Schulze Mönking H. Lithium treatment of a patient with Addison's disease and affective psychosis. Pharmacopsychiatry. 1989;22(2):84-6.
464. Thompson WF. Psychiatric aspects of Addison's disease: report of a case. The Medical annals of the District of Columbia. 1973;42(2):62-4.

465. Abdel-Motleb M. The neuropsychiatric aspect of Addison's disease: a case report. Innovations in clinical neuroscience. 2012;9(10):34-6.
466. Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci. 2006;18(4):450-9.
467. Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. J Clin Endocrinol Metab. 2001;86(7):2909-22.
468. Lovas K, Husebye ES, Holsten F, Bjorvatn B. Sleep disturbances in patients with Addison's disease. Eur J Endocrinol. 2003;148(4):449-56.
469. Gillin JC, Jacobs LS, Snyder F, Henkin RI. Effects of ACTH on the sleep of normal subjects and patients with Addison's disease. Neuroendocrinology. 1974;15(1):21-31.
470. Henry M, Wolf PS, Ross IL, Thomas KG. Poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in patients with Addison's disease. Physiology & behavior. 2015;151:379-85.
471. Klement J, Hubold C, Hallschmid M, Loeck C, Oltmanns KM, Lehnert H, et al. Effects of glucose infusion on neuroendocrine and cognitive parameters in Addison disease. Metabolism: clinical and experimental. 2009;58(12):1825-31.
472. Klement J, Hubold C, Cords H, Oltmanns KM, Hallschmid M, Born J, et al. High-calorie glucose-rich food attenuates neuroglycopenic symptoms in patients with Addison's disease. J Clin Endocrinol Metab. 2010;95(2):522-8.
473. Blacha AK, Rahvar AH, Flitsch J, van de Loo I, Kropp P, Harbeck B. Impaired attention in patients with adrenal insufficiency - Impact of unphysiological therapy. Steroids. 2021;167:108788.
474. Tiemensma J, Andela CD, Biermasz NR, Romijn JA, Pereira AM. Mild cognitive deficits in patients with primary adrenal insufficiency. Psychoneuroendocrinology. 2016;63:170-7.
475. Henry M, Ross IL, Wolf PSA, Thomas KGF. Impaired quality and efficiency of sleep impairs cognitive functioning in Addison's disease. Psychoneuroendocrinology. 2017;78:237-45.
476. Henry M, Thomas KG, Ross IL. Episodic memory impairment in Addison's disease: results from a telephonic cognitive assessment. Metabolic brain disease. 2014;29(2):421-30.
477. Schultebraucks K, Wingenfeld K, Heimes J, Quinkler M, Otte C. Cognitive function in patients with primary adrenal insufficiency (Addison's disease). Psychoneuroendocrinology. 2015;55:1-7.
478. Tytherleigh MY, Vedhara K, Lightman SL. Mineralocorticoid and glucocorticoid receptors and their differential effects on memory performance in people with Addison's disease. Psychoneuroendocrinology. 2004;29(6):712-23.
479. Schultebraucks K, Wingenfeld K, Otte C, Quinkler M. The Role of Fludrocortisone in Cognition and Mood in Patients with Primary Adrenal Insufficiency (Addison's Disease). Neuroendocrinology. 2016;103(3-4):315-20.
480. Giebels V, Repping-Wuts H, Bleijenberg G, Kroese JM, Stikkelbroeck N, Hermus A. Severe fatigue in patients with adrenal insufficiency: physical, psychosocial and endocrine determinants. J Endocrinol Invest. 2014;37(3):293-301.
481. van der Valk ES, Smans LC, Hofstetter H, Stubbe JH, de Vries M, Backx FJ, et al. Decreased physical activity, reduced QoL and presence of debilitating fatigue in patients with Addison's disease. Clinical endocrinology. 2016;85(3):354-60.
482. Blacha AK, Kropp P, Rahvar AH, Flitsch J, van de Loo I, Harbeck B. Poor quality of life and sleep in patients with adrenal insufficiency-another cause of increased mortality? Ir J Med Sci. 2021.

483. Born J, Schenk U, Späth-Schwalbe E, Fehm HL. Influences of partial REM sleep deprivation and awakenings on nocturnal cortisol release. Biol Psychiatry. 1988;24(7):801-11.
484. Petersen KS, Rushworth RL, Clifton PM, Torpy DJ. Recurrent nocturnal hypoglycaemia as a cause of morning fatigue in treated Addison's disease--favourable response to dietary management: a case report. BMC Endocr Disord. 2015;15:61.
485. German A, Suraiya S, Tenenbaum-Rakover Y, Koren I, Pillar G, Hochberg Z. Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy. J Clin Endocrinol Metab. 2008;93(12):4707-10.
486. Krekeler C, Kropp P, Blacha AK, Rahvar AH, Harbeck B. Dual-release hydrocortisone and its benefits on cognitive function and quality of sleep. Endocrine. 2021;72(1):223-33.
487. Werumeus Buning J, Brummelman P, Koerts J, Dullaart RP, van den Berg G, van der Klauw MM, et al. Hydrocortisone Dose Influences Pain, Depressive Symptoms and Perceived Health in Adrenal Insufficiency: A Randomized Controlled Trial. Neuroendocrinology. 2016;103(6):771-8.
488. Wechsler D. WAIS-IV administration and scoring manual: San Antonio, TX: Psychological Corporation; 2008.
489. Wechsler D. WMS-III: Wechsler memory scale - Third edition: San Antonio, TX: Psychological Corporation; 2008.
490. Golden CJ, Freshwater SM. The Stroop color and word test-A manual for clinical and experimental uses: Chicago: Stoelting Co; 1998.
491. Barkley RA. Barkley deficits in executive functioning scale (BDEFS for adults): Guilford Press; 2011.
492. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. Health Qual Life Outcomes. 2005;3:82.
493. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.
494. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
495. Ware Jr JE. SF-36 health survey. 1999.
496. Westerlund A, Brandt L, Harlid R, Åkerstedt T, Lagerros YT. Using the Karolinska Sleep Questionnaire to identify obstructive sleep apnea syndrome in a sleep clinic population. Clin Respir J. 2014;8(4):444-54.
497. Team RC. R: A language and environment for statistical computing. 2013.
498. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968-80.
499. Arbo BD, Ribeiro FS, Ribeiro MF. Astrocyte Neuroprotection and Dehydroepiandrosterone. Vitamins and hormones. 2018;108:175-203.
500. Saponaro S, Guarnieri V, Pescarmona GP, Silvagno F. Long-term exposure to dehydroepiandrosterone affects the transcriptional activity of the glucocorticoid receptor. The Journal of steroid biochemistry and molecular biology. 2007;103(2):129-36.
501. Amaya JM, Viho EMG, Sips HCM, Lalai RA, Sahut-Barnola I, Dumontet T, et al. Gene expression changes in the brain of a Cushing's syndrome mouse model. J Neuroendocrinol. 2022;34(4):e13125.
502. Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, et al. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. Neuroimage. 2007;35(2):478-87.

503. Arlt W, Callies F, Allolio B. DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition. Endocr Res. 2000;26(4):505-11.
504. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, et al. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. J Clin Endocrinol Metab. 2000;85(12):4650-6.
505. Skoglund O, Walhelm T, Thyberg I, Eriksson P, Sjöwall C. Fighting Fatigue in Systemic Lupus Erythematosus: Experience of Dehydroepiandrosterone on Clinical Parameters and Patient-Reported Outcomes. J Clin Med. 2022;11(18).
506. Turknett J, Wood TR. Demand Coupling Drives Neurodegeneration: A Model of Age-Related Cognitive Decline and Dementia. Cells. 2022;11(18).
507. Mälstam E, Bensing S, Asaba E. Everyday managing and living with autoimmune Addison's disease: Exploring experiences using photovoice methods. Scand J Occup Ther. 2018;25(5):358-70.
508. Claessen K, Andela CD, Biermasz NR, Pereira AM. Clinical Unmet Needs in the Treatment of Adrenal Crisis: Importance of the Patient's Perspective. Front Endocrinol (Lausanne). 2021;12:701365.
509. Webb SM, Kristensen J, Nordenström A, Vitali D, Amodru V, Wiehe LK, et al. Patient journey experiences may contribute to improve healthcare for patients with rare endocrine diseases. Endocr Connect. 2022;11(12).