Aus dem Max-Planck-Institut für Psychiatrie München

Vorstand: Prof. Dr. Dr. Elisabeth Binder

Oxytocin-Mangel in Kraniopharyngeom-Patienten

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

Anna Maria Dorothea Gebert

aus

Bayreuth

Jahr

2021

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter :	Prof. Dr. Günter Stalla
Mitberichterstatter:	Dr. Dominic Landgraf PD Dr. Bernhard G. Weiß Prof. Dr. Martin Reincke
Mitbetreuung durch die promovierte Mitarbeiterin:	Dr. Anna Kopczak
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	23.06.2021

Eidesstattliche Versicherung

Gebert, Anna Maria Dorothea

_____

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Oxytocin-Mangel in Kraniopharyngeom-Patienten

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Berlin, 9.7.2021 _____

Ort, Datum

Dorothea Gebert _____

Unterschrift Doktorandin

Contents

1 Abbreviations

ACIPS	Anticipatory and Consummatory Interpersonal Pleasure Scale
ACTH	adrenocorticotrope hormone
ADH	anti-diuretic hormone
AN	accessory nucleus of the hypothalamus
AQ	Autism Spectrum Quotient
AQ-AD	Autism Spectrum Quotient - attention to detail
AQ-AS	Autism Spectrum Quotient - attention switching
AQ-C	Autism Spectrum Quotient - communication
AQ-I	Autism Spectrum Quotient - imagination
AQ-S	Autism Spectrum Quotient - social skills
ARNT2	Aryl Hydrocarbon Receptor Nuclear Translocator 2
ASD	Autism Spectrum Disorder
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BDI-II	Beck-Depression-Inventory-II
BMI	body mass index
CP	craniopharyngioma
CPK	Corey-Pauling-Koltun model / space-filling model
CSF	cerebrospinal fluid
DI	diabetes insipidus neurohormonalis/ diabetes insipidus centralis
ECG	electrocardiogram
EQ	Empathy Quotient
FrACT	Freiburg Visual Acuity Test
FSH	follicle stimulating hormone
GH	growth hormone
GLM	general linear modeling
HC	healthy controls
HCG	human choriongonadotropin
LH	luteinizing hormone
LMU	Ludwig-Maximilians-Universität Munich
MPI-P	Max-Planck-Institute of Psychiatry Munich
MRI/MRT	Magnetic Resonance Imaging / Magnet-Resonanz-Tomographie
NFPA	non-functioning pituitary adenoma
OT	oxytocin
P	patients
PVN	paraventricular nucleus of the hypothalamus
REMT	"Reading the Mind in the Eyes" Test
SON	supraoptic nucleus of the hypothalamus
STAI	State-Trait-Anxiety-Inventory
TSH	thyroid-stimulating hormone
VA	visual acuity
WHO	World Health Organisation
YARE	Young Active Research in Endocrinology

2 List of publications

Publication 1:

Gebert D, Auer MK, Stieg MR, Freitag MT, Lahne M, Fuss J, Schilbach K, Schopohl J, Stalla G, Kopczak A. De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. *Psychoneuroendocrinology*. 2018;88:61-69.

Published in: Psychoneuroendocrinology
Date of acceptance: 10.11.2017
Date of Publication: 14.11.2017
Journal impact factor 2017: 4.731
InCites Journal Citation Report rank 2017: 26th of 142 journals

Publication 2:

Brandi, M-L, Gebert, D, Kopczak, A, Auer, MK, Schilbach, L. Oxytocin release deficit and social cognition in craniopharyngioma patients. *J Neuroendocrinol*. 2020; 32:e12842.

Published in: Journal of Neuroendocrinology
Date of acceptance: 05.03.2020
Date of publication: 09.03.2020
Journal impact factor most recent year (2018): 3.040
InCites Journal Citation Report rank (2018): 75th of 145 journals

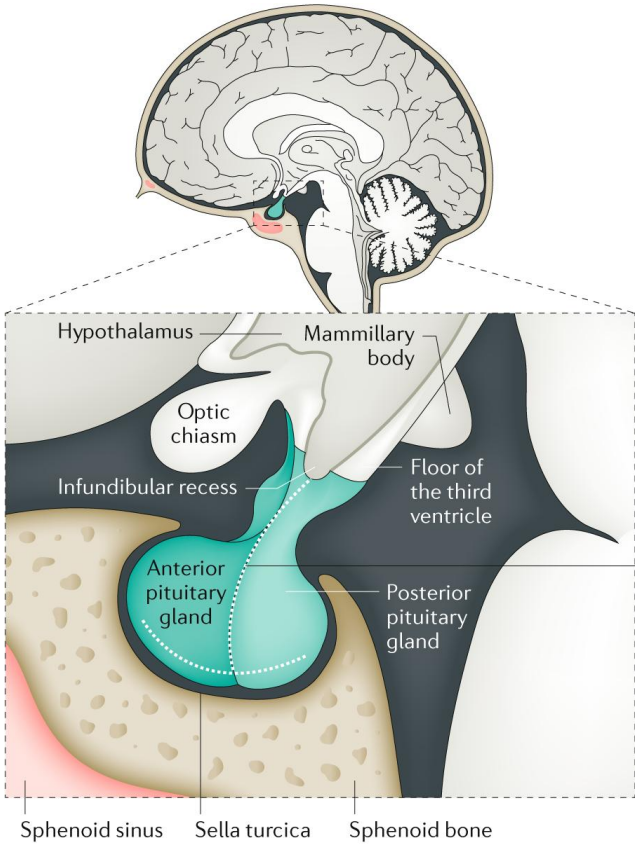
3 Introduction

3.1 Overarching research question

The research presented in this doctorate dissertation investigates the role of the neurohypophyseal hormone oxytocin in patients suffering from craniopharyngioma (CP). We aimed to answer the following questions: Do craniopharyngioma patients show a measurable oxytocin-deficiency? If yes, does this account for psychosocial dysfunction observed in this patient group? Finally, are there other not-yet described oxytocin-related deficits observable in craniopharyngioma patients that in turn might inform new treatment targets?

3.2 Craniopharyngioma

With an overall incidence of 0.5 to 2 cases per million person years[1], craniopharyngiomas are rare intracranial tumours of the sellar and parasellar region (see Figure 1). Age at initial diagnosis shows a bimodal distribution, with one peak in childhood (age 5-14 years) and one in later life (age 50-74 years)[1]. Two distinct histological types of craniopharyngioma are recognized. Paediatric cases typically show the adamantinomatous type which likely originates from dysontogenic embryonic tissue of the craniopharyngeal duct, and presents with cyst formations and calcifications easily visible on neuroimaging. More prevalent in adults, on the other hand, is the papillary craniopharyngioma, which instead of deriving from embryonic tissue likely develops through metaplasia of adenohypophyseal cells, and rarely shows calcifications[2]. Though only of low-grade malignancy (WHO 1°) with 10 year survival rates being as high as 85%[3], CP is associated with a critical degree of morbidity. This is due to their strategic location and unusually invasive growth behaviour. Growing aggressively along the pituitary stalk, only 3-6% of CP cases are restricted to intrasellar tissue and the pituitary region[4]. Instead, in most cases damage extends to surrounding tissue including the optic nerve, hypothalamic nuclei and the third ventricle[5; 6]. As a result, patients at diagnosis typically suffer from headache, visual disturbance, raised intracranial pressure, and varying degrees of endocrine dysfunction, including polydipsia, polyuria, and, in pediatric cases, growth retardation[7]. Long-term sequelae include chronic pituitary insufficiency[8], persistent visual field defects[9], and disabling hypothalamic dysfunction, with the latter leading to symptoms such as hypothalamic obesity, heightened psychopathology, cognitive problems, disruption of the circadian rhythm and severe homeostatic imbalances including diabetes insipidus[2; 3; 10-14]. As a consequence of this high tumour-related morbidity[3], CP patients often suffer from reduced quality of life and increased long-term mortality rates.



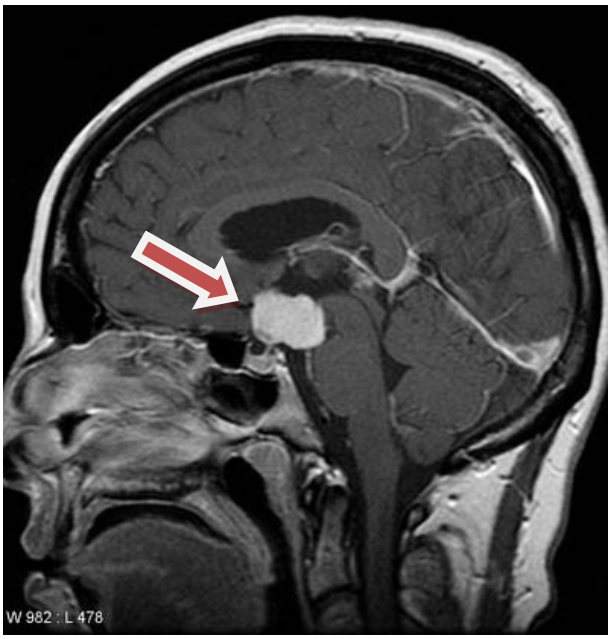


Figure 1 On the left: anatomical sketch of sellar region and the respective structures potentially affected by CP (adapted from Müller et al[15]); on the right: sagittal T1-MRI of a case example with papillary craniopharyngioma[16].

Even after satisfactory initial tumour removal, CP is therefore best characterised as a frequently chronic disease requiring continuous clinical management[2].

3.3 Endocrine sequelae of craniopharyngioma

In order to minimize resection of vital tissue while reducing the comparatively high tumour recurrence rates over time (17-45%)[17], initial treatment focuses on complete surgical resection, usually combined with radiotherapy[5]. Long-term endocrinological care then focuses on the functionality of the impacted endocrine axes (for an overview of physiological pituitary function, see Figure 2). Depending on tumour growth and extent of treatment-associated lesions, craniopharyngioma patients present with a multitude of endocrine insufficiencies. Ten years after initial diagnosis, almost all patients (98%) show chronic insufficiency of at least one endocrine axis[10], with deficiencies of somatotropic,

gonadotropic, adrenocorticotropic, thyroid-stimulating and antidiuretic hormone ranging at 88%, 90%, 86%, 80% and 65%, respectively[5]. According to the current German S1-guidelines of the *Association for Pediatric Oncology and Hematology*[18], the diagnostic work-up for detecting endocrine insufficiencies in craniopharyngioma patients therefore includes extensive laboratory testing for almost all of the potentially affected pituitary axes. Crucially, however, this work-up does not include the neurohypophyseal hormone oxytocin. This omission is remarkable since oxytocin is produced in the same brain regions (hypothalamic nuclei) and released into the blood stream from the same pituitary area (posterior pituitary gland) as the anti-diuretic hormone (ADH)[19; 20]. Given that ADH-insufficiency is a prevalent feature in craniopharyngioma patients with 30-65% requiring life-long treatment for central diabetes insipidus[5; 10; 21], it is likely that oxytocin is affected, too.

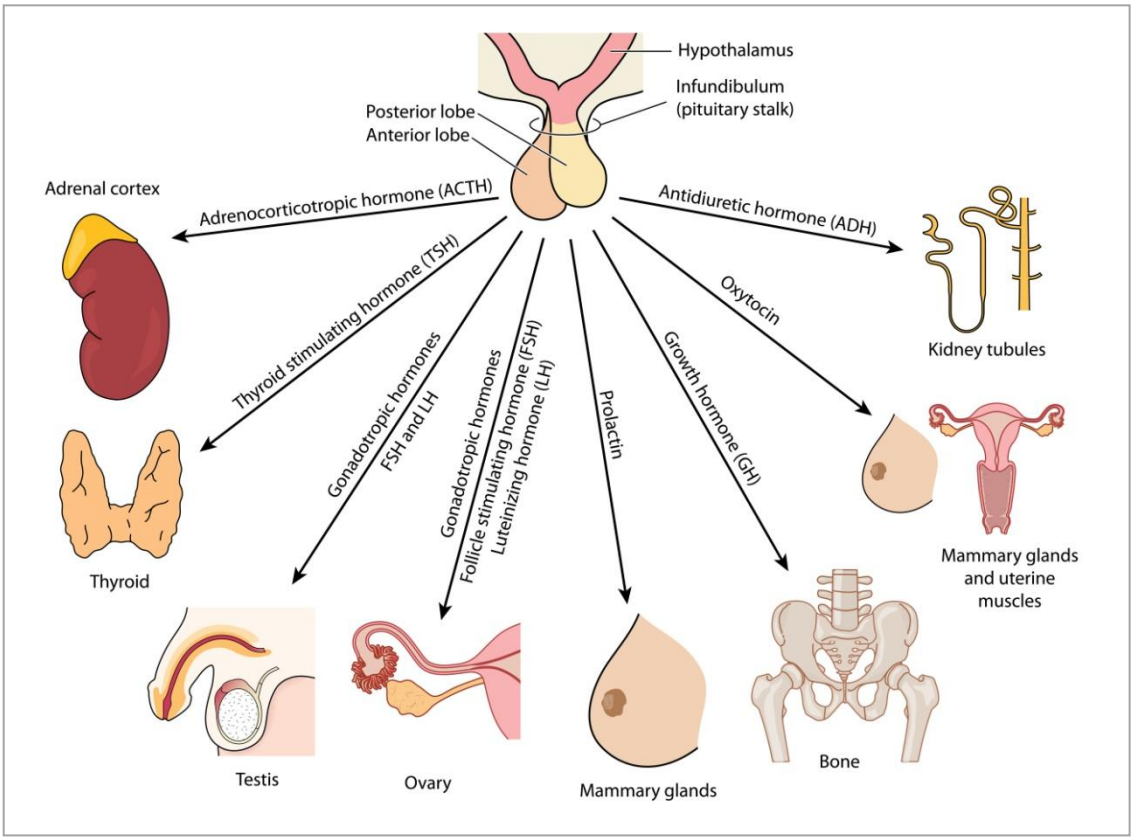


Figure 2 Overview of endocrine pituitary axes. Anteriorally released hormones include adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), gonadotropic hormones (FSH/LH), somatotropic growth hormone (GH), melanocyte-stimulating hormone (MSH, not shown) and prolactin. Posterior hormones include anti-diuretic hormone (ADH) and oxytocin. As key relay station between the central nervous system and peripheral organs, the pituitary gland affects all major aspects of vital homeostatic function[22].

3.4 The case for a clinically relevant oxytocin-deficiency in craniopharyngioma

The specific anatomical features of CP growth and the observed endocrine sequelae strongly suggest that CP patients should show to some degree an impairment of the oxytocin-axis. Why would this be clinically relevant?

Oxytocin is a cyclic nonapeptide with an overall molar mass of 1007.19 g/mol (for a CPK model, see Figure 3). It is mainly produced by magno- and parvocellular neurons found in the supraoptic (SON), paraventricular (PVN) and accessory nuclei (AN) of the hypothalamus, functioning both as a peptide hormone in various peripheral tissues and as a neuropeptide directly within the brain[19; 20].

Originally thought to affect uterine contraction and lactation only[23], the scientific appraisal of oxytocin has changed drastically over recent years. In addition to their well-known pituitary projections, oxytonergic magnocellular neurons connect via long-range projections directly to other brain regions (including the amygdala, septum, nucleus accumbens and hippocampus)[24], providing the basis for oxytocin to directly influence the neural circuits of complex social behaviour[25]. For example, oxytocin was shown to influence body weight by modulating energy metabolism and insulin sensitivity as well as eating behaviour[26; 27]. It appears to reduce addiction vulnerability through interacting with the dopamine-reward system and hampering psychological withdrawal symptoms[28; 29]. It was found to affect sexual reproduction by influencing physical orgasm function and changing pair bonding behaviour[30]. Furthermore, regarding complex psychosocial cognition, studies have now repeatedly demonstrated oxytocin-effects on cooperation and altruism[31], empathy[32], emotion processing[33], and fear appraisal[34; 35]. This particular role in psychosocial cognitive processes has led to clinical research identifying oxytocin as a relevant factor in the pathology of several psychiatric disorders including depression[36; 37], anxiety[38; 39], autism spectrum disorder[33; 40] and borderline personality disorder[41]. Thus, oxytocin is not anymore thought to only act peripherally on reproductive organs but instead to function as a neuromodulator, driving behavioural changes by influencing neuroplasticity for the underlying cognitive processes, doing so both during development as well as in adulthood[42].

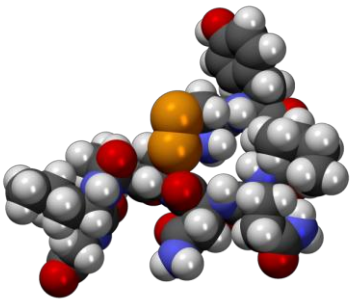


Figure 3 CPK model of oxytocin molecule $C_{43}H_{66}N_{12}O_{12}S_2$

These somatic and psychosocial effects of oxytocin are likely to be specifically relevant in craniopharyngioma. A study in childhood-onset craniopharyngioma has found patients to show pathological eating behaviour[43], a finding that agrees well with the above described influence of oxytocin on body weight[26; 27], and that becomes particularly relevant when considering the high prevalence of treatment-resistant obesity (39-56%) in CP patients[5; 10]. Regarding psychosocial morbidity, adult CP patients show heightened levels of depression, anxiety and harm avoidance - importantly, with scores being higher than in patient control groups[44; 45]. Furthermore, studies in paediatric CP patients revealed psychosocial dysfunction including social withdrawal in school, anxiety, depression, as well as aggressiveness, irritability, impulsivity and emotional outbursts[43; 46]. In addition, tentative direct evidence comes from a case study which administered intranasal oxytocin over several weeks to a paediatric patient with positive effects on socialization and interaction with her family[47]. Studies in the general population have proven psychological morbidity to present a substantial long-term burden directly increasing mortality, with median years of potential life lost to be estimated around 10 years[48]. In craniopharyngioma, this becomes even more relevant when considering the specific age distribution of CP incidence: About half of patients are diagnosed in childhood[1], meaning that potential psychosocial deficits fall into a particularly crucial time of the young patients' development. Correspondingly, patients with childhood-onset show greater long-term psychiatric morbidity than adult-onset patients[10], despite tumour growth and recurrence rates being similar at both age peaks[5].

Taken together, the case for a clinically relevant oxytocin-deficiency in CP patients is thus based on two observations. First, the specific anatomical features of CP growth pattern and their extensive endocrine sequelae including the high prevalence of diabetes insipidus strongly suggest that CP patients should show some degree of impairment of the oxytocin-axis. Second, while the underlying causes for psychosocial deficits in craniopharyngioma patients are likely to be multifactorial, the oxytocin-effects identified over the last decades of research might represent a promising target for new treatment strategies in this disease entity.

3.5 The rationale for publication 1

The research conducted for publication 1 aimed to address two questions: first, whether CP patients would indeed show an oxytocin-deficiency; second, whether differences in self-reported levels of depression, anxiety and empathy could be explained by patients' oxytocin levels.

At the time of study design, there had not been any research measuring oxytocin levels in CP patients. There was also no data directly linking any of the clinical symptoms of this patient group with the functionality of the oxytocin axis. In order to reach a sufficiently large patient sample for this rare disease entity, we set up a multi-centred study between the Ludwig-Maximilians-Universität Munich (LMU) and Max-Planck-Institute of Psychiatry Munich (MPI-P) enabling recruitment from both outpatient clinics. Regarding measuring oxytocin-levels, we decided to use a paradigm that would not only assess baseline levels but also provide a reliable stimulation condition. We deemed this to be crucial for the following reasons: first, oxytocin has a relatively short half-life, ranging between 3-9 minutes[49]. Thus, measuring oxytocin directly after stimulation is likely to de-mask a latent oxytocin-deficiency more reliably. Second, measuring after stimulation does not only have methodological advantages but instead might in itself be more representative of the physiological functioning of the oxytocin system. Research has shown that oxytocin is released momentarily in response to external or internal cues, especially stress, touch, sexual stimulation or emotion processing[50-54]. It might be exactly this additional release driving its effects on psychosocial functions. Third, recent data from other neuroscientific areas highlight the need to differentiate between baseline and stimulus-driven oxytocin-effects: Structural MRI-data in healthy people revealed opposite effects of a single dose versus repeated administration of oxytocin on grey matter volume in hippocampal areas[55]. And a study combining functional MRI-data in humans and neurochemical data in animals recently found that distinct neurobiological mechanisms are activated after acute in comparison to repeated oxytocin administration[56]. Distinguishing between baseline and stimulated levels thus becomes a crucial methodological feature.

Regarding the stimulation method itself, it had previously been established that physical exercise stimulates oxytocin release with similar reliability as sexual activity and breast feeding (Regensburg Oxytocin Challenge)[53]. Since we were looking to use a paradigm that could easily be applied in future hospital routines, we decided to use a bicycle ergometer normally utilized for cardiological assessments. Regarding the sampling of oxytocin, we

chose to collect oxytocin from saliva. This presents a method previously validated to detect short-term oxytocin changes in response to stimulation[53; 54; 57; 58]. It further presents a non-invasive measure easily undertaken in future clinical routine. Most importantly however, though the underlying mechanisms are still unclear, central and peripheral oxytocin-levels have repeatedly been shown to be tightly connected[50; 51; 59-61]. One recent study, which applied the same salivary sampling technique and whose samples were measured via the exact same oxytocin-assay in the same laboratory as our own samples, reported that endogenous oxytocin levels in saliva correlated strongly with endogenous levels in cerebral spinal fluid, and did so even more than serum oxytocin levels with cerebral spinal fluid[62]. Regarding the preparation and measurement of oxytocin samples, we commissioned a radioimmunoassay provided by Riagnosis© (Munich, Germany). This assay had been validated in both animal and human studies[37; 53; 63], showing a detection limit of 0.1µg per sample, a crossreactivity with related peptides of less than 0.7% and interassay variabilities of less than 10% (official data from the assay provider). Importantly, it utilizes lyophilization to extract interfering factors before assaying. A recent methodological review has found this extraction process to be crucial for immunoassays in order to yield measurements consistent with bioassays, as they would otherwise "generate impossibly high and wholly erroneous measurements"[64]. Moreover, all collected samples were extracted and assayed in the same batch at the same time to eliminate interassay variability between samples.

In addition to oxytocin samples, we also assessed the extent of structural pituitary and hypothalamic lesions for each patient by examining their most recent MRI-data acquired during previous routine check-up appointments.

Regarding the selection of relevant psychosocial functions, we first wanted to gain qualitative data to better inform our study design. To this end, we conducted 6 semi-structured patient interviews in addition to the standard literature search. Collaborating with a qualitative research scientist, we drafted a set of interview questions focussing on those functions that we expected to be affected in oxytocin-deficiency, and exploring which of these patients themselves found to be important. Interviews took place in the patients' homes and lasted about 45 min each. Based on the qualitative analysis of these data, we then decided to focus on depression, anxiety and empathy for the first study.

Our hypotheses for study 1 were as follows[65]:

1) Salivary oxytocin-levels at baseline were expected to be lower in patients compared to healthy controls, and lower oxytocin levels were expected to be associated with greater hypothalamic damage and with symptoms of diabetes insipidus.

2) We further expected patients to show a blunted oxytocin-response to stimulation (i.e. physical exercise), further indicating an oxytocin-deficiency.

3) Third, we expected oxytocin-levels to account for a significant amount of variance of affective dysfunction, with oxytocin-deficiency being linked to higher depression scores, higher anxiety, and lower empathy on clinically established questionnaires.

3.6 The rationale for publication 2

The second study focused on the suspected link between oxytocin levels in craniopharyngioma patients and social cognition. Social cognitive processes like facial emotion recognition or judging the trustworthiness of another person depend on fast automatic processing[66]. Oxytocin is suggested to be a key player in these cognitive functions, likely influencing automatic processing by heightening the saliency of socially relevant information over others[50; 67; 68]. We expected that CP patients would show deficits in automatic social cognitive processes that previously had not been described in this patient group. By identifying such differences, we hoped to gain relevant insight into the cognitive mechanisms that influence the development and maintenance of psychosocial dysfunction in craniopharyngioma patients, subsequently informing treatment approaches in the future. Second, in addition to identifying new treatment targets, CP patients might also provide important insight into our general understanding of the effects of oxytocin on social cognition. Studies have typically focused either on healthy people or on patients whose disorder is defined by the psychosocial deficit, such as autism spectrum disorder[69-71]. In both cases, the oxytocin system is assumed to be anatomically intact. Craniopharyngioma patients potentially provide the other side of the same coin by being able to start from a lesion and then assessing its effect on automatic cognitive function.

To address the question of a possible link between oxytocin levels in CP patients and social cognition, we initiated the collaboration with the *Social Neuroscience Research Group* and

the *Clinic for Disorders of Social Interactions* at the MPI-P in Munich. We designed a social cognition paradigm that enabled us to link baseline and stimulated oxytocin-levels with real-time psychosocial cognitive processing, including an eye-tracking paradigm recording automatic gaze behaviour.

Our hypotheses for this second study were as follows[72]:

1) As assessed with self-report questionnaires, craniopharyngioma patients were expected to show higher autistic traits, lower theory of mind abilities and greater social anhedonia than healthy controls.

2) Craniopharyngioma patients were expected to show lower accuracy rates when recognising facial emotions than healthy controls, while general facial processing was expected to be intact.

3) Craniopharyngioma patients were expected to show pathological gaze behaviour when processing facial information. We further expected this gaze behaviour to be associated with an oxytocin-deficiency as measured before in the first study.

3.7 Contribution of the candidate

The candidate designed the here-presented scientific study together with M.Auer and A.Kopczak. In order to gain first insight as to whether and how patients subjectively noticed symptoms that in theory would be linked with oxytocin, the candidate was in charge of carrying out six semi-structured one-on-one interviews with patients of the participating outpatient clinics. Moreover, the candidate assisted in physician-guided self-help groups. The impact of endocrine insufficiency on quality of life was reported and analysed according to qualitative methods of empirical research[73].

Based on the gained qualitative data, the candidate then developed the research paradigm for study 1 together with M.Auer and A.Kopczak. Together with A.Kopczak, the candidate also approached the *Social Neuroscience Research Group* and the *Clinic for Disorders of Social Interactions* at the MPI-P Munich in order to gain neuroscientific expertise for the design of study 2. The candidate together with A.Kopczak wrote the application for ethical approval for

all of the here-presented research as well as further studies currently being undertaken by the collaborating groups.

The candidate contributed to the recruitment of participants and was in charge of collecting the pre-existing radiological data used to grade lesion extent. The candidate also carried out the actual testing including oxytocin sampling during testing sessions, as well as the preparation of saliva samples after initial collection for further assaying, taking turns with M.Auer and M.Stieg. The candidate also collected all of the data of the self-report questionnaires.

The doctoral candidate carried out the full statistical analysis of publication 1. She also wrote the manuscript of publication 1, with significant comments from M.Auer and A.Kopczak. She led the peer-review-process during the submission to scientific journals. Given that the initial idea of a potential oxytocin-deficit was also provided by M.Auer and this author was also the main intellectual contributor to the oxytocin-measurement method, the first authorship for publication 1 was shared between the doctoral candidate and M.Auer. Regarding publication 2, the candidate wrote the draft of publication 2 jointly with M.Brandi, with comments by M.Auer, A.Kopczak and L.Schilbach, and undertook the peer-review-process for this publication jointly with M.Brandi. Since the specific methodological design of this neuroscientific study, the data collection of automatic social cognition data, as well as the statistical analysis of those data was undertaken by M.Brandi, the first-authorship for this publication was not shared.

Finally, the doctoral candidate presented this work at several conferences. She provided a poster presentation at the 60th *Deutscher Kongress für Endokrinologie 2017* in Würzburg and gave two invited talks at the *Annual YARE Meeting 2017* in Berlin and the *Herbst-Sitzung 2017 AG Hypophyse und Hypophysentumore* in Berlin.

4 Summary

4.1 Summary in English

Craniopharyngiomas are rare intracranial tumours of the sellar and parasellar region. Due to their growth pattern along the pituitary stalk, optic chiasm, hypothalamic regions and the third ventricle, they are associated with a critical degree of morbidity[2]. This includes permanent visual field defects, disruption of various endocrine pituitary axes and potentially extensive hypothalamic dysfunction[2; 74]. In addition to surgical and radiological treatment, routine patient care comprises the assessment and at times life-long substitution of almost all affected pituitary axes except for the neuropeptide oxytocin[75]. This omission of oxytocin is surprising since there are anatomical as well as clinical grounds to suspect a functionally relevant oxytocin-deficiency in this patient group. First, craniopharyngiomas regularly result in damage to anatomical sites pivotal for oxytocin production and release[19; 20]. Second, CP patients exhibit clinical symptoms (e.g. depression, anxiety, social withdrawal in school, aggressiveness and impulsivity[43-46]) which agree well with complex psychoaffective functions shown to be oxytocin-mediated in healthy people (e.g. cooperation and altruism[31], empathy[32], emotion processing[33], fear appraisal[34; 35]) and to modulate pathology in psychiatric populations (including patients with depression[36; 37], anxiety[38; 39], autism spectrum disorder[33; 40] and borderline personality disorder[41]). Furthermore, a single case study administering intranasal oxytocin to a young girl with craniopharyngioma reported improved socialization towards her family[47].

Based on this rationale, a multi-centre, prospective study in CP patients and healthy controls was designed to answer the following questions:
(a) Do patients with craniopharyngioma show a measurable oxytocin-deficiency?
(b) Does oxytocin-deficiency account for psychosocial dysfunction previously observed in this patient group?
(c) Drawing from well-documented oxytocin-effects in healthy people and psychiatric patient groups, are there other not-yet described oxytocin-related deficits observable in patients with craniopharyngioma that in turn might inform new treatment targets?

Akin to the assessment of other endocrine axes, we used a stimulation test to assess oxytocin levels. Since at the time of study design, oxytocin had never been measured in craniopharyngioma patients, we designed a new stimulation paradigm using exercise as

stimulation trigger[53]. Oxytocin was measured via salivary samples, collected from 23 patients and 23 healthy controls both before and after exercising on a bicycle ergometer.
Standard self-report questionnaires were used for the assessment of depression, anxiety, and empathy. The questionnaire selection was based on preparatory semi-structured patient interviews specifically conducted to inform the design of the present study.

Results from study 1 showed that CP patients indeed exhibit an oxytocin-deficiency. This was already measurable at baseline levels when hypothalamic damage was extensive. When tumour lesions were limited to the pituitary region alone, an oxytocin-deficiency became de-masked under stimulation conditions: Irrespective of hypothalamic damage, CP patients were less able than healthy controls to release additional oxytocin under stimulation with exercise.
Regarding psychoaffective function, our results further underlined the dissociation between baseline and stimulation measures. As expected, an oxytocin release-deficit was associated with greater state anxiety levels. However, baseline measures behaved contrarily, with *higher* oxytocin levels at baseline being associated with higher depression and trait anxiety scores. Self-reported empathy levels failed to show an association with oxytocin levels in the present study.

These results suggest the following conclusions: For one, the intracranial tumour craniopharyngioma can affect all endocrine axes including the oxytocin-axis. Second, patients differ in whether their oxytocin-deficiency affects short-term stimulus-triggered release or also baseline levels. Third, this differentiation is important as the present results suggest that it might affect psychopathology in CP patients differently. This finding ties in well with other present research, with recent neurochemical evidence from human and animal studies showing that distinct neurobiological mechanisms are activated after acute in comparison to repeated oxytocin administration[55; 56].
Based on this, our findings have direct implications for future substitution paradigms in craniopharyngioma, as it highlights the importance of controlling not only *dosage* but specifically the *timing* of oxytocin substitution regimens. Furthermore, the present findings provide an explanation for much-debated discrepancies in the literature, with previous studies at times observing opposing effects of oxytocin on depression and anxiety in psychiatric patient groups[37; 50; 76-78]. Thus, when aiming to treat psychoaffective dysfunction in CP patients, oxytocin substitution should not be considered as a blanket treatment. Instead, careful evaluation is warranted regarding substitution regimen and specific target symptom, as oxytocin likely can have both positive and negative treatment effects on psychopathology

in CP patients. Third, in addition to informing new treatment targets, the present results suggest that CP patients might also provide important insight into our general understanding of the effects of oxytocin on psychoaffective functions. Studies have typically focused either on healthy people or on patients whose disorder is explicitly defined by their psychosocial deficit, such as autism spectrum disorder[69-71]. In both cases, the oxytocin system is assumed to be anatomically intact. Craniopharyngioma patients potentially provide the other side of the same coin by being able to start from a lesion and then assessing its effect on clinical function.

In study 2, we investigated whether CP patients show other oxytocin-related deficits previously not reported in this patient group. Social cognition, including automatic facial emotion processing and theory of mind abilities, has been shown to be oxytocin-dependent and potentially contribute to psychopathology in various psychiatric disorders including autism spectrum disorder and major depression[36; 79-83]. The potential effects of oxytocin-deficiency on psychosocial development are particularly relevant in craniopharyngioma. For one, deficits in psychosocial behaviour have been reported to substantially impair quality of life in CP patients[14; 74]. Second, given that half of patients are diagnosed in childhood, deficits in automatic social cognition would hit during a particularly vulnerable developmental phase, i.e. during childhood and teenage years, presenting a potential mechanism for the development and maintenance of psychosocial deficits in this patient group over time.

Based on the in study 1 detected oxytocin-deficiency in CP patients, we hypothesised patients to exhibit deficits in different aspects of social cognition. First, to assess potential long-term effects, we used questionnaires measuring social behavioural traits associated with social disorders such as autism spectrum disorder[84; 85]. Second, given that a key aspect of social cognition is fast processing and giving adequate, immediate reactions to another person's mental state, an interactive computer-based task was applied, this way potentially detecting more direct effects on ongoing social cognitive processes. Adapted from cognitive neuroscientific studies, the standardized task included an eye-tracking technology to assess differences in automatic gaze behaviour while participants performed a facial emotion recognition task.

The results of study 2 indeed revealed previously not reported deficits of social cognition. For one, patients self-reported increased autistic traits and social anhedonia, with scores ranging between healthy controls and the clinical cut-off for patients with autism spectrum disorder.

Second, CP patients were less able to quickly recognize facial emotions in comparison to healthy controls. Furthermore, participants who exhibited a lower responsiveness of their oxytocin system (in response to exercise) were also less likely to change their gaze towards socially informative regions of the viewed face.

These results suggest the following conclusions: behavioural traits as well as fast and automatic processes that are crucial to social cognition can be impaired in CP patients. Furthermore, these processes are linked to differences in dynamic oxytocin release. Taking together that oxytocin has elsewhere been shown to be an important factor in psychosocial development, that it has been suggested to directly modulate the course of psychopathology in psychiatric disease, and considering the high number of pediatric-onset cases in CP, targeting associated cognitive deficits with medical and behavioural therapy thus might particularly improve long-term patient outcome[86].

During data collection and write-up of the present research, several studies from other research groups on oxytocin in CP patients reached publication. Investigating oxytocin-associated obesity, a single case study reported sustained changes in eating behaviour as well as reduction of BMI with continuous intranasal oxytocin administration[87]. A clinical study in childhood-onset craniopharyngioma patients reported oxytocin levels to be similar to healthy controls, both before and after a standardized meal. Importantly, baseline oxytocin was significantly lower only in a small subgroup of patients with anterior hypothalamic damage (N=6)[88]. Looking at psychoaffective function, the same patient sample then showed an improved ability to categorize negative emotions after receiving intranasal oxytocin[89]. Finally, another study reported lower salivary oxytocin-levels at baseline and reduced empathic abilities in patients with anterior hypopituitarism and diabetes insipidus, which among other pituitary disease included 9 CP patients in their sample[90].

The results of the here-presented thesis tie in well with these data. More importantly, however, they directly pave the way for future research. When aiming to target other oxytocin-associated comorbidities such as hypothalamic obesity with oxytocin, experimental set-up needs to define whether substitution should aim to change long-term baseline levels or instead be acute and stimulus-tied, for example by coinciding with meal intake during the day. For future studies, the present thesis now also puts forward a feasible clinical stimulation test that could be used to establish standardized oxytocin values for routine endocrine

assessment, both in craniopharyngioma as well as various pituitary disorders in the future. In the present, this research paradigm has already been used to launch a social neuroscientific study investigating oxytocin-effects in patients with autism spectrum disorder, with results yet to come (Albantakis et al, *not yet published*).

While more research is needed to establish standardized values of oxytocin-levels as well as define specific target symptoms for oxytocin-substitution, working towards incorporating oxytocin-substitution in the future and tailoring it to the individual patient's symptoms and developmental needs will likely alleviate life-long disease burden and ultimately improve quality of life.

4.2 Zusammenfassung auf Deutsch

Kraniopharyngeome sind seltene intrakranielle Tumore der sellären und parasellären Region. Trotz geringer Malignität (WHO 1°) sind sie mit einem vergleichsweise hohen Morbiditätsgrad assoziiert[2]. Aufgrund ihres Wachstums entlang der Hypophyse bis zum Chiasma opticum, Hypothalamus und dritten Ventrikel leiden Patienten häufig an einschneidenden und chronischen Folgeerscheinungen[91]. Hierzu gehören insbesondere Gesichtsfelddefekte, Ausfall verschiedener hypophysärer Hormonachsen und teilweise ausgeprägte hypothalamische Dysfunktion mit Adipositas, psychopathologischen und kognitiven Defiziten, Störung des zirkadianen Rhythmus und schweren homöostatischen Dysbalancen inklusive Diabetes insipidus neurohormonalis[2; 3; 10-14].
Nach neurochirurgischer und zusätzlich meist strahlentherapeutischer Behandlung besteht die langfristige endokrinologische Therapie aus Überwachung und, falls nötig, der lebenslangen medikamentösen Substitution der betroffenen Hormonachsen (S1-AWMF-Leitlinie 2019)[75]. Diese Substitutionsbehandlung wird für fast alle hypophysären Hormonachsen durchgeführt, mit Ausnahme des Neuropeptids Oxytocin. Die Oxytocin-Achse wird nicht untersucht, obwohl es sowohl anatomische als auch klinische Hinweise für einen Oxytocin-Mangel in Kraniopharyngeom-Patienten gibt. Die hier vorgestellte wissenschaftliche Arbeit nahm es sich daher zum Ziel, die Möglichkeit eines Oxytocin-Mangels in Kraniopharyngeom-Patienten zu überprüfen und in Kontext mit psychoaffektiven Defiziten dieser Patientengruppe zu setzen.

Die Hypothese bezüglich eines wahrscheinlichen Oxytocin-Defizits basiert auf zwei Argumenten. Zum einen führt das spezifische Wachstumsmuster von Kraniopharyngeomen häufig zu Läsionen, die anatomisch den Hauptarealen der Oxytocin-Produktion (hypothalamische Nuclei SON, PVN, AN) und Ausschüttung (Neurohypophyse) entsprechen[19; 20] und somit bei Kraniopharyngeom-Patienten mitbetroffen sein sollten. Zum anderen werden in dieser Patientengruppe häufig psychoaffektive Defizite beobachtet, die mit Funktionen überlappen, für die in anderen wissenschaftlichen Bereichen sowohl bei gesunden als auch psychiatrischen Kohorten eine Oxytocin-Assoziation gezeigt werden konnte. So wurden für Oxytocin modulierende Einflüsse auf Kognitionen wie Altruismus[31], Empathie[32], Emotionserkennung[33] und Angstbewertung[34; 35] nachgewiesen sowie auch auf psychiatrische Erkrankungen wie Depression[36; 37], Angststörung[38; 39], Autismus-Spektrum-Erkrankung[33; 40] und Persönlichkeitsstörung vom Borderline-Typ[41]. Diese Effekte spiegelnd weisen Kraniopharyngeom-Patienten vermehrt Depression und Angststörungen,

Vermeidungsverhalten, Aggressivität und Impulsivität auf – insbesondere auch im Vergleich zu Patientenkontrollgruppen[43-46]. Des Weiteren konnte eine Fallstudie mit einer pädiatrischen Kraniopharyngeom-Patientin zeigen, dass sich nach 22 Wochen intranasaler Oxytocin-Substitution eine relevante und positive Änderung bezüglich Sozialisierungs- und Affektverhalten abzeichnete[47].

Basierend auf dieser zweiteiligen Rationale wurde eine multi-zentrische, prospektive Studie mit Patienten und gesunden Kontrollen konzipiert, die die folgenden Fragestellungen eruiert:

(a) Weisen Kraniopharyngeom-Patienten einen messbaren Oxytocin-Mangel auf?

(b) Lässt sich ein Teil der psychosozialen Defizite dieser Patientengruppe durch einen Oxytocin-Mangel erklären?

(c) Basierend auf bekannten Oxytocin-assoziierten Dysfunktionen in anderen psychiatrischen Patientengrupppen, lassen sich bei Kraniopharyngeom-Patienten bisher nicht beschriebene Defizite in sozialen Kognitionsprozessen aufdecken und damit potenziell neue Therapieansätze definieren?

Zum Zeitpunkt des Studiendesigns dieser Dissertation gab es keine publizierten Daten zu Oxytocin-Messungen in Kraniopharyngeom-Patienten. Es wurde daher ein Studienparadigma entworfen, welches – angelehnt an die klinischen Funktionstests anderer Hormonachsen – sowohl basale als auch stimulierte Hormonspiegel bestimmte. Auf der Basis früherer Studien mit gesunden Probanden wurde Sport als Oxytocin-Trigger genutzt[53]. Patienten absolvierten eine standardisierte Sporteinheit auf einem Fahrrad-Ergometer. Von 23 Patienten und 23 gesunden Kontrollen wurden vor und nach Stimulation Speichelproben gesammelt. Um die psychoaffektive Funktion zu messen, beantworteten Probanden standardisierte Fragebögen, die die Ausprägung von Depression, Angst und Empathiefähigkeit erhoben. Die Auswahl der angewendeten Fragebögen beruhte zum einen auf den in der Literatur für Kraniopharyngeom-Patienten beschriebenen psychoaffektiven Defiziten, zum anderen auf sechs semi-strukturierten Patienteninterviews, die in Vorbereitung der hier präsentierten klinischen Studie durchgeführt wurden.

Als Hauptergebnis der Studie 1 konnte – die primäre Hypothese unterstützend - nachgewiesen werden, dass Kraniopharyngeom-Patienten einen messbaren Oxytocin-Mangel aufweisen. Während Patienten mit geringer Läsionsausdehnung (limitiert auf die Hypophyse) vor Stimulation noch Oxytocin-Spiegel vergleichbar mit der gesunden Kontrollgruppe

zeigten, wiesen Patienten mit ausgedehnterer Läsion und insbesondere hypothalamischer Beteiligung bereits einen Mangel in den basalen Messwerten auf. Unter Stimulationsbedingungen nach Sport wurde sichtbar, dass Kraniopharyngeom-Patienten auch unabhängig von der Läsionsausdehnung signifikant weniger Oxytocin ausschütteten als Gesunde.

Die zweite Hypothese, dass Oxytocin-Spiegel der Kraniopharyngeom-Patienten mit Defiziten in psychoaffektiver Funktion assoziiert sind, wurde teilweise bestätigt. Wie erwartet war ein Oxytocin-Mangel unter Stimulation mit erhöhter Ängstlichkeit verbunden, insbesondere mit situationsbedingter Zustandsangst (state anxiety). Interessanterweise ergaben die Messung der basalen Oxytocin-Spiegel gegenläufige Ergebnisse, mit einer Assoziation zwischen *höheren* basalen Oxytocin-Spiegeln einerseits und *höheren* Scores bezüglich Depression und Ängstlichkeit (trait anxiety) andererseits. Für Empathiefähigkeit konnten in der aktuellen Studie keine Unterschiede zwischen Patienten und Gesunden und auch keine Assoziation mit Oxytocin-Spiegeln nachgewiesen werden.
Diese Parallele zwischen basalen Oxytocin-Spiegeln sowie Depression und Ängstlichkeit auf der einen Seite, und Stimulations-getriggerten Oxytocin-Spiegeln sowie situationsbedingter Zustandsangst auf der anderen ist ein besonders interessantes Ergebnis. Es stellt eine mögliche Erklärung für die sich teilweise diametral widersprechenden Studienergebnisse in der Oxytocin-Forschung der vergangenen Jahre dar, in der sowohl negative als auch positive Assoziationen zwischen Oxytocin-Spiegeln und Depression bzw. Angststörungen beobachtet wurden[37; 50; 76-78]. Dies bedeutet für zukünftige Studien, dass Oxytocin-Substitution zwar eine mögliche Behandlungsoption für einen Teil der bestehenden psychoaffektiven Defizite bei Kraniopharyngeom-Patienten darstellen könnte. Allerdings war dies in Bezug auf die hier erhobenen Parameter nur im Bereich von situationsbedingter Zustandsangst der Fall. Potenziell *verstärkende* Effekte von Oxytocin-Substitution auf andere affektive Dysfunktionen hingegen müssen engmaschig überwacht werden.
Eine dritte Schlussfolgerung aus Studie 1 besteht darin, dass Kraniopharyngeom-Patienten aufgrund des hier beobachteten Oxytocin-Mangels zum generellen Verständnis von Oxytocin beitragen können. Studien haben bisher typischerweise entweder Gesunde untersucht oder solche Patientengruppen, die sich durch funktionelle, Oxytocin-assoziierte Defizite ausweisen (z. B. Autismus-Patienten)[69-71]. In beiden Fällen geht man von einem anatomisch intakten Oxytocin-System aus. Auf Grundlage der aktuellen Ergebnissen können Studien mit Kraniopharyngeom-Patienten eine für die weitere Oxytocin-Forschung wertvolle Umkehrung

der bisherigen Herangehensweise ermöglichen − nämlich in zukünftigen Studien von einer anatomischen Läsion aus zu beginnen und dann die daraus resultierenden funktionellen Konsequenzen zu definieren.

Basierend auf dem Nachweis eines Oxytocin-Mangels in Kraniopharyngeom-Patienten in Studie 1 wurde in Studie 2 untersucht, ob Kraniopharyngeom-Patienten bisher nicht beschriebene Oxytocin-assoziierte Defizite der sozialen Kognition aufweisen.
Im Bereich der Kognitionswissenschaften wurde wiederholt nachgewiesen, dass Oxytocin neuronale Prozesse moduliert, die die entscheidende Fähigkeit steuern, sich anhand (nonverbaler) Signale in eine andere Personen hineinzuversetzen und deren Absichten korrekt einzuschätzen (*theory of mind abilities*)[92-94]. Hierzu gehört auch der komplexe Prozess, mit schnellen, reflexartigen Blickbewegungen ein gegenüberstehendes Gesicht bezüglich dessen Emotion zu scannen und richtig einzuordnen[70]. Die klinische Relevanz von Defiziten in diesen Prozessen wurde in Patientenkohorten mit Autismus-Spektrum-Erkrankung, Persönlichkeitsstörung vom Borderline-Typ und Major-Depression gezeigt[36; 79-82; 95]. Inzwischen gibt es Hinweise darauf, dass derartige Veränderungen nicht nur ein diagnostisches Merkmal darstellen, sondern wahrscheinlich auch einen aktiven Anteil an der Entwicklung und Aufrechterhaltung dieser Psychopathologien haben[80; 83; 96] und Ansatzpunkt für sowohl medikamentöse als auch spezifische verhaltenstherapeutische Maßnahmen bieten[86].

Mit Hinblick auf den in Studie 1 nachgewiesenen Oxytocin-Mangel bei Kraniopharyngeom-Patienten erwarteten wir, dass diese Patientengruppe ebenfalls Defizite in sozialer Kognition aufweisen würde und dass sich dies in Unterschieden bezüglich der automatischen Verarbeitungsprozesse widerspiegeln würde. Hierzu wurden zum einen Fragebögen angewendet, die Persönlichkeitsmerkmale und Verhaltensweisen messen, welche mit sozialer Interaktionsfähigkeit assoziiert sind[84; 85]. Zum anderen wurde ein interaktives, Computer-basiertes Experiment erstellt, in dem Probanden in Echtzeit die Emotionen von auf dem Bildschirm gezeigten Gesichtern einordnen mussten. Um Rückschlüsse auf die dahinterliegenden automatischen Prozesse zu ziehen, wurden gleichzeitig Augenbewegungen und damit das jeweilige automatische Blickverhalten der Probanden aufgezeichnet.

Als Hauptergebnis der Studie 2 konnten tatsächlich bisher nicht beschriebene Defizite der sozialen Kognition von Kraniopharyngeom-Patienten nachgewiesen werden.

Die Auswertung der Fragebögen ergab, dass Patienten im Vergleich zu gesunden Probanden vermehrt Verhaltensweisen angaben, die sonst mit Erkrankungen des autistischen Spektrums assoziiert sind[84; 85]. Hierzu gehört eine Verminderung der sozialen Hedonie sowie der Fähigkeit, die eigene Aufmerksamkeit auf einen neuen Stimulus zu lenken. Die Auswertung der interaktiven Daten der Studie 2 ergab, dass Kraniopharyngeom-Patienten im Vergleich zu Gesunden signifikant mehr Fehler beim schnellen Erkennen emotionaler Gesichtsausdrücke machten. Die bezüglich des automatischen Blickverhaltens erhobenen Daten ergaben drittens, dass eine verminderte Oxytocin-Ausschüttung unter Stimulationsbedingungen tatsächlich mit atypischen Augenbewegungsmustern in der Verarbeitung von den Gesichtsausdrücken verbunden war.
Zukünftige Studien sollten nun untersuchen, wie die hier aufgedeckten Defizite bezüglich unbewusster Prozesse der sozialen Kognition sich auf die langfristige psychosoziale Entwicklung der Patienten auswirken. Die Hälfte aller Kraniopharyngeome manifestieren sich im Kindesalter. Die hier beobachteten Veränderungen von sozialer Kognition treten daher wahrscheinlich in einem für die psychosoziale Entwicklung besonders wichtigen Zeitfenster auf und stellen damit möglicherweise einen treibenden Faktor auch für die langfristige Aufrechterhaltung psychosozialer Defizite dar.

Während der Datenerhebung und Manuskriptverfassung dieser Dissertation wurden mehrere Oxytocin-Studien mit Kraniopharyngeom-Patienten von anderen Arbeitsgruppen publiziert. Eine Einzelfallstudie eines pädiatrischen Kraniopharyngeom-Patienten mit hypothalamisch bedingter Adipositas berichtete von anhaltenden Veränderungen des Essverhaltens und eine BMI-Reduktion nach langfristiger intranasaler Oxytocin-Substitution[87]. Eine weitere klinische Studie untersuchte basale Oxytocin-Spiegel vor und nach einer standardisierten Mahlzeit. Zwar ergaben sich keine Veränderungen durch Nahrungsaufnahme als Stimulationsbedingung, doch konnten in einer Subgruppe der Patienten (N=6, mit Läsionen des anterioren Hypothalamus) verminderte basale Oxytocin-Spiegel nachgewiesen werden[88]. Direkt nach Oxytocin-Substitution zeigten genau die Patienten mit basal vermindertem Oxytocin eine Verbesserung der Fähigkeit, emotionale Gesichtsausdrücke richtig zu erkennen[89]. Eine weitere Studie mit Patienten unterschiedlicher hypophysärer Erkrankungen (davon 9 Kraniopharyngeom-Patienten) konnte schließlich ebenfalls reduzierte basale Oxytocin-Spiegel sowie verminderte empathische Fähigkeiten beobachten[90].
Basierend auf einer größeren Fallzahl bestätigen die aktuellen Daten der hier vorgestellten Dissertation diese ersten Hinweise auf einen Oxytocin-Mangel in Kraniopharyngeom-

Patienten. Allerdings präzisieren sie das sich aktuell entwickelnde Verständnis entscheidend: Die hier erstmalig in Patienten angewandte Stimulationsmethode liefert eine mögliche Erklärung dafür, warum in den vorherigen Studien teilweise nur in Subgruppen ein Oxytocin-Mangel nachgewiesen werden konnte. Aktuell publizierte Daten aus anderen neurowissenschaftlichen Fachbereichen bestätigen genau diese Notwendigkeit, zwischen basaler und stimulierter Oxytocin-Ausschüttung zu unterscheiden. Eine MRT-Studie in gesunden Probanden zeigte, dass einzelne Oxytocin-Gaben gegensätzliche Effekte auf das Volumen von grauer Hirnsubstanz im Hippocampus hatten im Vergleich zu wiederholten Oxytocin-Substitutionen[55]. Eine weitere Studie mit funktionellen MRT-Daten von menschlichen Probanden sowie gleichzeitig erhobenen neurochemischen Daten aus Tier-Experimenten konnte des Weiteren zeigen, dass situative und kontinuierliche Oxytocin-Substitution unterschiedliche neuronale Pfade aktivierten und zu unterschiedlichen Verhaltensweisen führten[56]. Diese Erkenntnisse dürfen in zukünftigen Substitutions-Studien bei Kraniopharyngeom-Patienten nicht unbeachtet bleiben. Beispielsweise sollte bei dem Versuch, hypothalamisch bedingte Adipositas zu behandeln, kontrolliert werden, ob basale Oxytocin-Spiegel das eigentliche Substitutionsziel darstellen oder ob die Verabreichung eher Stimulus-gebunden vorgenommen werden sollte, d.h. zeitlich assoziiert mit Nahrungsaufnahme im Tagesverlauf. Basierend auf den hier erhobenen Daten sollte eine ähnliche Differenzierung vorgenommen werden, wenn psychoaffektive Komorbiditäten der Kraniopharyngeom-Patienten adressiert werden.

Für derartige zukünftige Studien aber auch für den klinischen Alltag bietet das in dieser Dissertation erstmalig angewendete Paradigma einen vergleichsweise einfach durchführbaren Stimulationstest. Die hier begonnene Arbeit wird dazu bereits in einer neurowissenschaftlichen Studie bei Patienten mit Autismus-Spektrum-Erkrankung fortgesetzt, deren Ergebnisse aktuell noch ausstehen (Albantakis et al, *not yet published*).

Zusammenfassend lässt sich festhalten: Kraniopharyngeom-Patienten wiesen in dem hier vorgestellten Paradigma einen Oxytocin-Mangel auf. Ob nur stimulierte oder zusätzlich auch basale Oxytocin-Spiegel betroffen waren, war abhängig vom Ausmaß der Tumor-assoziierten Läsion. Oxytocin-Mangel konnte des Weiteren teilweise mit psychoaffektiven Defiziten in Verbindung gesetzt werden. Um langfristig das routinemäßige Screening auf Oxytocin-Mangel in den endokrinologischen Leitlinien zu verankern, sind vorerst weitere Studien sowohl bezüglich der Definition von Oxytocin-Standardwerten als auch der weiteren

Einengung der jeweiligen Zielsymptome notwendig. Dazu liefert die hier vorgestellte wissenschaftliche Arbeit entscheidende Grundlagen. Insgesamt weisen die aktuellen Ergebnisse daraufhin, dass zukünftige Therapiestudien mit Oxytocin einen maßgeblichen Beitrag dazu leisten könnten, den bei Kraniopharyngeom-Patienten verhältnismäßig hohen Leidensdruck und die manifesten Einschränkungen der Lebensqualität nachhaltig zu verbessern.

5 Publication 1

De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function

Dorothea Gebert* (1), Matthias K. Auer* (1,2), Mareike R. Stieg (1,2), Martin T. Freitag (3), Madlén Lahne (1), Johannes Fuss (4), Katharina Schilbach (2), Jochen Schopohl (2), Günter K. Stalla (1), Anna Kopczak (1)

*both authors contributed equally to this work and thus share the first authorship

Affiliations:

(1) Research Group Clinical Neuroendocrinology, Max Planck Institute of Psychiatry

(2) Medizinische Klinik und Poliklinik IV, Klinikum der Universität München

(3) Department of Radiology, German Cancer Research Center, Heidelberg

(4) Human Behavior Laboratory, Institute for Sex Research and Forensic Psychiatry, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Keywords: Hypothalamus, Craniopharyngioma, Oxytocin, Depression, Anxiety, Empathy

Psychoneuroendocrinology 88 (2018) 61–69

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function

Dorothea Gebert[a,1], Matthias K. Auer[a,b,*,1], Mareike R. Stieg[a,b], Martin T. Freitag[c], Madlén Lahne[a], Johannes Fuss[d], Katharina Schilbach[b], Jochen Schopohl[b], Günter K. Stalla[a], Anna Kopczak[a]

[a] Research Group Clinical Neuroendocrinology, Max Planck Institute of Psychiatry, Munich, Germany
[b] Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany
[c] Department of Radiology, German Cancer Research Center, Heidelberg, Germany
[d] Human Behavior Laboratory, Institute for Sex Research and Forensic Psychiatry, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ARTICLE INFO

Keywords:
Hypothalamus
Craniopharyngioma
Oxytocin
Depression
Anxiety
Empathy

ABSTRACT

Despite the high prevalence of panhypopituitarism and diabetes insipidus in patients with craniopharyngioma (CP), little is known about the functioning of the neuropeptide oxytocin in these patients. This is of special interest as tumor-associated lesions often impair sites critical for oxytocin production and release, and affective dysfunction in CP links with elsewhere reported prosocial, antidepressant and anxiolytic oxytocin effects. Using a prospective study-design, we tested whether oxytocin is reduced in CP-patients, and whether altered oxytocin levels account for affective and emotional dysfunction. 26 adult CP-patients and 26 healthy controls matched in sex and age underwent physical exercise, a stimulus previously shown to induce oxytocin release. Baseline and stimulated salivary oxytocin levels, as well as empathy, depression and anxiety scores were measured. Results showed that patients overall did not present with lower baseline oxytocin levels than controls ($F[1,30] = 0.21$, $p = 0.649$), but baseline oxytocin levels were indeed reduced in patients with hypothalamic damage, as assessed by MRI-based grading ($F[2,9.79] = 4.54$, $p = 0.040$). In response to exercise-induced stimulation, *all* CP-patients showed a blunted oxytocin-release compared to controls ($F[1,30] = 9.36$, $p = 0.005$). DI was not associated with oxytocin levels. Regarding affective function, unexpectedly, higher *baseline* oxytocin was related to higher trait anxiety ($b = 2.885$, $t(43) = 2.421$, $p = 0.020$, CI[.478; 5.292]); the positive link with higher depression failed to reach statistical significance ($b = 1.928$, $t(43) = 1.949$, $p = 0.058$, CI[−0.070; 3.927]). A blunted *oxytocin-release* was linked with higher state anxiety ($b = -0.133$, $t(43) = -2.797$, $p = 0.008$, CI [-0.230; −0.037]). Empathy was not associated with oxytocin measures. In conclusion, we observed reduced baseline oxytocin levels only in CP-patients with hypothalamic damage. Exercise-induced stimulation de-masked an oxytocin-deficiency in all CP-patients. Baseline oxytocin levels and stimulated OT-responses might have different effects on affective function, which should be considered in future substitution paradigms.

1. Introduction

Craniopharyngiomas (CP) are rare epithelial tumors arising along the path of the craniopharyngeal duct with an overall incidence of 0.13 cases per 100,000 person-years (Bunin et al., 1998). Though histologically benign, they are associated with a high degree of morbidity. This is due to their disadvantageous location, growth pattern, and the consequences of their surgical and radiotherapeutical treatment. Up to 85% of patients suffer from hormonal deficiencies because of damage to the pituitary gland (Duff et al., 2000). About 95% show suprasellar extensions, putting basally-located hypothalamic nuclei at risk (Karavitaki et al., 2005), commonly resulting in hypothalamic dysfunction such as hyperphagia, obesity, and severe homeostatic imbalances (Karavitaki et al., 2006; Müller, 2014; Wijnen et al., 2017). Treatment of these tumors includes routine screenings of hypothalamic-pituitary endocrine axes, and if necessary, pharmacological substitution of the hormones affected. Current clinical practice, however, does not assess the neurohypophyseal hormone oxytocin (OT). This is the case although there is both indirect and direct evidence for impairment of OT in CP.

* Corresponding author at: Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ziemsenstr 1, 80336 Munich, Germany.
E-mail address: Matthias.Auer@med.uni-muenchen.de (M.K. Auer).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.psyneuen.2017.11.006
Received 11 August 2017; Received in revised form 9 November 2017; Accepted 10 November 2017

First, indirect evidence comes from CP-patients often showing anatomical lesions which in theory should affect both OT-production and –release: OT is produced in the same hypothalamic nuclei (supraoptic and paraventricular nuclei, SON/PVN) and released from the same pituitary region (posterior pituitary gland) as anti-diuretic hormone (ADH). This hormone, responsible for the sensation of thirst and renal re-absorption of free water, is known to be deficient in at least one third of CP-patients (DeVile et al., 1996; Karavitaki et al., 2005). ADH-imbalances then result in the symptoms of diabetes insipidus (DI). Yet, while clinical tests and pharmacological substitution for DI are hallmarks of CP-treatment, OT is currently neither measured nor substituted in clinical routine.

Second, in addition to these anatomical parallels, psychoemotional impairment in CP-patients mirrors some of the assumed functional effects of OT. Previously only known for its role in child birth, there is now a rapidly growing body of literature linking OT with empathy and psychopathology: It has been shown to improve the ability to empathize in healthy people and enhance social awareness in patients of the autism spectrum (Feeser et al., 2015). Lower endogenous OT has also been linked with higher anxiety levels in children (Carson et al., 2015), while intranasal OT administration appears to buffer amygdala activation in response to fear-inducing stimuli in healthy adults (Kirsch et al., 2005) as well as reduce fear reactivity (Labuschagne et al., 2010) and improve self-representations in patients with anxiety disorder (Guastella et al., 2009). OT also increases attention to happy stimuli in depressed patients (Domes et al., 2016), possibly representing a new treatment option for depressive symptoms (Neumann and Landgraf, 2012). Mirroring these OT-effects, CP-patients show increased psychosocial morbidity (Pereira et al., 2005): Psychopathological symptoms include depression, anxiety and social withdrawal, as well as greater harm avoidance and fatigability both in childhood-onset as well as adult CP-patients (Karavitaki et al., 2005; Karavitaki et al., 2006; Müller, 2014; Roemmler-Zehrer et al. 2017; Wijnen et al., 2017). The causes for affective impairment in CP may certainly be multi-factorial. Particularly the effect of concomitant obesity should not be underestimated. However, it is tempting to assume that at least some of the known difficulties are attributable to currently undiagnosed OT insufficiencies.

In contrast to the anatomical and psychopathological parallels, direct evidence for the impairment of OT in CP is scarce. A single case study indicated that intranasal OT in a child with CP did improve the child's desire for socialization and affection towards her family (Cook et al., 2016). A recent study in childhood onset CP suggests that OT-levels and positive treatment effects of OT administration might be hypothalamic lesion-dependent: basal salivary OT-levels did not differ between patients and healthy controls, neither at baseline, nor 1 h after intake of a standardized meal (Daubenbüchel et al., 2016). Baseline levels were only lower in a small subgroup of patients with anterior hypothalamic damage (N = 6). Subsequent administration of OT in this subgroup improved the previously impaired ability to categorize negative emotions (Hoffmann et al., 2017). Normal OT-levels at baseline, however, have not been found consistently. A recent study reported reduced salivary OT-levels at baseline and reduced empathic abilities in patients with anterior hypopituitarism, including 9 CP-patients, compared to healthy controls (Daughters et al., 2017). In this case, however, extent of hypothalamic lesion was not controlled for.

As OT-effects in vivo likely rely on short-acting release in response to certain cues such as stress, touch, sexual stimulation or emotion perception (Bartz et al., 2011; de Jong et al., 2015; Meyer-Lindenberg et al., 2011; Wotjak et al., 2001), it appears reasonable to perform a stimulation when measuring OT, similar to stimulation tests used for diagnosis of other endocrine dysfunction. This way, not only baseline levels but also the responsiveness of the OT-system can be assessed, demasking a possibly underlying deficiency more reliably. In the current study, we therefore aimed to assess OT and its link with affective function in CP-patients by measuring OT-levels both at baseline and after stimulation. Since we wanted a paradigm easily applied in clinical routine, we chose a simple physical exercise regimen as stimulation method, since exercise has previously been shown to stimulate OT-release (de Jong et al., 2015). Regarding OT-measurements, we chose to collect salivary OT, a method validated in various previous studies (Daubenbüchel et al., 2016; Daughters et al., 2017; de Jong et al., 2015; Fujii et al., 2016; Grewen et al., 2010). Using a more direct representation of central OT-levels, i.e. OT in cerebrospinal fluid (CSF), would present a technique too invasive for daily clinical practice. Furthermore, while the underlying mechanisms are still unclear, it has been shown that central and peripheral OT-levels are closely interconnected: administration of OT in the periphery (intravenously and intranasally) leads to elevated OT-levels in CSF (Freeman et al., 2016; Striepens et al., 2013) as well as to changes in centrally generated behaviours (Bartz et al., 2011; Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011). In addition, it has been shown recently that peripheral OT can even cross the blood brain barrier back into the brain, directly affecting OT-levels in CSF (Lee et al., 2017) although it remains to be shown if endogenous OT from peripheral sources can cross the blood brain barrier and therefore influence CSF levels.

We nonetheless deem salivary OT to provide a non-invasive and feasible window into the functioning of the OT-system in our participants.

We expected saliva OT-levels at baseline to be lower in CP compared to healthy controls (HC), especially in patients with hypothalamic damage or symptoms of DI. We further expected patients to present with a blunted OT-response to physical exercise. Lastly, we wanted to assess the functional relevance and possible treatment implication of OT in this patient group. We expected that reduced OT-levels would be linked with reduced empathy and that it would at least partially explain affective dysfunction, with lower OT levels being linked to higher anxiety and higher depression scores on clinically established questionnaires.

2. Subjects and methods

2.1. Participants

Patients were recruited from the Neuroendocrine Outpatient Unit of the Max-Planck Institute of Psychiatry (MPIP) and the Endocrine Department of the Medical Clinic IV, Ludwig Maximilian University, Munich, Germany. Eighty eligible patients aged 18–65 years were identified by the local electronic databases and invited both by letter and phone to participate in the study. Reasons for non-participation were: letters did not reach their recipient (n = 5), not interested in the study in general (n = 4), high effort to participate in the study (n = 10), living too far away (n = 19), not having the time to participate due to work-related or personal liabilities (n = 16). Finally, N = 26 patients participated in this study. N = 26 controls were recruited by public advertising and were only included if they had not been using hormonal contraceptive medication during the previous 6 months before study. They were rewarded with 50€ for participation. Patients and controls were matched in sex (50% women in each group) and age (patients: 39.7 ± 12.1 years, controls: 36.7 ± 12.8 years). Patients and controls also reported similar habits regarding smoking, drinking, and physical exercise. Patients, however, had higher BMI-values than healthy controls (patients: 30.6 ± 8.5 kg/m^2, controls: 25.2 ± 6.5 kg/m^2; $p = 0.012$). Statistical analyses included corrections for this difference. For further clinical characteristics of CP-patients, see Table 1.

The prospective study was approved by the local ethics committee (#712-15) and conducted in accordance with the 2013 Declaration of Helsinki. All participants gave their written informed consent.

2.2. Oxytocin measurements

52 participants arrived at the outpatient unit of the MPIP at 8:30

Table 1
Clinical characteristics of craniopharyngioma patients (n = 26) in this study.

Hypothalamic damage and pituitary insufficiency		Usage of substitution medication		Surgery-related characteristics	
Hypothalamic damage	n	Corticotrophic	n	Type of surgery	n
Unable to classify	4	Hydrocortisone	18	Transcranial	23
Grade 0	7	Plenadren	4	Transphenoidal	3
Grade 1	8	Mean dosage: 19.75 ± 5.50 mg		**Radiation**	4
Grade 2	7			**Ommaya-Reservoir**	3
Number of affected anterior pituitary axes		**Vasopressin-Analoga**		**Weight gain after surgery**	
Any	25	Tablets	9	Yes	21
0	1	Spray	7	No	4
1	1	Mean dosage: 0.22 ± 0.26 mg		Unclear	1
2	1			**Amount of weight gain**	
3	2	**Thyreotrophic**		Weight gain 1–10 kg	7
4	21	L-Thyroxin	24	Weight gain > 20 kg	12
		Somatotrophic		Amount unclear	2
Type of affected anterior pituitary axis		Growth hormone	15		
Corticotrophic	22	**Gonadotrophic (females)**	10		
Thyreotrophic	24	Transdermal	3		
Somatotrophic	24	Oral	5		
Gonadotrophic	23	Contraceptive Pill	2		
		Not substituted/menopausal	4		
Diabetes insipidus	17	**Gonadotrophic (males)**	9		
Daily drinking > 3l	4	Testosterone undecanoate	7		
Of which don't have DI medication	1	Human chorionic gonadotropin	2		

Notes: Hypothalamic damage is classified according to a previously used grading system (Muller et al., 2012) with *grade 0* = no hypothalamic lesions, *grade 1* = anterior hypothalamic lesions, *grade 2* = anterior and posterior hypothalamic lesions including mammillary bodies. Patients' mean age at first diagnosis was 24.5 ± 13.8 years, and mean years since first diagnosis were 15.2 ± 11.5 years.

Table 2
Detailed exercise paradigm using a bicycle ergometer for oxytocin stimulation.

Exercise steps	Duration overall in minutes	Duration of each step in minutes	Wattage (W) at which participants exercise during each step	When to measure lactate	When to terminate exercising
–	Take baseline salivary sample				
1	0–2	+2	50 W	–	–
2	2–7	+5	100 W	between step 2 and 3	Stop after step 2 if lactate > 4.0 mmol/l
3	7–12	+5	200 W – age in years	between step 3 and 4	Stop after step 3 if lactate > 4.0 mmol/l
4	12–x (max. overall 25)	+x (max. +13)	220 W – age in years	every 2–3 min	Stop when lactate > 4.0 mmol/l or after max. of 25 min duration overall
–	Take stimulated salivary sample				

AM in fasting state (food > 12 h, water > 1 h). Patients suffering from hypopituitarism were asked to take their morning hydrocortisone and L-thyroxin dose approximately one hour before arrival. Having undergone a physical examination, one patient was excluded due to ECG abnormalities and one patient withdrew at this point because of high effort. Three controls were excluded because they reported that they were not in fasting state despite contrary instructions. Salivary OT was collected using a cylindrical chewing swab (Salivetten© 51.1534.002, Nümbrecht, Germany), after which participants exercised on a bicycle ergometer (Kettler Ergometer TXl, Germany). Lactate in capillary blood was measured repeatedly (Lactate Pro2, Japan (Pyne et al., 2000)) in order to standardize for individual exertion. A detailed description of the exercise paradigm can be found in Table 2. Briefly, participants exercised for > 7 min, and then stopped either a) whenever lactate levels reached > 4 mmol/l (considered to be the anaerobic threshold (Beneke, 1995)), or b) if lactate continuously remained < 4 mmol/l when participants either reached physical exhaustion or after overall 25 min of exercise. Saliva samples were taken immediately afterwards. Three patients stopped prematurely, one due to feeling dizzy and two others because of not willing to exercise strenuously. Two saliva samples were not collected correctly due to technical difficulties and participants not chewing enough on the swab. Thus, from patients, two baseline samples and 22 complete pairs (baseline + after stimulation), and from controls 23 complete pairs were available for analysis.

2.3. Sample preparation

Samples were centrifuged at 3000*g* for 5 min at 4 °C, as recommended by Riagnosis© (Munich, Germany) and then stored at −20 °C. After data collection was finished, all collected samples were treated identically (i.e. extracted and assayed in the same batch at the same time) to eliminate interassay variation. This is a major advantage over studies that used different procedures or assays without extraction as this likely reduces validity (Leng and Sabatier, 2016; Szeto et al., 2011). The lyophilised extract was then assayed using a highly sensitive and specific radioimmunoassay with a detection limit of 0.1 µg/sample, cross-reactivities with related peptides of < 0.7% and interassay variabilities < 10% (RIAgnosis, Munich, Germany), which has been validated in previous animal and human studies (de Jong et al., 2015; Kagerbauer et al., 2013; Neumann and Landgraf, 2012).

2.4. Affective function: questionnaires

In order to explore effects of OT-levels on depression and anxiety, all participants self-completed a set of questionnaires. Depressive symptoms were measured using the Beck-Depression-Inventory-II (BDI-II, range 0–63) (Beck et al., 1961), anxiety levels with the State-Trait-Anxiety-Inventory (STAI, range 20–80 each) (Spielberger et al., 1970). OT-related empathy function was assessed using the Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004). For all questionnaires,

official German translations were used.

2.5. Hypothalamic lesion: MRI

Based on patients' most recent post-surgical MRI-data, a board-certified radiologist blinded to the clinical data assessed the degree of individual hypothalamic damage according to a previously applied grading system (Muller et al., 2012), assigning patients to one of three groups: grade 0 = no hypothalamic lesion, grade 1 = anterior hypothalamic lesions sparing mammillary bodies, or grade 2 = anterior and posterior hypothalamic lesion including mammillary bodies.

2.6. Statistical analysis

Data were checked for normality and homogeneity of variance. First, in order to test the underlying assumption that the exercise paradigm had presented a sufficient stimulus for participants to release oxytocin, we conducted a paired *t*-test comparing baseline and stimulated OT-levels within the control group. Then, to assess differences in OT-levels between patients and controls, mixed-measures general linear modeling (GLM) was conducted, using *time* (within-subjects) and *group* (between-subjects), while controlling for the exercise-related factors of *amount of time* exercised, *wattage* reached during stimulation, and *peak lactate level* at the end of exercising, as well as controlling for confounders *sex, age*, and *BMI*. Subgroup analysis within patients was conducted with GLM, assessing the effects of the disease specific features *grade of hypothalamic damage*, *diabetes insipidus* and *dosage of ADH-analogue* on baseline OT measures and its changes following stimulation. Since the homogeneity of variance assumption was violated in the subgroup analysis of hypothalamic damage, we used the more robust Welch-ANOVA to correct for Type 1 error rates (Moder, 2010). Bonferroni correction was used for post-hoc comparisons between MRI-groups. Assessing affective function, we first used GLM to compare questionnaires scores between groups while controlling for BMI. We then used linear regression to analyse the relationship between OT measures and those affective function scores, in which patients significantly differed from controls. The most parsimonious model was reached through backwards selection, which allowed us to observe the relative impact of OT factors even in those cases where they were not included in the final model. Normality of residuals was checked with Q–Q plots, multicollinearity with a tolerance of $T > 0.1$ and a variance inflation factor of $VIF < 10$. Auto-correlation was assessed with the Durbin-Watson test, and homoscedasticity visually checked with scatterplots. Statistical analysis was performed with SPSS 24 ® for Windows (IBM Corporation, USA), with $p < 0.05$ considered statistically significant.

3. Results

3.1. Oxytocin at baseline and stimulation effects

In order to check that the paradigm had actually stimulated participants to release additional OT, we first compared mean OT-levels before and after stimulation in healthy participants only. A paired *t*-test revealed a significant increase with stimulation ($t[22] = -1.83$, $p = 0.040$). We then applied general linear modeling to assess differences between groups: OT-levels overall did not differ between patients and controls (factor *group*: $F[1,30] = 0.21$, $p = 0.649$) and across groups, oxytocin levels also did not differ before and after stimulation (factor *time*: $F[1,30] = 3.34$, $p = 0.078$). However, patients and controls differed in their respective response to stimulation, i.e. healthy controls showed an OT-increase with exercise (+24.8%) whereas CP-patients did not (-13,7%; interaction *time* x *group*, $F[1,30] = 9.36$, $p = 0.005$, for means see Table 3). Regarding confounding variables corrected for in this model, OT-levels and OT-response to exercise were unaffected by the covariates *sex* and *age*. In line with patients in this study having a significantly higher BMI ($p < 0.012$) than controls, however, we found OT-increase to co-vary with BMI. Specifically, participants with higher BMI showed less OT-response to exercise than those with lower BMI (interaction of *time* x *BMI*, $F[1,30] = 5.10$, $p = 0.031$). Regarding exercise-related parameters, stimulated OT-response across groups varied with neither the amount of time participants spent exercising in total (interaction of *time x amount of time exercised*, $F[1,30] = 1.26$, $p = 0.271$), nor with the maximum *wattage* participants reached during exercise (interaction of *time x wattage*, $F[1,30] = 0.10$, $p = 0.755$), nor with the peak *lactate level* participants presented at the end of exercising (interaction of *time x lactate* $F[1,30] = 0.31$, $p = 0.581$). Between-group comparisons showed that patients exercised for equally as many minutes ($p = 0.538$), reached maximum wattage levels that were not significantly lower ($p = 0.332$), and presented with final lactate levels not significantly different ($p = 0.128$) from those of healthy controls (Table 3). Finally, to ensure that the observed non-response in salivary OT-levels was not due to a difference in saliva secretion rates, we also compared the amount of retrieved saliva from patients before and after stimulation with that of healthy controls. There was no significant difference between groups, neither at baseline ($p = 0.386$) nor after stimulation ($p = 0.351$).

Table 3
Exercise-related parameters and affective function scores of craniopharyngioma patients (CP) and healthy controls (HC).

	CP	HC	p-Values
Baseline OT-levels in pg/ml	1.46 ± 1.20	1.33 ± 1.13	*p = 0.731*
Stimulated OT-levels in pg/ml	1.26 ± 0.87	1.66 ± 1.76	*p = 0.391*
Time exercised in min	13.6 ± 4.3	13.0 ± 3.8	p = 0.538
Wattage in W	153.25 ± 39.31	162.71 ± 18.60	p = 0.332
Lactate in mmol/l	4.23 ± 1.23	4.71 ± 0.94	p = 0.128
EQ	48.0 ± 14.4	45.8 ± 9.0	p = 0.491
BDI-II	12.0 ± 10.9	3.2 ± 4.1	**p = 0.002**
STAI1	36.5 ± 11.4	32.2 ± 9.2	p = 0.084
STAI2	39.3 ± 11.3	32.8 ± 8.0	**p = 0.042**

Notes: Values represent means ± standard deviation. Time exercised indicates the amount of time in minutes that participants spent exercising. Wattage pertains to the maximum wattage level that participants reached during exercise. Lactate refers to the peak lactate level measured at the end of exercising. Affective function scores include measures of empathy levels (empathy quotient, EQ), depressive symptoms (Beck Depression Inventory–II, BDI-II) as well as state and trait anxiety levels (State-Trait-Anxiety-Inventory: STAI1 represents subscores for state anxiety, STAI2 represents subscores for trait anxiety).
Bold values indicate significant differences between both groups.

3.2. Effects of hypothalamic damage and diabetes insipidus

In a subgroup analysis within CP-patients, we assessed the effects of hypothalamic damage based on MRI-data and diagnosis of DI on OT-levels. Hypothalamic damage had a significant effect on baseline OT levels (Levene's Test $p = 0.001$; corrected Welch-ANOVA $F[2,9.79] = 4.54$, $p = 0.040$) but not on OT increase after exercise ($F[2,19] = 0.94$, $p = 0.410$). Bonferroni post-hoc comparisons between baseline measures showed that patients *without* hypothalamic damage showed significantly higher baseline OT-levels compared to patients with grade 2 lesions ($p = 0.024$), and there was a trend for higher OT levels compared with grade 1 ($p = 0.077$) (see Fig. 1). The latter two groups did not differ ($p = 0.999$). Diabetes insipidus parameters were not associated with OT-levels in CP. Presence of DI ($F[1,17] = 0.36$, $p = 0.558$) did not have a main effect on OT-levels. It also did not affect OT-level change in response to exercise (*time* x *DI*: $F[1,17] = 0.91$, $p = 0.354$). The same was true for dose of ADH-analogues (for mean dosage, see Table 1), with neither a significant main effect ($F[1,17] = 0.003$, $p = 0.961$) nor an interaction effect (*time* x *dose ADH-analogue*: $F[1,17] = 0.32$, $p = 0.578$).

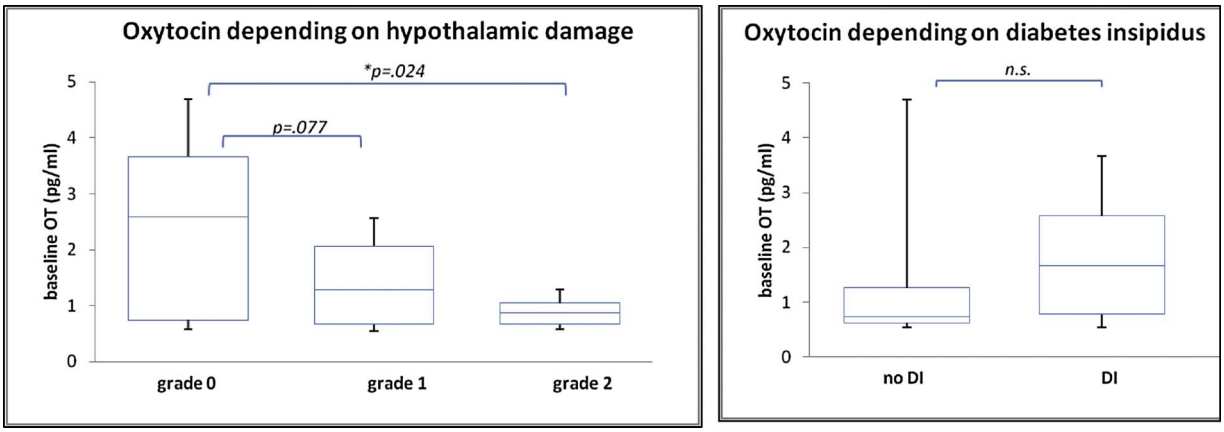


Fig. 1. Baseline oxytocin levels within craniopharyngioma patients differs according to hypothalamic damage but not presence of diabetes insipidus.
Legend: Horizontal lines indicate mean oxytocin levels at baseline. Top and bottom edges of the box depict the 1st and 3rd quartile. Whiskers indicate minimum and maximum values. Hypothalamic damage is classified according to a previously used grading system (Muller et al., 2012) with *grade 0* = no hypothalamic lesions, *grade 1* = anterior hypothalamic lesions, *grade 2* = anterior and posterior hypothalamic lesions including mammillary bodies. DI, diabetes insipidus; n.s., non-significant.

3.3. Oxytocin and affective function

Mean psychoemotional scores are presented in Table 3. Using general linear modeling to correct for BMI, patients showed significantly higher depression levels, $F(1.42) = 10.414$, $p = 0.002$, and significantly higher trait anxiety levels, $F(1.42) = 4.401$, $p = 0.042$, in comparison to healthy controls. There was a trend for patients showing higher levels of state anxiety, $F(1.42) = 3.142$, $p = 0.084$, but there was no significant difference in empathy scores, $F(1.42) = 0.483$, $p = 0.491$. Regression analysis showed that empathy scores were not significantly related to any of the included factors, i.e. sex, age, BMI, or group (CP vs. controls), $F(1.44) = 1.307$, $p = 0.259$. There was a trend for higher depression scores to correlate with higher baseline OT levels ($b = 1.928$, $t(43) = 1.949$, $p = 0.058$, not significant). Together with the significant factor of belonging to CP-group ($b = -6.764$, $t(43) = -2.994$, $p = 0.005$), this accounted for 26.7% of variance in the most parsimonious model, $F(2.43) = 7.471$, $p = 0.002$. Trait anxiety scores significantly correlated with baseline OT-levels ($b = 2.885$, $t(43) = 2.421$, $p = 0.020$), which together with the non-significant factor of being of female sex ($b = -4.589$, $t(43) = -1.688$, $p = 0.099$), presented the most parsimonious model accounting for a significant proportion of variance in trait anxiety scores (19.0%, $F(2.43) = 4.797$, $p = 0.013$).

Δ%-OT was neither related to depression nor trait anxiety scores. It did, however, significantly predict state anxiety scores alone ($b = -0.133$, $t(43) = -2.797$, $p = 0.008$), linking lower Δ%-OT with higher state anxiety, and accounting for 15.7% of the observed variance, $F(1.43) = 7.826$, $p = 0.008$. See Fig. 2 for an illustration of the relationship between OT-measures and affective function.

4. Discussion

4.1. Reduced baseline levels of oxytocin only in patients with hypothalamic damage

CP-patients did not have lower OT-levels at baseline than healthy controls, indicating that baseline OT-deficiency is not a general characteristic of patients suffering from this tumor and its sequelae. While this replicates previous results of a study in childhood onset CP (Daubenbüchel et al., 2016), it nevertheless remains surprising, as it suggests that baseline OT-levels are relatively unaffected by pituitary damage. In our study, patients suffered from extensive clinical pituitary impairment, with 84.5% showing complete anterior pituitary insufficiency and 60% showing both complete anterior and posterior pituitary insufficiency. These patients are unlikely to have a pituitary gland able to normally release OT. A possible explanation pertains to evidence that OT can be expressed in endocrine organs peripherally (Elands et al., 1990; Ivell et al., 1997, 1990; Jankowski et al., 1998), thus explaining preserved salivary OT-levels despite pituitary impairment. Alternatively, there is evidence from early animal and human studies suggesting that parahypophyseal release mechanisms might develop after pituitary tumor growth or surgery (Beck and Daniel, 1959; Moll and de, 1962; Sloper, 1960). While the exact underlying mechanisms remain speculative, the present results suggest that pituitary damage can functionally spare baseline OT-release.

OT, however, is probably not preserved in the presence of hypothalamic damage. Subgroup analysis showed that in patients with extensive hypothalamic damage (grade 2), baseline OT-levels were lower than in patients *without* hypothalamic damage. In patients with damage only affecting anterior nuclei (grade 1), OT-levels were also lower, but this failed to reach statistical significance ($p = 0.077$). Our data differs in this regard to the previous study in childhood onset CP (Daubenbüchel et al., 2016), which reported reduced levels with anterior damage but normal levels with lesions to both anterior and posterior regions. Since we are not aware of a mechanism that rehabilitates OT-release through additional damage to posterior nuclei, we attribute the variance between results to small sample sizes in both studies. Thus, baseline OT-deficiency is not CP-specific; but instead probably hypothalamic lesion-specific.

4.2. Oxytocin-deficiency is de-masked with stimulation

Salivary OT-levels in healthy controls increased with physical exercise, whereas in CP-patients it did not. This dynamic OT-deficiency was found in all patient subgroups, irrespective of hypothalamic damage. On the one hand, this could indicate that, in contrast to baseline levels, immediate fast-acting OT-release might indeed require an intact posterior pituitary route and thus would be impaired by pituitary damage. In that case, dynamic OT release would also be deficient in various other diseases affecting posterior pituitary structural integrity, such as adenomas or inflammatory processes. As another explanation, the blunted OT-response might be an indirect consequence of anterior pituitary insufficiency in CP. It is currently unclear how additional OT-release after stimulation is mediated; it might depend solely on direct release from the pituitary gland, but there is also evidence that OT is closely intertwined with other endocrine axes (Elands et al., 1990; Ivell et al., 1997, 1990; Jankowski et al., 1998). Therefore, its release might depend on the functionality of these axes in turn. This is supported by a recent study reporting patients with anterior hypopituitarism (including 9 CP-patients) to show lower salivary OT-levels than healthy

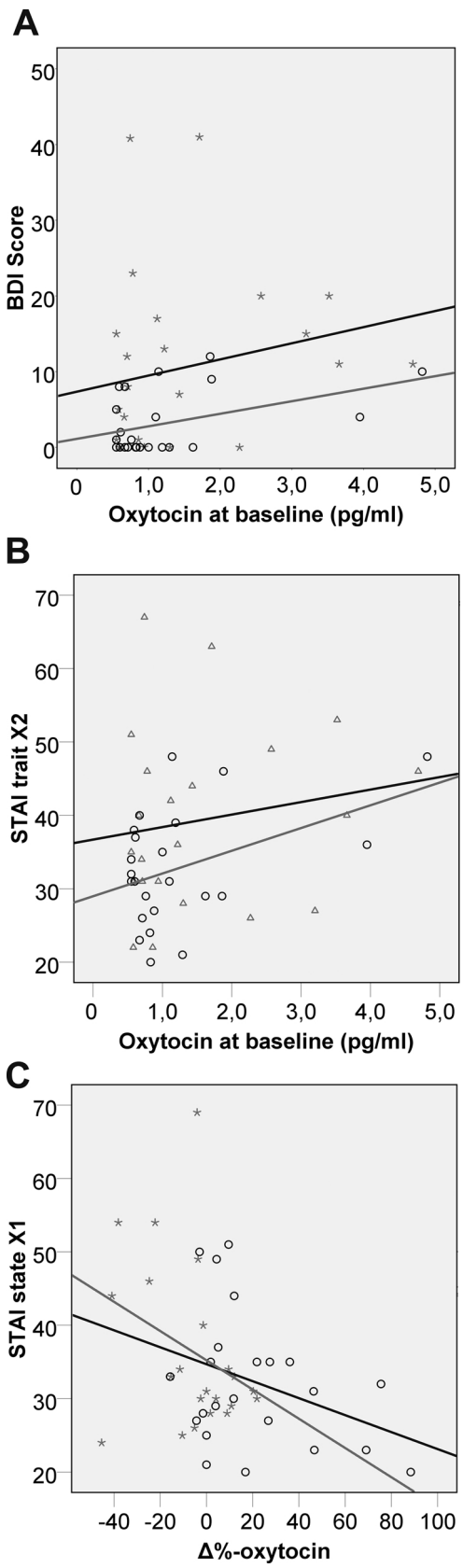


Fig. 2. Depression and trait anxiety are positively associated with baseline oxytocin levels; higher state anxiety is associated with a reduced oxytocin-response to stimulation. Regression coefficients of craniopharyngioma patients (grey stars, grey regression line) and healthy controls (black circles, black regression line) are depicted separately in each graph.
(A) shows the relationship between symptoms of depression (assessed by BDI-II scores) and oxytocin levels at baseline (pg/ml), (B) shows the relationship between trait anxiety scores (assessed by STAI2 scores) and oxytocin levels at baseline (pg/ml), and (C) the relationship between state anxiety scores (assessed by STAI1 scores) and the percent oxytocin level change in response to stimulation.

controls (Daughters et al., 2017). More specifically, there is also evidence for a positive correlation between OT- and cortisol-levels (Heinrichs and Domes, 2008), in particular for similar release patterns in response to exercise (de Jong et al., 2015). Most of our CP-patients suffered from secondary adrenal insufficiency, and thus likely lacked an exercise-mediated stimulation of the adrenal glands. It is possible that this in turn led to the reduced OT-response to physical stimulation. Unfortunately, the number of individuals without pituitary or adrenal insufficiency in our CP group was too small to draw solid conclusions. In addition, the exact relationship between cortisol- and OT-dynamics is still under debate (Heinrichs and Domes, 2008). Nevertheless, whether an impaired pituitary-adrenal axis additionally affects OT-release, merits further investigation, in which patients with isolated secondary adrenal insufficiency, e.g. NFPA, might present a suitable control group. As a third possible reason, the observed differences between CP and controls might have resulted from methodological issues. Exercise is potentially a questionable stimulus in participants who are overweight. Patients might have exercised less strenuously and be less stimulated to release OT. However, we would argue this to be unlikely. Patients and controls reported similar weekly exercise habits, and during stimulation, patients exercised equally as long and at similar intensity, reaching similar maximum wattages on the ergometer and presenting with similar peak serum lactate levels as controls. The observed association between higher BMI and lower OT-response to stimulation is thus unlikely to be a sign of patients having exerted themselves less. Instead, BMI might act as indicator for an impaired OT-responsiveness. Interestingly, this is corroborated by the previous study in childhood-CP, which found that CP-patients with high BMI showed smaller OT-changes – in that case in response to eating a standardized meal (Daubenbüchel et al., 2016). The BMI-associated reduced OT-responsiveness therefore has now been observed in two separate CP-studies, and appears independent from the particular mode of stimulation. This tentatively supports the previous claim that OT-substitution might present a treatment option for diseases with hypothalamic dysfunction and associated obesity (Daubenbüchel et al., 2016).

4.3. DI does not predict OT-levels

In our study, OT-measures were unaffected by the presence of DI, both at baseline and after stimulation. They were also unrelated to doses of ADH-analogues. Anecdotally, the patient with the highest desmopressin dosage of 1 mg/d was amongst those with the highest baseline OT-levels, and showed a 9% increase following exercise. The previous study measuring OT-levels in CP also reported DI as having no effect on baseline OT (Daubenbüchel et al., 2016), and a different study comparing OT-levels in pituitary patients showed no difference between patients with and without central diabetes insipidus (Daughters et al., 2017). All of these results are surprising, given the proximity of ADH- and OT-producing hypothalamic neurons in SON and PVN, as well as the parallel release-mechanisms through the posterior pituitary. On a methodological level, diagnosis of DI might be an unsuitable indicator for true ADH-function. However, we corrected for miscategorisation by counting patients as DI-positive either if they used ADH-substitution therapy or (to counter possible under-diagnosis) if they did not use medication but reported clinical signs of DI (n = 1). At this point, it remains unclear why OT-insufficiency does not parallel clinical symptoms of ADH-insufficiency. However, until this question is addressed through further research, DI does not present a suitable

proxy for suspected OT-insufficiency in CP.

4.4. Clinical relevance for affective function

Our data revealed two main aspects about OT and affective function. First, baseline OT-deficiency is unlikely to be a contributing factor to elevated psychopathology in our sample of CP-patients. Neither reduced baseline OT levels nor a blunted response to stimulation significantly predicted elevated depression or trait anxiety scores. On the contrary, higher OT-levels at baseline predicted *higher* depression and *higher* trait anxiety scores. This is surprising since higher depression and anxiety was previously found to be associated with lower oxytocin

(for example in anorexia nervosa patients who are in remission, (Afinogenova et al., 2016)), and thus, our results contradict the currently prevalent appraisal of OT as an overall antidepressant and anxiolytic agent (for reviews, see Bartz et al., 2011; Neumann and Landgraf, 2012). There is, however, also supportive evidence for a positive correlation between OT-levels and psychopathological symptoms: Endogenous OT-levels can be increased in major depression (Parker et al., 2010), and OT-administration has been linked with greater post-natal depression and increased anxiety (Kroll-Desrosiers et al., 2017; Mah, 2016). Furthermore, higher subclinical depressive symptomatology in healthy adults is linked with higher saliva and plasma OT-levels, and a behavioural intervention aimed at reducing stress simultaneously reduced OT-levels (Holt-Lunstad et al., 2011). The underlying cause for these opposing results is unclear, and may indeed vary between underlying diseases. Regarding CP-patients we suggest that, based on our own results, baseline substitution of OT does not present a suitable treatment option for elevated affective dysfunction in CP.

Second, our data suggest a further conclusion, which might account for some of the observed discrepancies in the current literature: that baseline OT-levels on the one hand and OT-responsiveness to stimulation on the other hand might in fact have different effects on affective function. In direct contradiction to baseline levels, we found *lower* OT-release in response to exercise to be associated with *higher* state anxiety levels. This finding needs to be interpreted with caution, as patients showed only a trend for higher state anxiety levels compared to controls ($p = 0.084$). Thus, we deem substitution treatment for state anxiety in CP not to be warranted either – at least until future studies in larger patient samples replicate this finding. Nevertheless, our data provide a possibly important characterization for substituting or administrating OT: OT-effects might differ depending on timing of release/timing of administration; specifically, continuous baseline levels possibly influence affective function differently than dynamic short-term OT-changes in response to momentary cues.

Finally, while previous research found links between OT-levels and empathy (Feeser et al., 2015), this was not the case in our study. Empathy levels of CP-patients did not differ from controls, and empathy was associated with neither baseline OT-levels nor OT-responsiveness to stimulation. It is possible that variance within our sample was too small to reliably detect effects. It is also possible that using questionnaires posed a method not sensitive enough, and studies applying active social paradigms might yield different results in the future. Data from a very recent study further indicate that a suitable test to define the link between OT and empathy in pituitary patients still needs to be found: OT-levels predicted lower empathic abilities in patients with hypopituitarism only if they additionally suffered from DI. This was despite the fact that patients without DI presented with equally reduced salivary OT-levels and equally reduced empathic abilities in comparison to healthy controls, and presence of DI had not been found to affect OT-levels (Daughters et al., 2017).

4.5. Strengths and limitations

An important strength of our study pertains to measuring OT both at baseline and after stimulation in a well-characterized group suffering from this rare tumor entity. We showed that an OT-deficiency can be de-masked with exercise-induced stimulation. Importantly, the stimulation method is similar to the well-established exercise-electrocardiogram widely used in cardiology diagnostics, with the necessary equipment thus likely being available in most clinical settings. An important limitation of the present study pertains to the fact that, as of now, research still disagrees regarding the precise relationship between peripherally measured OT and centrally generated behaviour. Our results are based on peripheral OT-measures, which given the at times extensive pituitary and hypothalamic damage in our CP patients, quite possibly originate solely from peripheral sources. Since we did not measure central OT-levels directly, a limitation of this study is that we cannot exclude that central OT-levels might have influenced behavioural measures in a different manner than salivary OT-levels, and that indeed central OT-levels might have differed between groups. Future research, including more precise imaging technology or the use of biomolecularly tagged oxytocin, might be able to disentangle the possibly diverging effects of central and peripheral OT-levels on emotions and behaviour.

The results need to be appraised in the context of the small sample size despite our multi-centred recruitment approach. This is especially the case for subgroup analyses as well as for the interpretation regarding future OT-administration in state anxiety. The small sample size also made it not possible to undertake a more detailed analysis disentangling the effects of different patient characteristics, such as age at disease onset, actual weight gain since disease onset, and social aspects like current status of relationship. Whether (and how) these factors influence OT-levels and psychopathology in CP remains open to further research. As a further limitation, recruiting healthy controls with similar characteristics as patients (BMI) proved to be difficult and required statistical correction. In addition, there may be a selection bias as those patients might have been more willing to participate in this study who suffered from greater psychopathological burden. Furthermore, it is known that gonadal steroid hormones can influence OT-release (de Jong et al., 2015). While we did not directly measure gonadal hormone levels, we made sure to only include healthy controls who did not use hormonal medication like contraception, and to only include those patients, who according to their most recent medical files were adequately substituted (see Methods, Table 1). In the future, with higher resolution MRI, lesions might be analysed according to individual hypothalamic nuclei, not only general anterior and posterior regions, allowing for better differentiation between affected sites and a more detailed grading of hypothalamic damage, linking it to distinct functional deficits. The potential of a more detailed grading system has e.g. recently been demonstrated for the risk of developing obesity, one of the most clinically relevant sequelae in CP patients (Roth et al., 2015).

4.6. Outlook: OT-deficiency beyond affective function

In future studies, OT-deficiency will likely be relevant in other contexts: the possible interplay between OT and other endocrine axes might present a relevant research focus. In addition, it has been suggested elsewhere that OT plays an important role in cardio-protection (Jankowski et al., 2016), and that it might be a promising agent in the treatment of obesity (Amri and Pisani, 2016). Our present results corroborate the link between OT-deficiency and BMI, and given that obesity and long-term cardiovascular morbidity rates are high in CP-patients (Pereira et al., 2005), the here-demonstrated dynamic OT-deficiency might present a promising treatment target in the future. One study in a small sample of CP-patients has already demonstrated positive substitution effects for certain aspects of psychoemotional functioning, reporting patients to recognise negative emotions better immediately after nasal OT-administration (Hoffmann et al., 2017). Future OT-replacement studies in CP will likely focus on further

pathologies of this complex disease. While doing so, treatment efforts might benefit from differentiating between substituting baseline levels on the one hand and targeting dynamic short-term OT-responses on the other.

Author contributions

Dorothea Gebert and Matthias Auer contributed equally to this work and thus share the first authorship.

Conception and design: AK, DG, MA
Recruitment: AK, DG, KS, JS, GK
Data acquisition: MA, MS, DG
Data Analysis: DG, MA, MTF, JF
Drafting or Revising the script: DG, MA, AK, MTF

Funding

Anna Kopczak is supported by the Bavarian Gender Equality Grant (BGF) 2014.

Disclosure

The authors have nothing to disclose.

Acknowledgments

We express our gratitude to Marie-Luise Brandi for helping to recruit healthy subjects and to Kathrin Popp for support with data collection. We are particularly thankful for statistical advice from the Institute for Informatics, Biometrics, and Epidemiology. We also thank Caroline Sievers for supportive discussions of our study protocol. Rainer Landgraf helped with advice on oxytocin measurements. Fabian Wadsworth and Alexandra Clement proof-read the manuscript with regard to language. We thank our anonymous reviewers who really helped to improve earlier versions of this manuscript.

We gratefully thank all our patients and healthy controls for participation in our study.

References

Afinogenova, Y., Schmelkin, C., Plessow, F., Thomas, J.J., Pulumo, R., Micali, N., Miller, K.K., Eddy, K.T., Lawson, E.A., 2016. Low fasting oxytocin levels are associated with psychopathology in anorexia nervosa in partial recovery. J. Clin. Psychiatry 77, e1483–e1490.
Amri, E.Z., Pisani, D.F., 2016. Control of bone and fat mass by oxytocin. Hormone Mol. Biol. Clin. Investig. 28, 95–104.
Baron-Cohen, S., Wheelwright, S., 2004. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. J. Autism Dev. Disord. 34, 163–175.
Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15, 301–309.
Beck, E., Daniel, P., 1959. Some changes in the hypothalamus and proximal pituitary stalk after stalk section. J. Physiol.–London 146, 22–24.
Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.
Beneke, R., 1995. Anaerobic threshold, individual anaerobic threshold, and maximal lactate steady state in rowing. Med. Sci. Sports Exerc. 27, 863–867.
Bunin, G.R., Surawicz, T.S., Witman, P.A., Preston-Martin, S., Davis, F., Bruner, J.M., 1998. The descriptive epidemiology of craniopharyngioma. J. Neurosurg. 89, 547–551.
Carson, D.S., Berquist, S.W., Trujillo, T.H., Garner, J.P., Hannah, S.L., Hyde, S.A., Sumiyoshi, R.D., Jackson, L.P., Moss, J.K., Strehlow, M.C., Cheshier, S.H., Partap, S., Hardan, A.Y., Parker, K.J., 2015. Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. Mol. Psychiatry 20, 1085–1090.
Cook, N., Miller, J., Hart, J., 2016. Parent observed neuro-behavioral and pro-social improvements with oxytocin following surgical resection of craniopharyngioma. J. Pediatr. Endocrinol. Metab. 29, 995–1000.
Daubenbüchel, A.M.M., Hoffmann, A., Eveslage, M., Özyurt, J., Lohle, K., Reichel, J., Thiel, C.M., Martens, H., Geenen, V., Müller, H.L., 2016. Oxytocin in survivors of childhood-onset craniopharyngioma. Endocrine 54, 524–531.
Daughters, K., Manstead, A.S.R., Rees, D.A., 2017. Hypopituitarism is associated with lower oxytocin concentrations and reduced empathic ability. Endocrine 57, 166–174.
DeVile, C.J., Grant, D.B., Hayward, R.D., Stanhope, R., 1996. Growth and endocrine sequelae of craniopharyngioma. Arch. Dis. Child. 75, 108–114.
Domes, G., Normann, C., Heinrichs, M., 2016. The effect of oxytocin on attention to angry and happy faces in chronic depression. BMC Psychiatry 16, 92.
Duff, J.M., Meyer, F.B., Ilstrup, D.M., Laws Jr., E.R., Schleck, C.D., Scheithauer, B.W., 2000. Long-term outcomes for surgically resected craniopharyngiomas. Neurosurgery 46, 291.
Elands, J., Resink, A., De Kloet, E.R., 1990. Neurohypophyseal hormone receptors in the rat thymus, spleen, and lymphocytes. Endocrinology 126, 2703–2710.
Feeser, M., Fan, Y., Weigand, A., Hahn, A., Gärtner, M., Böker, H., Grimm, S., Bajbouj, M., 2015. Oxytocin improves mentalizing –pronounced effects for individuals with attenuated ability to empathize. Psychoneuroendocrinology 53, 223–232.
Freeman, S.M., Samineni, S., Allen, P.C., Stockinger, D., Bales, K.L., Hwa, G.G., Roberts, J.A., 2016. Plasma and CSF oxytocin levels after intranasal and intravenous oxytocin in awake macaques. Psychoneuroendocrinology 66, 185–194.
Fujii, T., Schug, J., Nishina, K., Takahashi, T., Okada, H., Takagishi, H., 2016. Relationship between salivary oxytocin levels and generosity in preschoolers. Sci. Rep. 6, 38662.
Grewen, K.M., Davenport, R.E., Light, K.C., 2010. An investigation of plasma and salivary oxytocin responses in breast-and formula-feeding mothers of infants. Psychophysiology 47, 625–632.
Guastella, A.J., Howard, A.L., Dadds, M.R., Mitchell, P., Carson, D.S., 2009. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34, 917–923.
Heinrichs, M., Domes, G., 2008. Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. Prog. Brain Res. 170, 337–350.
Hoffmann, A., Ozyurt, J., Lohle, K., Reichel, J., Thiel, C.M., Muller, H.L., 2017. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. Endocrine 56, 175–185.
Holt-Lunstad, J., Birmingham, W., Light, K.C., 2011. The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention. Psychoneuroendocrinology 36, 1249–1256.
Ivell, R., Hunt, N., Abend, N., Brackman, B., Nollmeyer, D., Lamsa, J.C., McCracken, J.A., 1990. Structure and ovarian expression of the oxytocin gene in sheep. Reprod. Fertil. Dev. 2, 703–711.
Ivell, R., Balvers, M., Rust, W., Bathgate, R., Einspanier, A., 1997. Oxytocin and male reproductive function. Adv. Exp. Med. Biol. 424, 253–264.
Jankowski, M., Hajjar, F., Kawas, S.A., Mukaddam-Daher, S., Hoffman, G., McCann, S.M., Gutkowska, J., 1998. Rat heart: a site of oxytocin production and action. Proc. Natl. Acad. Sci. U. S. A. 95, 14558–14563.
Jankowski, M., Broderick, T.L., Gutkowska, J., 2016. Oxytocin and cardioprotection in diabetes and obesity. BMC Endocr. Disord. 16, 34.
Kagerbauer, S.M., Martin, J., Schuster, T., Blobner, M., Kochs, E.F., Landgraf, R., 2013. Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. J. Neuroendocr. 25, 668–673.
Karavitaki, N., Brufani, C., Warner, J.T., Adams, C.B.T., Richards, P., Ansorge, O., Shine, B., Turner, H.E., Wass, J.A.H., 2005. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin. Endocrinol. (Oxf.) 62, 397–409.
Karavitaki, N., Cudlip, S., Adams, C.B., Wass, J.A., 2006. Craniopharyngiomas. Endocr. Rev. 27, 371–397.
Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., Meyer-Lindenberg, A., 2005. Oxytocin modulates neural circuitry for social cognition and fear in humans. J. Neurosci. 25, 11489–11493.
Kroll-Desrosiers, A.R., Nephew, B.C., Babb, J.A., Guilarte-Walker, Y., Moore Simas, T.A., Deligiannidis, K.M., 2017. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. Depress. Anxiety 34, 137–146.
Labuschagne, I., Phan, K.L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., Stout, J.C., Nathan, P.J., 2010. Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. Neuropsychopharmacology 35, 2403–2413.
Lee, M.R., Scheidweiler, K.B., Diao, X.X., Akhlaghi, F., Cummins, A., Huestis, M.A., Leggio, L., Averbeck, B.B., 2017. Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay. Mol. Psychiatry [Epub ahead of print].
Leng, G., Sabatier, N., 2016. Measuring oxytocin and vasopressin: bioassays, immunoassays and random numbers. J. Neuroendocrinol. 28, 12413.
Müller, H.L., 2014. Craniopharyngioma. Endocr. Rev. 35, 513–543.
Mah, B.L., 2016. Oxytocin postnatal depression, and parenting: a systematic review. Harv. Rev. Psychiatry 24, 1–13.
Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12, 524–538.
Moder, K., 2010. Alternatives to F-test in one way ANOVA in case of heterogeneity of variances (a simulation study). Psychol. Test Assess. Model. 52, 343–353.
Moll, J., de, W., 1962. Observations on the hypothalamoposthypophyseal system of the posterior lobectomized rat. Gen. Comp. Endocrinol. 2, 215–228.
Muller, H.L., Gebhardt, U., Faldum, A., Warmuth-Metz, M., Pietsch, T., Pohl, F., Calaminus, G., Sorensen, N., 2012. Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations. J. Clin. Endocrinol. Metab. 97, 3935–3943.
Neumann, I.D., Landgraf, R., 2012. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. 35, 649–659.
Parker, K.J., Kenna, H.A., Zeitzer, J.M., Keller, J., Blasey, C.M., Amico, J.A., Schatzberg,

A.F., 2010. Preliminary evidence that plasma oxytocin levels are elevated in major depression. Psychiatry Res. 178, 359–362.
Pereira, A.M., Schmid, E.M., Schutte, P.J., Voormolen, J.H., Biermasz, N.R., Van Thiel, S.W., Corssmit, E.P., Smit, J.W., Roelfsema, F., Romijn, J.A., 2005. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. Clin. Endocrinol. (Oxf.) 62, 197–204.
Pyne, D.B., Boston, T., Martin, D.T., Logan, A., 2000. Evaluation of the Lactate Pro blood lactate analyser. Eur. J. Appl. Physiol. 82, 112–116.
Roemmler-Zehrer, J., Geigenberger, V., Störmann, S., Ising, M., Pfister, H., Sievers, C., Stalla, G.K., Schopohl, J., 2017. Specific behaviour, mood and personality traits may contribute to obesity in patients with craniopharyngioma. Clin. Endocrinol. 82, 106–114.
Roth, C.L., Eslamy, H., Werny, D., Elfers, C., Shaffer, M.L., Pihoker, C., Ojemann, J., Dobyns, W.B., 2015. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity 23, 1226–1233.
Sloper, J., 1960. The presence of a posterior pituitary-like structure in the hypothalamus after hypophysectomy. Acta Endocrinol. (Copenh.) 34, S101–S124.
Spielberger, C.D.G., R.L, Lushene, R.E., 1970. Manual for the State-Trait Anxiety Inventory (STAI). Consulting Psychologists Press, Palo Alto, CA.
Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wüllner, U., Maier, W., Hurlemann, R., 2013. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci. Rep. 3, 3440.
Szeto, A., McCabe, P.M., Nation, D.A., Tabak, B.A., Rossetti, M.A., McCullough, M.E., Schneiderman, N., Mendez, A.J., 2011. Evaluation of enzyme immunoassay and radioimmunoassay methods for the measurement of plasma oxytocin. Psychosom. Med. 73, 393–400.
Wijnen, M., van den Heuvel-Eibrink, M.M., Janssen, J.A., Catsman-Berrevoets, C.E., Michiels, E.M., van Veelen-Vincent, M.C., Dallenga, A.H., van den Berge, J.H., van Rij, C.M., Van der Lely, A.J., Neggers, S.J., 2017. Very long-term sequelae of craniopharyngioma. Eur. J. Endocrinol. 176, 755–767.
Wotjak, C.T., Naruo, T., Muraoka, S., Simchen, R., Landgraf, R., Engelmann, M., 2001. Forced swimming stimulates the expression of vasopressin and oxytocin in magnocellular neurons of the rat hypothalamic paraventricular nucleus. Eur. J. Neurosci. 13, 2273–2281.
de Jong, T.R., Menon, R., Bludau, A., Grund, T., Biermeier, V., Klampfl, S.M., Jurek, B., Bosch, O.J., Hellhammer, J., Neumann, I.D., 2015. Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. Psychoneuroendocrinology 62, 381–388.

6 Publication 2

Oxytocin-release-deficit and social cognition in craniopharyngioma patients

Marie-Luise Brandi, PhD (1), Dorothea Gebert, MD MSc (2), Anna Kopczak, MD (2;3), Matthias K Auer, MD (2;4), Leonhard Schilbach, MD (1)

Affiliations:

1) Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, Munich, Germany.

2) Research Group Clinical Neuroendocrinology, Max Planck Institute of Psychiatry, Munich, Germany.

3) Klinikum der Universtität München, Institute for Stroke and Dementia Research, Feodor-Lynen-Str 17, 81377 Munich, Germany.

4) Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Marchioninistr 15, 81377 Munich, Germany.

Keywords: neuropeptide, oxytocin, craniopharyngioma, emotion recognition, eye-tracking

Received: 25 September 2019 | Revised: 19 February 2020 | Accepted: 5 March 2020

DOI: 10.1111/jne.12842

ORIGINAL ARTICLE

Journal of Neuroendocrinology WILEY

Oxytocin release deficit and social cognition in craniopharyngioma patients

Marie-Luise Brandi[1] | Dorothea Gebert[2] | Anna Kopczak[2] | Matthias K. Auer[3] | Leonhard Schilbach[1]

[1]Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, Munich, Germany

[2]Research Group Clinical Neuroendocrinology, Max Planck Institute of Psychiatry, Munich, Germany

[3]Medizinische Klinik and Poliklinik IV, Klinikum der Universität München, LMU München, Munich, Germany

Correspondence
Marie-Luise Brandi, Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, 80804 Munich, Germany.
Email: marie-luise_brandi@psych.mpg.de

Present address
Anna Kopczak, Klinikum der Universtität München, Institute for Stroke and Dementia Research, Munich, Germany

Funding information
Max-Planck-Institut für Psychiatrie

Abstract

Oxytocin is a neuropeptide known to affect social behaviour and cognition. Craniopharyngioma patients are considered to have an oxytocin-release-deficit caused by a rare tumour affecting the pituitary and/or the hypothalamus relevant for oxytocin production and release. To assess social behaviour and socio-cognitive abilities in this patient group, we tested 13 patients and 23 healthy controls on self-report questionnaires and an eye-tracking paradigm including fast facial emotion recognition. Additionally, saliva oxytocin levels acquired before and after a physical stress induction were available from a previous study, representing the reactivity of the oxytocin system. The data revealed three major results. First, patients with an oxytocin-release-deficit scored higher on self-reported autistic traits and reduced levels of hedonia for social encounters, although they showed no impairments in attributing mental states. Second, patients showed more difficulties in the fast emotion recognition task. Third, although automatic gaze behaviour during emotion recognition did not differ between groups, gaze behaviour was related to the reactivity of the oxytocin system across all participants. Taken together, these findings demonstrate the importance of investigating the reactivity of the oxytocin system and its relationship with social cognition. Our findings suggest that reduced emotional processing abilities may represent a pathological feature in a group of craniopharyngioma patients, indicating that this patient group might benefit from specific treatments within the social domain.

KEYWORDS

craniopharyngioma, emotion recognition, eye-tracking, neuropeptide, oxytocin

1 | INTRODUCTION

Originally considered to be limited to childbirth and maternal care, the neuropeptide oxytocin has been shown to affect various functions, such as prosocial behaviour,[1,2] social motivation[3] and emotion recognition.[4] Furthermore, a natural increase in oxytocin levels in humans has been documented after physical exercise, social stress, social encounters and sexual activity.[5] This is why oxytocin is now being recognised as a key player in social cognition.[6-8] A particularly critical ingredient of social cognition is emotion processing:

The peer review history for this article is available at https://publons.com/publon/10.1111/jne.12842

instantly recognising facial expressions as a particular emotion allows for shifting attention towards it, inferring the underlying intentions, and finally responding adequately within a social interaction. Research indicates that oxytocin affects those automatic processes of emotion recognition. A meta-analysis, for example, showed that participants are better at identifying facial emotions after receiving intranasal oxytocin,[4] and genetic research has recently linked emotion recognition performance in women with a polymorphism in the oxytocinergic pathway gene *ARNT2*.[9] Furthermore, oxytocin has been shown to affect automatic gaze behaviour in facial processing.[10-13] Thus, it has been suggested that oxytocin is essential for regulating the salience of social information and orienting attention towards socially relevant cues.[14-17]

Although smaller variations in social cognition skills likely fall within the normal spectrum, social impairments have been recognised as core elements of various psychiatric disorders.[18] Tackling behavioural and neurobiological mechanisms of such impairments is therefore likely to provide valuable insight into psychopathological processes and may open up new treatment strategies. For example, patients with autism-spectrum disorder (ASD) show profound difficulties in social interactions, a finding that in turn led to the suggestion that oxytocin might have a crucial role in ASD aetiology and treatment.[19,20] Polymorphisms in the oxytocin receptor gene,[21] as well as peripheral oxytocin levels,[22,23] have previously been connected to autistic traits. Yet, research results are still not consistent to verify that an oxytocin deficit is present in ASD.[24] Still, some studies could show that oxytocin administration alleviates certain social deficits in ASD, with patients, for example, showing better performance in emotional recognition of faces after oxytocin administration.[25,26] As another example, patients with chronic depression have been found to show attentional biases towards negative stimuli such as sad over happy faces. Intranasal oxytocin nearly normalises this bias by enhancing selective attention towards positive stimuli, this way re-shaping the patients' social cognition process from a very early perceptual step onwards.[27]

Until now, research in humans has been assessing the link between oxytocin and social cognition either with healthy subjects or with patients selected as a result of their social cognitive deficits in the absence of neuroanatomical abnormalities. Recently, studies have started to consider the link between oxytocin and social cognition from another angle: are there patient groups with an oxytocin release deficit as a result of specific anatomical lesions, and, if yes, do these patients actually show relevant social cognitive deficits?

Oxytocin is mainly produced by magno- and parvocellular neurones that to a varying degree are found in the bilateral supraoptic (SON), paraventricular and accessory nuclei of the hypothalamus.[28,29] Oxytocin is then released via the pituitary gland to the peripheral blood stream. In addition to their pituitary projections, however, magnocellular neurones have recently been demonstrated to simultaneously connect via long-range axonal projections directly to various other brain regions, such as the amygdala, septum, nucleus accumbens and hippocampus,[30-32] this way directly affecting the neural circuits of complex social behaviours via central oxytonergic projections.[33] Tumour lesions to oxytocin-producing hypothalamic brain structures thus are likely to potentially lead to changes in social behaviour. One group of patients who present with lesions to these hypothalamic brain areas are patients with a rare peri-pituitary tumour of the Rathke's cleft called craniopharyngioma. Because of its specific growth pattern, this tumour type often damages both the pituitary gland and hypothalamus. Moreover, tumour treatment such as surgery or radiotherapy may lead to hypothalamic damage. Previous research has found a high prevalence for social and emotional deficits in this patient group,[34,35] although the underlying cause for the higher rate of such deficits has not been established. Recently, several studies have been able to show that the oxytocin system is impaired in these patients.[36-38] Importantly, in healthy people, oxytocin increases in different situations such as social stress, sexual stimulation or physical exercise,[5] whereas craniopharyngioma patients cannot release additional oxytocin in response to stimulation.[36] This is crucial because a recent meta-analysis has found that peripheral oxytocin measures correspond to central oxytocin levels only after stimulation but not at baseline levels.[39] Changes in oxytocin release might therefore more reliably characterise oxytocin-functioning than baseline levels, particularly when relating oxytocin to central cognitive processes and behavioural observations. Thus, an impairment of this stimulus-driven release function might represent an interesting player in healthy social processes, as well as psychopathology.[40]

In the present study, we therefore set out to assess the link between the dynamic, stimulus-driven responsiveness of oxytocin release on the one hand, and the automatic processes of social cognition on the other. Experiments were carried out in collaboration with a previously published study by Gebert et al[36] who measured the responsiveness of oxytocin after exercise-induced stimulation in craniopharyngioma patients and healthy controls. A subgroup of this sample participated in the presently described social cognition paradigm. To compare general social characteristics between healthy participants and patients, autistic traits, abilities to attribute mental states and the capacity to experience pleasure in social encounters were acquired with self-report questionnaires. Additionally, healthy participants and patients performed a well-established computer-based task measuring emotion recognition performance and reflexive gaze behaviour while viewing faces.[12,41,42] The paradigm is suited to quantify reflexive gaze behaviour toward informative regions of a face for emotional categorisation. The clinical relevance of this effect has been demonstrated in studies with autistic individuals,[43,44] patients with borderline personality disorder[45] and a case study of a patient with bilateral amygdala lesion.[42] Importantly, oxytocin administration modulates such automatic gaze behaviour by increasing the percentage of saccades towards emotionally informative regions of a viewed face.[12,45]

Based on the specific anatomical lesions impairing the oxytocin system in craniopharyngioma patients and as shown by Gebert et al,[36] an oxytocin response deficit was known to be present in this subgroup of patients. We therefore expected social cognition to differ between patients and healthy controls in three specific aspects. First, regarding social characteristics, we hypothesised that patients

would self-report higher autistic traits, as well as demonstrate reduced abilities to attribute mental states and lower experience of social pleasure than healthy participants. Furthermore, we expected patients to have reduced emotion recognition abilities in the applied eye-tracking paradigm. Third, based on the salience theory of oxytocin,[16] we expected patients to show fewer reflexive saccades toward emotionally relevant features of a face compared to healthy participants, and we expected these differences in reflexive gaze behaviour to be associated with the oxytocin release measures.

2 | MATERIALS AND METHODS

2.1 | Participants

The sample of the present study comprises a subset of craniopharyngioma patients who also participated in a study measuring differences in oxytocin levels in response to stimulation.[36] Participants were recruited through the Department of Neuroendocrinology at the Max-Planck Institute of Psychiatry, Munich. The healthy control group had no history of neurological or psychiatric disorder. Because hormonal contraception has been shown to interact with oxytocin-related social behaviour,[46] healthy controls using hormonal contraception were excluded. Patients continued to receive their standard hormonal substitution depending on degree of pituitary insufficiency (Table 1). A detailed description of the recruitment process, as well as of the collection of oxytocin measurements, is provided in Gebert et al.[36] A short overview of the applied oxytocin stimulation paradigm is outlined further below.

As a result of prevalent vision impairments in this patient population following tumour growth, pituitary surgery and radiation, not all patients from the original sample could be included in the present study. Regarding the eye-tracking measurements, it was ensured that the only patients who participated were those who were able to see the presented visual stimuli. To do so, visual acuity (VA) was measured with the Freiburg Visual Acuity Test (FrACT)[47,48] in all participants. Furthermore, an adapted perimetry test was conducted prior to the experiments in which participants had to name letters appearing on different locations all over the screen when fixating a cross in the middle. Participants showing a limited field of vision particularly in areas of the screen relevant for the experimental procedure were not included in the data sample. Based on these criteria, 10 patients from the original study sample by Gebert et al[36] were not included because of relevant visual impairments. This left 13 patients (P) who were diagnosed with a craniopharyngioma (six female; age: mean $[M]_P$ = 37.153, SD_P = 11.081; FrACT: M_P = 0.447 SD_P = 0.008) and 23 healthy controls (HC) (11 female; age: M_{HC} = 36.826, SD_{HC} = 12.995; FrACT: M_{HC} = 0.447, SD_{HC} = 0.014) to participate in the eye-tracking experiments. There was no significant difference in age or VA between the groups ($t_{age\,34}$ = 0.076, P_{age} = 0.940; $t_{VA\,34}$ = 0.166, P_{VA} = 0.869).

To confirm that the present subsample of patients shows oxytocin characteristics similar to the overall patient sample that originally included the visually impaired patients measured by Gebert et al,[36] we conducted *t* tests for comparison on a subset of the previously collected oxytocin data. As in the original sample, the present subsample showed a decreased oxytocin release in response to stimulation (Δ% oxytocin: M_P = −7.898%; SD_P = 20.600) compared to healthy controls (Δ% oxytocin: M_{HC} = 21.256%; SD_{HC} = 27.417) U = 54.5, P < 0.001; Figure 2A), but no significant difference in baseline levels (Oxy1: M_{HC} = 1.240 pg mL^{-1}; SD_{HC} = 1.078; Oxy 2: M_P = 1.903 pg mL^{-1}; SD_P = 1.432), U = 183, P = 0.865.

Patients' degree of hypothalamic damage was assessed using an established grading system for classification,[49] which categorises lesion extent into three grades: grade 0 = no hypothalamic lesion; grade 1 = anterior hypothalamic lesions sparing mammillary bodies; grade 2 = anterior and posterior hypothalamic lesion including mammillary bodies. Because it was not possible to acquire new structural magnetic resonance imaging (MRI) images specifically for the present study, the most recent acquired post-surgical anatomical MRI images of the patients were evaluated by an independent radiologist. In the present group of patients, MRI images of seven patients were rated as showing no hypothalamic lesion (grade 0), whereas five patients showed grade 1 lesions. For one patient, no MRI data were available.

All participants provided their written consent. The study was approved by the local ethics committee and conforms to the Declaration of Helsinki.

2.2 | Experimental procedures and analysis

2.2.1 | Questionnaires

To investigate group differences in the social domain, autistic traits, social motivation and the ability to attribute mental states, self-report questionnaires including the Autism-Spectrum Quotient (AQ[50]), the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS[51,52]) and the "Reading the Mind in the Eyes" test (RMET[53]) were used. The AQ aims to measure the degree to which a person shows preferences or behaviours that are related to the autism spectrum including the sub-scores social skills (AQ-S), communication (AQ-C), attention switching (AQ-AS), attention to detail (AQ-AD) and imagination (AQ-I). The ACIPS assesses the hedonic capacity for social interactions and interpersonal engagement by measuring anticipatory and consummatory social pleasure. The RMET is a performance-based measure that evaluates an individual's ability to attribute mental states and the understanding of complex emotions from pictures of the eye region of a face.

2.2.2 | Oxytocin measurements

Only a short description of the oxytocin measurements is given here (an overview is provided in Table 2). A detailed report of the stimulation paradigm and specific preparation of oxytocin-samples is provided in Gebert et al.[36] Data collection started at 8.30 AM, with all participants arriving in fasting state (food >12 hours, water >1 hour). For stimulation, participants exercised on a bicycle ergometer

TABLE 1 Pituitary insufficiency of participating patients and the respective hormonal substitution

Type of pituitary insufficiency	N	%	Hormonal substitution of insufficiency	N	%
Gonadotrophic insufficiency	11	84.6	Any gonadotrophic substitution	9	81.8
			Intramuscular testosterone (M)	*4*	*75.0*[a]
			HCG (M)	*1*	*25.0*[a]
			Transdermal oestradiol + oral progesterone (W)	*4*	*66.7*[a]
			No substitution as a result of menopausal age (W)	*2*	*33.3*[a]
Adrenal insufficiency	10	76.9	Oral glucocorticoid	10	100.0
Central hypothyroidism	12	92.3	Oral levothyroxine	12	100.0
Diabetes insipidus	8	61.5	Nasal spray or oral desmopressin	8	100.0
Growth hormone deficiency	12	92.3	Subcutaneous somatropin	6	50.0

Abbreviations: HCG, human choriongonadotrophin; M, men; W, women.
Transdermal oestradiol + oral progesterone are administered every 14 days for 10 days.
[a]Of those having gonadotrophic insufficiency, % of men and women is shown separately.

TABLE 2 Detailed exercise paradigm using a bicycle ergometer for oxytocin stimulation (Gebert et al[36])

Exercise steps	Duration (min)	Wattage (W)	When to measure lactate	Termination of exercise
Baseline salivary sample (Oxy1)				
1	0-2	50	–	–
2	2-7	100	Between step 2 and 3	Stop after step 2 if lactate >4.0 mmol L^{-1}
3	7-12	200 - age in years	Between step 3 and 4	Stop after step 3 if lactate >4.0 mmol L^{-1}
4	12-*x* (maximum overall 25)	220 - age in years	Every 2-3 min	Stop when lactate >4.0 mmol L^{-1} or after maximum of 25 min in duration overall
Stimulated salivary sample (Oxy2)				

(Kettler Ergometer TXl; Kettler, Ense, Germany) with stepwise increasing wattage difficulty. Lactate in capillary blood was measured repeatedly (Lactate Pro2[54]) aining to standardise for individual exertion. Both at baseline and after stimulation, saliva oxytocin was sampled using a Salivette® (Sarstedt, Nümbrecht, Germany). Oxytocin levels were quantified using a radioimmunoassay at an external laboratory (RIAgnosis, Sinzing, Germany). Based on the obtained absolute oxytocin levels (pg mL^{-1}), the relative value of change (Δ% oxytocin; Oxy1: before stimulation; Oxy2: after stimulation) was calculated, representing the individual's reactivity of the oxytocin system in response to exercise-induced stress:

$$\Delta\%-\text{oxytocin}=\frac{(Oxy2-Oxy1)}{Oxy1}*100$$

2.2.3 | Experimental set-up

For the eye-tracking measurements participants were asked to sit in a headrest in front of a monitor (Intel Core i5-4690 CPU [Intel, Santa Clara, CA, USA], 3.5 GHz, 8 GB RAM, MS Windows 7 Enterprise [Microsoft Copr., Redmond, WA, USA], refresh rate = 59 Hz), an eye-tracking system (SR Research, Ottawa, ON, USA) and a standard computer keyboard. The distance between the eyes of the participants and the monitor was approximately 670 mm and, for the camera of the eye-tracker, approximately 500 mm. The experiment was presented with a resolution of 1024 × 768 pixels with PRESENTATION, version 18.0 (Neurobehavioral Systems, Inc., Albany, CA, USA). Participants remained in the described position for the FrACT, the perimetry test, as well as the experiment itself.

2.2.4 | Emotion recognition task

A well-established emotion recognition task was used to evaluate differences in both emotion recognition capabilitiesm as well as automatic gaze behaviour during the task, and the experimental procedure applied in the study was similar to that employed in previously published articles using the same task.[12,41,42] The stimulus set included 24 different individuals (12 female) retrieved from the FACES database.[55] Each individual was shown six times within the experiment, expressing three different emotions (happy, fearful, and angry). The individuals depicted in the image were young (n = 8), middle-aged (n = 8) or old (n = 8) as categorised by ratings of the used database. All images were cropped to show only the facial features excluding the hair, and they were transferred into black and white scale and adjusted for luminance with the SHINE toolbox.[56] The visual angle across all faces was approximately 13° vertically and 9° horizontally. In total, 144 trials were acquired (36 trials per emotion). In this paradigm, the faces were shown briefly for 150 ms after the presentation of a fixation cross for 2 seconds. Afterwards, a blank screen was shown for 1850 ms, followed by another fixation cross for 2 seconds. The faces were presented only for a short period of time, so that the recorded eye movements only occurred after the offset of the stimulus. The facial images were either shifted up leading to an initial fixation of the mouth of the presented face in half of the trials, or were shifted down leading to an initial fixation of the eye region of the face. Participants were asked, in half of the trials, to categorise the faces according to one of the three possible emotions (happy, fearful, angry) and, in the other half, according to the age of the individual of the photo (young, middle or old) by button presses. A screen with the cue "Emotion?" or "Age?" was presented before the initial fixation cross for 2 seconds to instruct the participant which of the two categorisations had to be performed in the given trial (Figure 1). The *age* condition was included as a control condition to ensure that possible group differences in performance are not a result of general difficulties in processing of facial features but rather to emotional processing. The task was trained before the actual experiment to ensure all participants were familiar with button assignments. The presentation of conditions was randomised across participants and all faces were presented multiple times depicting all emotions both in the emotion or age condition. After the experiment participants had to rate the difficulty of the two categorisation tasks on a scale from 1 to 5 (1 = very easy; 5 = very difficult).

2.2.5 | Statistical analysis

Data analysis of button presses, eye-tracking measurements, statistical analysis and data visualisation was conducted with MATLAB (MathWorks Inc., Natick, MA, USA) and SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). The present study includes groups with an unequal group-size, as well as a small sample size, which can lead to differences in variance between groups and non-normal distributions. Levene's test for equality of variance and the Shapiro-Wilk test for normality were conducted for the data to apply the appropriate statistical procedures. The results of the tests are shown in Table 3.

The Levene's test for equality of variance showed no significant differences in variance for any of the questionnaire scores and the oxytocin measures. The test for normality revealed that the ACIPS scores and the oxytocin measures of the healthy control group were not normally distributed. Therefore, a two-sample *t* test was used to test for significant differences in AQ, the AQ sub-scores and RMET, whereas a Mann-Whitney's *U* test was used to test for differences in ACIPS scores and the oxytocin measures between groups.

Performance in the *emotion* and *age* categorisation in the emotion recognition task is represented as the percentage of correct responses (% correct responses). The Levene's indicated a difference in variance between groups for the category *emotion*. To account for the difference in variance and skewness of data, the suggestion by Skovlund & Fenstad[57] is followed to transform data to a normal distribution (a Box Cox transformation is applied) and to use a one-sided Welch *t* test to investigate group-related differences of performance in the two conditions. A higher performance for the healthy controls in the emotion categorisation is assumed. One-sample *t* tests were used to test whether the performance of each group for both categorisation tasks was above chance level (33.33%) and a two-sample *t* test was used to test whether the performance differed across groups between the different categorisation tasks.

An ANOVA with the factor *condition* as within-subject and *group* as a between subject factor was conducted to evaluate condition or group-specific differences in experienced difficulty, as well as possible interactions of these factors. The test for equality of variance was not significant for the data on reported difficulty.

For the eye-tracking analysis, the main measure of interest was the first automatic saccade that derived 1° from the initial fixation towards the other relevant facial feature (eyes or mouth; the expected direction of the saccade is indicated by black arrows in Figure 1). The results are presented as the percentages of occurring fixation changes (% fixation changes). Fixation changes were expected in both categorisation conditions, since it has previously been shown that the automatic gaze response acquired in this type of paradigm occurs similarly in different categorisation tasks when faces are shown.[58] Therefore, the trials from both the *emotion* and *age* conditions were pooled to quantify the percentage of fixation changes towards facial features during emotional processing. A 2 × 3 ANOVA with the factor *group* as a between-subject measure was conducted including the factors initial *fixation* (mouth and eye) and *emotion* (angry, fearful, happy) as within-subject factors.

To investigate whether oxytocin baseline levels or oxytocin responsiveness to stimulation is related to automatic gaze during emotional processing, Δ% oxytocin and baseline levels were correlated to the % fixation changes in a partial Pearson correlation across the whole group including the factor *group* as a control variable. A one-tailed correlation was applied because previous literature suggests a positive association between oxytocin and reflexive gaze behaviour.[12,45]

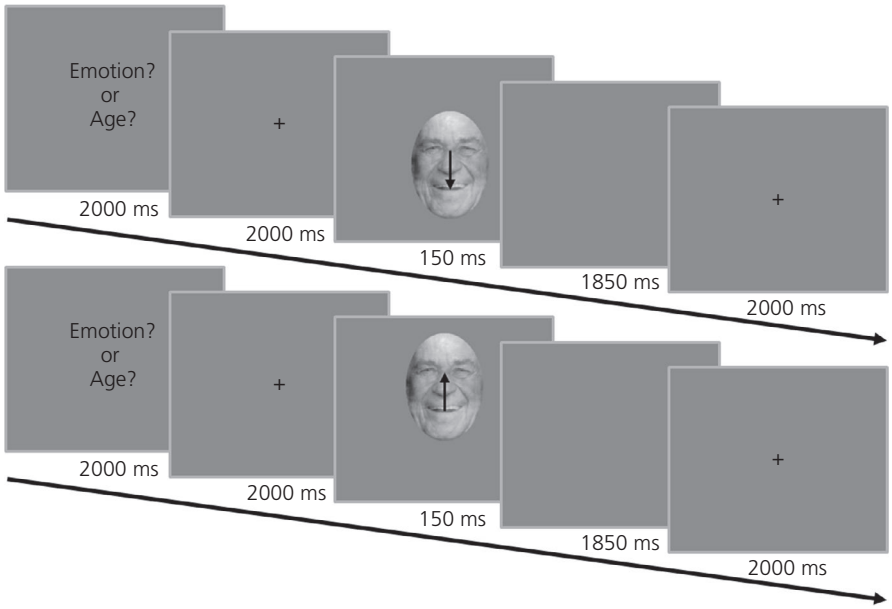


FIGURE 1 Experimental time course. Each trial starts by either showing the cue "Emotion?" or "Age?", followed by a fixation cross. After that, a face is shown for 150 ms either moved downwards so the initial fixation is located on the eyes (upper) or upwards so the initial fixation is located on the mouth (lower). The arrows layered over the face are not shown during the experiment but indicate the direction of the saccade that is measured in the analysis. The face is followed by a blank screen and another fixation cross

	Levene's test			Shapiro-Wilk test			
				HC		P	
	F	*df*	*P*	W	*P*	W	*P*
AQ	0.980	34	.329	0.923	.074	0.934	.388
ACIPS	0.328	33	.570	0.668	<.001	0.938	.434
RMET	0.418	33	.522	0.936	.168	0.956	.688
%Δ oxytocin	1.033	34	.316	0.881	.012	0.944	.512
emotion categorisation	8.478	34	.006	0.865	.005	0.742	.002
Age categorisation	0.0895	34	.766	0.969	.659	0.887	.089
% fixation changes	0.032	34	.858	0.934	.135	0.956	.697

TABLE 3 Statistical measures of the Levene's test for equality of variance and Shapiro-Wilk test for normality for all measures of interest

Abbreviations: ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale; AQ, Autism-Spectrum Quotient; HC, healthy control; P, patient; RMET, "Reading the Mind in the Eyes" test.

3 | RESULTS

3.1 | Questionnaires

To investigate differences in autistic traits, social hedonia and abilities to attribute mental states between healthy controls and patients, statistical tests comparing group differences were conducted. Autistic traits were significantly higher in the patient group compared to healthy controls as depicted in Figure 2B. Particularly, the AQ sub-scores AQ-S and AQ-AS were significantly higher in the patient group. In case of the ACIPS, a significant difference between the groups was found using Mann-Whitney's *U* test. No significant difference was found for the RMET between groups (Figure 2C,D). All descriptive and test-statistical values are shown in Table 4.

3.2 | Emotion recognition task

As a result of a significant difference in variance in the percentages of correct responses between groups tested by the Levene's test of equal variance and skewness of data, the data were transformed to a normal distribution and a Welch's test was chosen for the analysis. The test revealed a significant difference between the mean percentages of correct responses in the performance of the emotion categorisation for patients (M_P = 80.876%, SD_P = 17.341) compared to healthy controls (M_{HC} = 90.036%, SD_{HC} = 6.104, t = −1.819, P = 0.046). The performance in the age categorisation task was not significantly different between patients (M_P = 53.738%, SD_P = 7.965) and healthy controls (M_{HC} = 55.193%, SD_{HC} = 8.036, t = −0.521, P = 0.606). Testing the differences between the performance of the two categorisation tasks across the whole group revealed that

TABLE 4 Descriptive statistic of self-report measures and test-statistical measures

					Test statistic		
	Group	N	Mean	SD	*t*	*df*	*P*
AQ	P	13	19.076	6.317	2.506	34	.008
	HC	23	14.130	4.722			
AQ-S	P	13	3.153	2.409	2.058	34	.023
	HC	23	1.608	2.0167			
AQ-AS	P	13	5.307	2.175	2.500	34	.008
	HC	23	3.869	1.290			
AQ-AD	P	13	5.076	2.396	0.991	34	.164
	HC	23	4.260	2.359			
AQ-C	P	13	2.538	1.983	0.931	34	.179
	HC	23	1.956	1.691			
AQ-I	P	13	3.000	1.154	0.890	34	.189
	HC	23	2.434	2.106			
RMET	P	13	25.538	3.098	1.121	33	.864
	HC	22	24.227	3.476			
					U		*P*
ACIPS	P	13	78.076	12.757	87		.029
	HC	22	85.045	14.636			

Abbreviations: ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale; AQ, Autism-Spectrum Quotient; AQ-AD, attention to detail; AQ-AS, attention switching; AQ-C, communication; AQ-I, imagination; AQ-S, AQ sub-scores: social skills; HC, healthy control; P, patient; RMET, "Reading the Mind in the Eyes" test.

the performance of the emotion categorisation (M = 86.728%, SD = 12.101) was significantly higher compared to the age categorisation (M = 54.667%, SD = 7.927, t = −17.300, P < 0.001). A one-sample t test against the value of 33.33% across the whole group showed that performance was significantly higher than chance level in the categorisation of *age* (t = 16.149, P < 0.001) and *emotion* (t = 26.475, P < 0.001). Results are illustrated in Figure 3A.

The analysis on condition and group effects of experienced difficulty in the two conditions revealed a significant main effect for *condition* ($F_{1,34}$ = 57.805, P < 0.001, η^2 = 0.629) indicating higher difficulty in the emotion compared to the age condition (emotion: M_P = 2.269; SD_P = 0.599; M_{HC} = 2.000; SD_{HC} = 2.000; age: M_P = 3.385; SD_P = 0.870; M_{HC} = 3.174; SD_{HC} = 0.717), although no significant *group* × *condition* interaction ($F_{1,34}$ = 0.31, P < 0.862, η^2 = 0.000), nor a significant effect for group differences ($F_{1,34}$ = 0.844, P < 0.365, η^2 = 0.024).

The 2 × 3 ANOVA of % fixation changes showed a significant main effect for *fixation* (higher percentage of % fixation changes

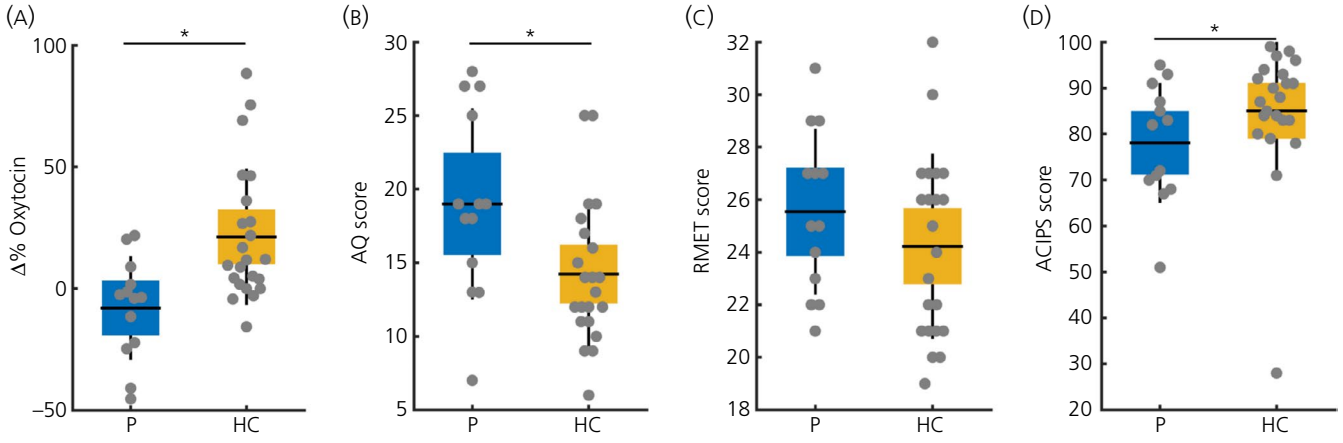


FIGURE 2 Plots showing the raw data points scattered over a 95% confidence interval (box) and one SD (vertical black line), as well as the mean (horizontal black line) for Δ% oxytocin (A), Autism-Spectrum Quotient (AQ) scores (B), RMET ("Reading the Mind in the Eyes") test scores (C) and Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) scores (D). The asterisk (*) indicates a significant difference of P < 0.05. Patients (P) are shown in blue; healthy controls (HC) are shown in yellow

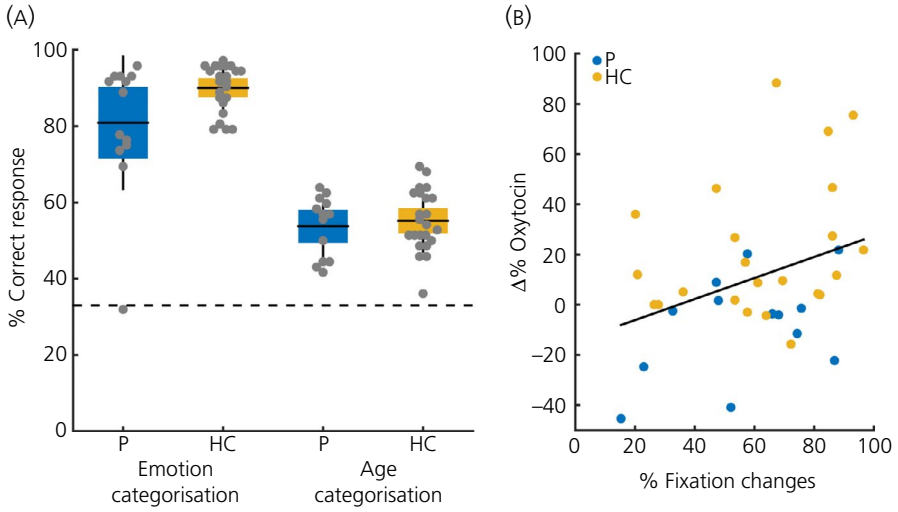


FIGURE 3 A, Plot showing the % correct responses for the emotion and age categorisation as raw data points scattered over a 95% confidence interval (box) and one SD (vertical black line), as well as the mean (horizontal black line). The patient's data (P) are shown in blue; healthy controls (HC) are shown in yellow. The dashed horizontal line indicates the chance level of 33.33%. B, Scatter plot showing the association between % fixation changes and Δ% oxytocin. The patient's data (P) are shown as blue dots; the data depicting the healthy controls (HC) are shown as yellow dots

for initial fixation on mouth) and a significant interaction between *fixation* and *emotion*. No significant differences for the groups or *group* × *condition* interactions were found. All descriptive statistics for each condition are shown in Table 5 and all statistical measures are shown in Table 6.

The partial one-tailed correlation between % fixation changes (M = 60.165%, SD = 23.354) and Δ% oxytocin (M = 10.713%, SD = 28.673), controlling for group effects, showed a significant association between the extent of oxytocin release in response to stimulation and reflexive gaze behaviour across both groups ($r = 0.327$, $P = 0.027$) (Figure 3B). A partial one-tailed correlation between baseline oxytocin measures (M = 1.480 pg mL^{-1}, SD = 1.237) and % fixation changes did not show significant results ($r = -0.006$, $P = 0.487$).

TABLE 5 Descriptive statistic of % fixation changes for each condition

		P		HC	
Condition		**Mean**	**SD**	**Mean**	**SD**
Fear	Eye	42.628	8.381	50.000	6.301
	Mouth	71.474	7.889	70.290	5.931
Angry	Eye	39.744	8.414	51.449	6.326
	Mouth	70.513	7.566	75.543	5.688
Happy	Eye	44.551	8.847	58.696	6.651
	Mouth	70.192	7.719	67.391	5.803

Note: The condition label "Eye" or "Mouth" indicates whether the initial fixation was positioned in that region of the face.

Abbreviations: HC, healthy control; P, patient.

4 | DISCUSSION

The present study aimed to assess the relationship between the endogenous oxytocin system and social cognition. Accordingly, we tested social cognitive abilities in healthy participants, as well as in craniopharyngioma patients who exhibit an oxytocin response deficit following pituitary and hypothalamic lesions. Compared to the control group, patients showed increased autistic traits as well as a lower capacity to enjoy social interactions. Abilities to attribute mental states as measured by the RMET, however, were similar between patients and controls. Regarding automatic emotional processing, patients showed more difficulties in the categorisation of emotion despite showing similar accuracy as healthy controls when categorising age, suggesting an emotion-specific impairment in face processing. Third, although reflexive saccades towards emotionally relevant regions of the face were positively related to an increased Δ% oxytocin, gaze behaviour, unexpectedly, did not differ between groups.

4.1 | Social cognition in craniopharyngioma patients

Difficulties in social communication and interaction are assumed to lie on a continuum, across the population with a diagnosis of ASD and people without the diagnosis. In the present study, autistic traits were measured with the AQ, which measures autistic-like behaviours concerning social skills, communication, imagination, attention switching and attention to detail.[50] Our results indicate that, regarding these traits, craniopharyngioma patients range in between these groups. Importantly, although higher than in healthy controls, the score was still below the suggested clinically relevant cut-off of 32 points. More specifically, we found significant differences in the AQ subscores measuring social skills (AQ-S) and attention switching (AQ-AS).

TABLE 6 Statistical measures of the 2 × 3 ANOVA of % fixation changes

	ANOVA			
	F	*df*	*P*	η^2
Within-subject effects				
Emotion	0.829	2	.441	0.024
Emotion × group	2.218	2	.117	0.061
Fixation	16.262	1	<.001	0.324
Fixation × group	0.880	1	.355	0.025
Emotion × fixation	7.487	2	.001	0.180
Emotion × fixation × group	1.995	2	.144	0.055
Between-subject effects				
Group	0.489	1	.489	0.014

The results somewhat contradict the previous findings reported by Daughters et al,[37] who found no difference in AQ scores for patients with hypopituitarism and central diabetes insipidus (CDI) compared to healthy controls. This discrepancy might be a result of differences in AQ measures (we used the 50-item AQ, Daughters et al[37] applied the 28-item short version[59]), as well as differences in patient groups (we included craniopharyngioma patients with a defined hypothalamic damage, Daughters et al[37] included patients with anterior hypopituitarism and an assumed lack of hypothalamic involvement). Next to the AQ, the ACIPS measuring interpersonal pleasure is also different in patients compared to healthy controls, which indicates that patients enjoy social encounters less than healthy individuals do. This is also in line with the previously mentioned findings on the AQ because research has shown that individuals with a greater number of autistic traits are more likely to report lower scores in the ACIPS.[60]

Furthermore, similar to patients with autism,[43] more craniopharyngioma patients showed a reduced accuracy in a facial emotion recognition task compared to healthy controls. Importantly, performance was similar to healthy participants when categorising the age of a viewed face, suggesting the deficit in face recognition to be emotion-specific. These results are in line with a previous study by Daugthers et al,[37] who also found lower facial emotion recognition scores in patients with hypopituitarism. Interestingly, our data show that emotion recognition was not impaired in all craniopharyngioma patients of our sample. This is comparable with a literature review analysing the prevalence of neurobehavioural, social and emotional dysfunction in this patient group across different studies, which found that a high number (approximately 40% of patients), but not all, show social as well as emotional impairments. More research is needed to fully understand the variability within this patient group.

It is noteworthy that, in the present study, no significant differences were found for the RMET. This is particularly interesting because both the RMET and the emotion recognition task use facial stimuli that need to be attributed to a certain intentional or emotional state. A possible reason for this discrepancy could be the specific experimental procedure of the implemented eye-tracking paradigm in our study. In contrast to the RMET, the eye-tracking paradigm presents the stimuli only for 150 ms, not leaving sufficient time for elaborate processing. Unfortunately, response times were not acquired for the RMET and it is therefore not possible to investigate whether patients might have taken more time to answer the questionnaire. The difference seen in the eye-tracking paradigm suggests that difficulties in social behaviour in craniopharyngioma patients might rather be related to fast automatic processes during emotion recognition instead of longer evaluations of facial features. This is important because real-time social interactions with another person likely rely exactly on such fast subconscious processing of multiple sensory cues, making this kind of fast-processing deficit even more relevant. Another factor influencing the RMET scores and possibly leading to the unexpected results is the difficulty of the RMET items. Domes el al.[61] have shown that differences in RMET scores after the application of oxytocin is most pronounced in difficult items. In relation to the data presented in the present study, this could suggest that participants with an oxytocin deficit might perform worse in the difficult items of the task, but these effects might be less pronounced in the total score. In contrast to our results, the previously mentioned study by Daughters et al[37] indeed found differences in the RMET in patients with hypopituitarism and, across patients and healthy controls, lower RMET scores were associated with lower salivary oxytocin levels. It is therefore also possible that a failure to detect significant differences between patients and controls might be a result of the limited sample size of the present study.

Given that the present study yielded results comparable to those of previous research despite applying a different emotion recognition paradigm in a different patient sample, our findings provide further support for the notion that reduced automatic emotional processing abilities might represent a pathological feature for some craniopharyngioma patients. Because emotion recognition deficits have been shown to be relevant in other psychopathologies including mood disorders and social interaction disorders,[62,63] such differences in automatic emotion recognition might at least partially account for the clinically observed difficulties in social behaviour in craniopharyngioma patients. It should be noted, however, that previously reported difficulties in social and emotional functioning cannot fully be explained by the oxytocin release deficit found in patients because we could not demonstrate differences in automatic gaze behaviour during emotional processing, and there was considerable heterogeneity in emotion recognition abilities within the patient group.

4.2 | Responsiveness of the oxytocin system in psychopathology

To better define the previously observed link between oxytocin and social cognitive processes, we applied an eye-tracking paradigm to measure the association between oxytocin and automatic gaze behaviour during emotional processing. According to the social salience hypothesis, oxytocin is essential for regulating the salience of social information and orienting attention towards socially relevant cues,[16] such as by redirecting gaze towards

informative regions of the face.[11] In keeping with this concept, we found that, across the whole study population, participants with a greater oxytocin response to stimulation also showed more fixation changes towards relevant facial areas. Unexpectedly, we found no significant difference in average fixation changes between groups.

As predicted further, changes in gaze behaviour were only found to be associated with Δ% oxytocin, and not with baseline levels. This particular differentiation matches well with the current notion that oxytocin can act as a dynamic neuromodulator on social cognition[64,65] responding to stimulation.[5] Particularly in response to social and emotional cues, oxytocin pathways are likely to become activated, and not only trigger peripherally measurable changes in oxytocin levels, but also simultaneously stimulate activity in specific central neural populations, in this way mediating complex social behaviour.[33,66] For example, in a recent optogenetic study in rodents, it was demonstrated that triggering axonal oxytocin release in the central amygdala decreased previously conditioned fear responses in rats.[30] There is also evidence for oxytocin-mediated activity of the amygdala in humans: face perception[67] and reflexive gaze behaviour during emotion recognition have been shown to be closely related to neural activation in the amygdala.[41] The amygdala was also found to be strongly modulated by oxytocin administration[12] and is assumed to have a key role in attentional processes reorienting to salient stimuli.[16] An oxytocin release deficit affecting central axonal projections might therefore be of clinical relevance in various social interaction disorders, and the responsiveness of the endogenous oxytocin system might present a key player in the understanding of the underlying psychopathological processes.

Another important aspect to discuss regards the success of treatment approaches with oxytocin. A case report of a craniopharyngioma patient indicated improvements in social behaviour after oxytocin administration.[68] In that case study, oxytocin administration led to increased motivation for social behaviour in the patient as well as an improvement in showing affection towards the family. A study by Hoffmann et al[69] showed that the effects of oxytocin administration were related to the patient's lesions. Emotional processing was only improved in patients with less severe lesions only limited to the anterior hypothalamus. The patients included in the present study had either no damage to the hypothalamus or only to the anterior hypothalamus. A recent meta-analysis on the effects of intranasal oxytocin administration in neurodevelopmental disorders on the other hand showed only limited improvements in social cognitive abilities across several studies.[70] Based on the stimulus-dependent nature of oxytocin and its effects in directing attention to social cues, treatment approaches should likely focus on coupling oxytocin administration with the right stimulus at the right time. In accordance with this notion, coupling targeted psychotherapy with oxytocin has already produced promising results in recent clinical studies, reducing depressive symptoms in patients with post-traumatic stress disorder [71] and improving self-evaluation in patients suffering from social anxiety.[72] In patients with social interaction difficulties, combining a stimulus-driven oxytocin administration with psychotherapy approaches like social interaction training might yield better treatment effects in the future.

4.3 | Limitations

The limitations of the present study include the small number of patients and a resulting unequal size of tested groups. This is mainly a result of the rarity of cases and also the strict inclusion criteria for patients excluding any basic deficits in vision that could bias the results in the behavioural eye-tracking paradigm. The patients included in the present study also had either no damage to the hypothalamus or only to the anterior hypothalamus because the patients with more extensive damage showed concurrent visual deficits and thus had to be excluded. Furthermore, there is a vast body of literature indicating that oxytocin-effects depend on sex.[73,74] It is thus likely that an oxytocin release deficit might have differential effects in male and female patients and thus might warrant sex-specific treatment approaches. Unfortunately, because of the small sample size, a sex-specific analysis was not possible in the current sample and should thus be explored in future studies.

Lastly, because direct measurement of central oxytocin levels in humans is not possible, the present study uses peripheral salivary oxytocin levels to infer central oxytocin dynamics and their link with social cognition. This inference is supported by different findings. First, there is evidence from animal studies indicating that the same hypothalamic neural populations project simultaneously to peripheral and central release sites.[66] Second, this simultaneous release is likely triggered in response to social and emotional cues.[75,76] Third, salivary oxytocin levels, in contrast to plasma levels, have been shown to correlate with cerebro-spinal fluid-levels in humans.[77]

Taken together, this suggests that finding a reduced oxytocin responsiveness (as seen for salivary levels in the present patient sample) might reflect an impaired central oxytocin release.

Given the closer anatomical proximity of the SON to Rathke's cleft in comparison to the paraventricular nucleus, one might even speculate that SON-projections are more likely to be affected in our patient sample, in turn theoretically helping to narrow down the specific neural circuits and associated social behaviours affected by this tumour. However, the available imaging data did not provide a sufficiently high resolution to allow for such differentiation.

5 | CONCLUSIONS

Taken together, the results of the present study suggest three main conclusions. In the present sample, craniopharyngioma patients show increased autistic traits, lower interpersonal pleasure and more difficulties in fast emotion categorisation, whereas the basic processing of facial features appears to be intact. Second, our results emphasise the importance of investigating the dynamics of the oxytocin response by showing that, across groups,

the reactivity of the oxytocin system is related to automatic gaze behaviour when viewing emotional facial expressions. Third, the reactivity of the oxytocin system instead of baseline levels might thus represent a feature particularly relevant for fast automatic emotional processing.

ACKNOWLEDGEMENTS

We thank Martin Freitag (Department of Radiology, German Cancer Research Center, Heidelberg, Germany) for assessing the clinical MRI data, Professor Günter Stalla for his scientific and financial support, and Professor Rainer Landgraf for advice how to measure oxytocin levels. Additionally, we thank Angelika Mahringer for her assistance with the data acquisition. This work was supported by a grant from the Max Planck Society for an independent Max Planck Research Group to Leonhard Schilbach.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

ORCID

Marie-Luise Brandi https://orcid.org/0000-0001-5283-2317
Dorothea Gebert https://orcid.org/0000-0003-1875-0267
Matthias K. Auer https://orcid.org/0000-0001-7153-8332

REFERENCES

1. Zak PJ, Stanton AA, Ahmadi S. Oxytocin increases generosity in humans. Brosnan S, ed. *PLoS ONE*. 2007;2:e1128.
2. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature*. 2005;435:673-676.
3. Caldwell HK, Albers HE. *Oxytocin, Vasopressin, and the Motivational Forces that Drive Social Behaviors*. Cham, Switzerland: Springer; 2015:51-103.
4. Shahrestani S, Kemp AH, Guastella AJ. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. *Neuropsychopharmacology*. 2013;38:1929-1936.
5. de Jong TR, Menon R, Bludau A, et al. Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: the Regensburg Oxytocin Challenge (ROC) study. *Psychoneuroendocrinology*. 2015;62:381-388.
6. Ebert A, Brüne M. *Oxytocin and Social Cognition*. Cham, Switzerland: Springer; 2017:375-388.
7. Kanat M, Heinrichs M, Domes G. Oxytocin and the social brain: Neural mechanisms and perspectives in human research. *Brain Res*. 2014;1580:160-171.
8. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci*. 2011;12:524-538.
9. Hovey D, Henningsson S, Cortes DS, et al. Emotion recognition associated with polymorphism in oxytocinergic pathway gene ARNT2. *Soc Cogn Affect Neurosci*. 2018;13:173-181.
10. Auyeung B, Lombardo MV, Heinrichs M, et al. Oxytocin increases eye contact during a real-time, naturalistic social interaction in males with and without autism. *Transl Psychiatry*. 2015;5:e507.
11. Tollenaar MS, Chatzimanoli M, van der Wee NJA, Putman P. Enhanced orienting of attention in response to emotional gaze cues after oxytocin administration in healthy young men. *Psychoneuroendocrinology*. 2013;38:1797-1802.
12. Gamer M, Zurowski B, Büchel C. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proc Natl Acad Sci USA*. 2010;107:9400-9405.
13. Guastella AJ, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry*. 2008;63:3-5.
14. Bartz JA, Lydon JE, Kolevzon A, et al. Differential effects of oxytocin on agency and communion for anxiously and avoidantly attached individuals. *Psychol Sci*. 2015;26:1177-1186.
15. Gao S, Becker B, Luo L, et al. Oxytocin, the peptide that bonds the sexes also divides them. *Proc Natl Acad Sci USA*. 2016;113:7650-7654.
16. Shamay-Tsoory SG, Abu-Akel A. The social salience hypothesis of oxytocin. *Biol Psychiatry*. 2016;79:194-202.
17. Yao S, Zhao W, Geng Y, et al. Oxytocin facilitates approach behavior to positive social stimuli via decreasing anterior insula activity. *Int J Neuropsychopharmacol*. 2018;21:918-925.
18. Schilbach L. Towards a second-person neuropsychiatry. *Philos Trans R Soc B Biol Sci*. 2016;371:20150081.
19. Yamasue H, Domes G. *Oxytocin and Autism Spectrum Disorders*. Cham, Switzerland: Springer; 2017:449-465.
20. Gurrieri F, Neri G. Defective oxytocin function: a clue to understanding the cause of autism? *BMC Med*. 2009;7:63.
21. Montag C, Sindermann C, Melchers M, et al. A functional polymorphism of the *OXTR* gene is associated with autistic traits in Caucasian and Asian populations. *Am J Med Genet Part B Neuropsychiatr Genet*. 2017;174:808-816.
22. Husarova VM, Lakatosova S, Pivovarciova A, et al. Plasma oxytocin in children with autism and its correlations with behavioral parameters in children and parents. *Psychiatry Investig*. 2016;13:174-183.
23. Zhang H-F, Dai Y-C, Wu J, et al. Plasma oxytocin and arginine-vasopressin levels in children with autism spectrum disorder in China: associations with symptoms. *Neurosci Bull*. 2016;32:423-432.
24. Rutigliano G, Rocchetti M, Paloyelis Y, et al. Peripheral oxytocin and vasopressin: biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. *Psychiatry Res*. 2016;241:207-220.
25. Aoki Y, Watanabe T, Abe O, et al. Oxytocin's neurochemical effects in the medial prefrontal cortex underlie recovery of task-specific brain activity in autism: a randomized controlled trial. *Mol Psychiatry*. 2015;20:447-453.
26. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry*. 2010;67:692-694.
27. Domes G, Normann C, Heinrichs M. The effect of oxytocin on attention to angry and happy faces in chronic depression. *BMC Psychiatry*. 2016;16:92.
28. Sofroniew MV. Morphology of vasopressin and oxytocin neurones and their central and vascular projections. *Prog Brain Res*. 1983;60:101-114.
29. Swanson LW, Sawchenko PE. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. *Annu Rev Neurosci*. 1983;6:269-324.
30. Knobloch HS, Charlet A, Hoffmann LC, et al. Evoked axonal oxytocin release in the central amygdala attenuates fear response. *Neuron*. 2012;73:553-566.
31. Menon R, Grund T, Zoicas I, et al. Oxytocin signaling in the lateral septum prevents social fear during lactation. *Curr Biol*. 2018;28:1066-1078.e6.
32. Mitre M, Marlin BJ, Schiavo JK, et al. A distributed network for social cognition enriched for oxytocin receptors. *J Neurosci*. 2016;36:2517-2535.

33. Grinevich V, Knobloch-Bollmann HS, Eliava M, Busnelli M, Chini B. Assembling the puzzle: pathways of oxytocin signaling in the brain. *Biol Psychiatry*. 2016;79:155-164.
34. Müller HL, Merchant TE, Puget S, Martinez-Barbera J-P. New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. *Nat Rev Endocrinol*. 2017;13:299-312.
35. Zada G, Kintz N, Pulido M, Amezcua L. Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: a systematic literature review. *PLoS ONE*. 2013;8:e76562.
36. Gebert D, Auer MK, Stieg MR, et al. De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. *Psychoneuroendocrinology*. 2018;88:61-69.
37. Daughters K, Manstead ASR, Rees DA. Hypopituitarism is associated with lower oxytocin concentrations and reduced empathic ability. *Endocrine*. 2017;57:166-174.
38. Daubenbüchel AMM, Hoffmann A, Eveslage M, et al. Oxytocin in survivors of childhood-onset craniopharyngioma. *Endocrine*. 2016;54:524-531.
39. Valstad M, Alvares GA, Egknud M, et al. The correlation between central and peripheral oxytocin concentrations: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;78:117-124.
40. Neumann ID, Slattery DA. Oxytocin in general anxiety and social fear: a translational approach. *Biol Psychiatry*. 2016;79:213-221.
41. Gamer M, Büchel C. Amygdala activation predicts gaze toward fearful eyes. *J Neurosci*. 2009;29:9123-9126.
42. Gamer M, Schmitz AK, Tittgemeyer M, Schilbach L. The human amygdala drives reflexive orienting towards facial features. *Curr Biol*. 2013;23:R917-R918.
43. Kliemann D, Dziobek I, Hatri A, Steimke R, Heekeren HR. Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. *J Neurosci*. 2010;30:12281-12287.
44. Kliemann D, Dziobek I, Hatri A, Baudewig J, Heekeren HR. The role of the amygdala in atypical gaze on emotional faces in autism spectrum disorders. *J Neurosci*. 2012;32:9469-9476.
45. Bertsch K, Gamer M, Schmidt B, et al. Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *Am J Psychiatry*. 2013;170:1169-1177.
46. Scheele D, Plota J, Stoffel-Wagner B, Maier W, Hurlemann R. Hormonal contraceptives suppress oxytocin-induced brain reward responses to the partner's face. *Soc Cogn Affect Neurosci*. 2016;11:767-774.
47. Bach M. The Freiburg Visual Acuity test--automatic measurement of visual acuity. *Optom Vis Sci*. 1996;73:49-53.
48. Bach M. The Freiburg visual acuity test-variability unchanged by post-hoc re-analysis. *Graefe's Arch Clin Exp Ophthalmol*. 2007;245:965-971.
49. Müller HL, Gebhardt U, Faldum A, et al. Xanthogranuloma, Rathke's Cyst, and Childhood Craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations. *J Clin Endocrinol Metab*. 2012;97:3935-3943.
50. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord*. 2001;31:5-17.
51. Gooding DC, Pflum MJ. The assessment of interpersonal pleasure: introduction of the anticipatory and consummatory interpersonal pleasure scale (ACIPS) and preliminary findings. *Psychiatry Res*. 2014;215:237-243.
52. Gooding DC, Pflum MJ. Further validation of the ACIPS as a measure of social hedonic response. *Psychiatry Res*. 2014;215:771-777.
53. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The ' ' Reading the Mind in the Eyes ' ' Test Revised Version : a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiat Assoc Child Psychol Psychiatry*. 2001;42:241-251.
54. Pyne DB, Boston T, Martin DT, Logan A. Evaluation of the Lactate Pro blood lactate analyser. *Eur J Appl Physiol*. 2000;82:112-116.
55. Ebner NC, Riediger M, Lindenberger U. FACES—A database of facial expressions in young, middle-aged, and older women and men: development and validation. *Behav Res Methods*. 2010;42:351-362.
56. Willenbockel V, Sadr J, Fiset D, Horne GO, Gosselin F, Tanaka JW. Controlling low-level image properties: the SHINE toolbox. *Behav Res Methods*. 2010;42:671-684.
57. Skovlund E, Fenstad GU. Should we always choose a nonparametric test when comparing two apparently nonnormal distributions? *J Clin Epidemiol*. 2001;54:86-92.
58. Scheller E, Büchel C, Gamer M. Diagnostic features of emotional expressions are processed preferentially. Whitney D, ed. *PLoS ONE*. 2012;7:e41792.
59. Kloosterman PH, Keefer KV, Kelley EA, Summerfeldt LJ, Parker JDA. Evaluation of the factor structure of the autism-spectrum quotient. *Pers Individ Dif*. 2011;50:310-314.
60. Novacek DM, Gooding DC, Pflum MJ. Hedonic capacity in the broader autism phenotype: should social anhedonia be considered a characteristic feature? *Front Psychol*. 2016;7:666.
61. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves "Mind-Reading" in humans. *Biol Psychiatry*. 2007;61:731-733.
62. Bourke C, Douglas K, Porter R. Processing of facial emotion expression in major depression: a review. *Aust New Zeal J Psychiatry*. 2010;44:681-696.
63. Lozier LM, Vanmeter JW, Marsh AA. Impairments in facial affect recognition associated with autism spectrum disorders: a meta-analysis. *Dev Psychopathol*. 2014;26:933-945.
64. Stoop R. Neuromodulation by oxytocin and vasopressin. *Neuron*. 2012;76:142-159.
65. Churchland PS, Winkielman P. Modulating social behavior with oxytocin: how does it work? What does it mean? *Horm Behav*. 2012;61:392-399.
66. Jurek B, Neumann ID. The oxytocin receptor: from intracellular signaling to behavior. *Physiol Rev*. 2018;98:1805-1908.
67. Sabatinelli D, Fortune EE, Li Q, et al. Emotional perception: meta-analyses of face and natural scene processing. *NeuroImage*. 2011;54:2524-2533.
68. Cook N, Miller J, Hart J. Parent observed neuro-behavioral and pro-social improvements with oxytocin following surgical resection of craniopharyngioma. *J Pediatr Endocrinol Metab*. 2016;29:995-1000.
69. Hoffmann A, Özyurt J, Lohle K, Reichel J, Thiel CM, Müller HL. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. *Endocrine*. 2017;56:175-185.
70. Keech B, Crowe S, Hocking DR. Intranasal oxytocin, social cognition and neurodevelopmental disorders: a meta-analysis. *Psychoneuroendocrinology*. 2018;87:9-19.
71. Flanagan JC, Sippel LM, Wahlquist A, Moran-Santa Maria MM, Back SE. Augmenting prolonged exposure therapy for PTSD with intranasal oxytocin: a randomized, placebo-controlled pilot trial. *J Psychiatr Res*. 2018;98:64-69.
72. Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. *Psychoneuroendocrinology*. 2009;34:917-923.
73. Rilling JK, DeMarco AC, Hackett PD, et al. Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. *Psychoneuroendocrinology*. 2014;39:237-248.

74. Caldwell HK. Oxytocin and sex differences in behavior. *Curr Opin Behav Sci*. 2018;23:13-20.
75. Neumann ID. Stimuli and consequences of dendritic release of oxytocin within the brain. *Biochem Soc Trans*. 2007;35:1252-1257.
76. Engelmann M, Wotjak CT, Landgraf R. Differential central and peripheral release of vasopressin and oxytocin in response to swim stress in rats. *Adv Exp Med Biol*. 1998;449:175-177.
77. Martin J, Kagerbauer SM, Gempt J, Podtschaske A, Hapfelmeier A, Schneider G. Oxytocin levels in saliva correlate better than plasma levels with concentrations in the cerebrospinal fluid of patients in neurocritical care. *J Neuroendocrinol*. 2018;30:e12596.

How to cite this article: Brandi M-L, Gebert D, Kopczak A, Auer MK, Schilbach L. Oxytocin release deficit and social cognition in craniopharyngioma patients. *J Neuroendocrinol*. 2020;32:e12842. https://doi.org/10.1111/jne.12842

7 References

1. Bunin, G.R., Surawicz, T.S., Witman, P.A., Preston-Martin, S., Davis, F., and Bruner, J.M. (1998). The descriptive epidemiology of craniopharyngioma. Journal of Neurosurgery 89, 547-551.
2. Müller, H.L. (2014). Craniopharyngioma. Endocrine Reviews 35, 513-543.
3. Sherlock, M., Ayuk, J., Tomlinson, J.W., Toogood, A.A., Aragon-Alonso, A., Sheppard, M.C., Bates, A.S., and Stewart, P.M. (2010). Mortality in Patients with Pituitary Disease. Endocrine Reviews 31, 301-342.
4. Pan, J., Qi, S., Liu, Y., Lu, Y., Peng, J., Zhang, X., Xu, Y., Huang, G.L., and Fan, J. (2016). Growth patterns of craniopharyngiomas: clinical analysis of 226 patients. Journal of neurosurgery Pediatrics 17, 418-433.
5. Karavitaki, N., Brufani, C., Warner, J.T., Adams, C.B.T., Richards, P., Ansorge, O., Shine, B., Turner, H.E., and Wass, J.A.H. (2005). Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clinical Endocrinology 62, 397-409.
6. Bao, Y., Pan, J., Qi, S.T., Lu, Y.T., and Peng, J.X. (2016). Origin of craniopharyngiomas: implications for growth pattern, clinical characteristics, and outcomes of tumor recurrence. J Neurosurg 125, 24-32.
7. Garnett, M.R., Puget, S., Grill, J., and Sainte-Rose, C. (2007). Craniopharyngioma. Orphanet Journal of Rare Diseases 2, 18.
8. Duff, J.M., Meyer, F.B., Ilstrup, D.M., Laws Jr, E.R., Schleck, C.D., and Scheithauer, B.W. (2000). Long-term outcomes for surgically resected craniopharyngiomas. Neurosurgery 46, 291.
9. Chen, C., Okera, S., Davies, P.E., Selva, D., and Crompton, J.L. (2003). Craniopharyngioma: a review of long-term visual outcome. Clinical & experimental ophthalmology 31, 220-228.
10. Wijnen, M., van den Heuvel-Eibrink, M.M., Janssen, J.A., Catsman-Berrevoets, C.E., Michiels, E.M., van Veelen-Vincent, M.C., Dallenga, A.H., van den Berge, J.H., van Rij, C.M., Van der Lely, A.J., et al. (2017). Very long-term sequelae of craniopharyngioma. European journal of endocrinology.
11. Pickering, L., Jennum, P., Gammeltoft, S., Poulsgaard, L., Feldt-Rasmussen, U., and Klose, M. (2014). Sleep-wake and melatonin pattern in craniopharyngioma patients. European journal of endocrinology 170, 873-884.
12. Carpentieri, S.C., Waber, D.P., Scott, R.M., Goumnerova, L.C., Kieran, M.W., Cohen, L.E., Kim, F., Billett, A.L., Tarbell, N.J., and Pomeroy, S.L. (2001). Memory deficits among children with craniopharyngiomas. Neurosurgery 49, 1053-1057; discussion 1057-1058.
13. Lobosky, J.M., Vangilder, J.C., and Damasio, A.R. (1984). Behavioural manifestations of third ventricular colloid cysts. Journal of neurology, neurosurgery, and psychiatry 47, 1075-1080.
14. Poretti, A., Grotzer, M.A., Ribi, K., Schonle, E., and Boltshauser, E. (2004). Outcome of craniopharyngioma in children: long-term complications and quality of life. Developmental medicine and child neurology 46, 220-229.
15. Müller, H.L., Merchant, T.E., Warmuth-Metz, M., Martinez-Barbera, J.-P., and Puget, S. (2019). Craniopharyngioma. Nature Reviews Disease Primers 5, 75.
16. Radiopedia.org. [Internet]. rID: 2728, Case courtesy of Assoc. Prof. Frank Gaillard. Available from http://www.radiopedia.org/.
17. Dandurand, C., Sepehry, A.A., Asadi Lari, M.H., Akagami, R., and Gooderham, P. (2017). Adult Craniopharyngioma: Case Series, Systematic Review, and Meta-Analysis. Neurosurgery.
18. Hämatologie, G.f.P.O.u. S1-Leitlinie Kraniopharyngeom im Kindes- und Jugendalter.
19. Sofroniew, M.V. (1983). Morphology of vasopressin and oxytocin neurones and their central and vascular projections. Progress in brain research 60, 101-114.
20. Swanson, L.W., and Sawchenko, P.E. (1983). Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annual review of neuroscience 6, 269-324.
21. DeVile, C.J., Grant, D.B., Hayward, R.D., and Stanhope, R. (1996). Growth and endocrine sequelae of craniopharyngioma. Archives of Disease in Childhood 75, 108-114.

22. Dreamstime.com. [Internet]. ID 60850471 © Legger [cited 2020 Jun 9]. Available from: http://www.dreamstime.com/.
23. Fuchs, A.R., and Fuchs, F. (1984). Endocrinology of human parturition: a review. British journal of obstetrics and gynaecology 91, 948-967.
24. Mitre, M., Marlin, B.J., Schiavo, J.K., Morina, E., Norden, S.E., Hackett, T.A., Aoki, C.J., Chao, M.V., and Froemke, R.C. (2016). A Distributed Network for Social Cognition Enriched for Oxytocin Receptors. The Journal of neuroscience : the official journal of the Society for Neuroscience 36, 2517-2535.
25. Grinevich, V., Knobloch-Bollmann, H.S., Eliava, M., Busnelli, M., and Chini, B. (2016). Assembling the Puzzle: Pathways of Oxytocin Signaling in the Brain. Biological psychiatry 79, 155-164.
26. Deblon, N., Veyrat-Durebex, C., Bourgoin, L., Caillon, A., Bussier, A.L., Petrosino, S., Piscitelli, F., Legros, J.J., Geenen, V., Foti, M., et al. (2011). Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats. PloS one 6, e25565.
27. Lawson, E.A. (2017). The effects of oxytocin on eating behaviour and metabolism in humans. Nature reviews Endocrinology 13, 700-709.
28. Faehrmann, T., Zernig, G., and Mechtcheriakov, S. (2018). [Oxytocin and the mechanisms of alcohol dependence]. Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Osterreichischer Nervenarzte und Psychiater 32, 1-8.
29. Kim, S., Kwok, S., Mayes, L.C., Potenza, M.N., Rutherford, H.J.V., and Strathearn, L. (2017). Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways. Annals of the New York Academy of Sciences 1394, 74-91.
30. Veening, J.G., de Jong, T.R., Waldinger, M.D., Korte, S.M., and Olivier, B. (2015). The role of oxytocin in male and female reproductive behavior. European journal of pharmacology 753, 209-228.
31. Hurlemann, R., and Marsh, N. (2017). Deciphering the modulatory role of oxytocin in human altruism. Reviews in the neurosciences 28, 335-342.
32. Feeser, M., Fan, Y., Weigand, A., Hahn, A., Gärtner, M., Böker, H., Grimm, S., and Bajbouj, M. (2015). Oxytocin improves mentalizing – Pronounced effects for individuals with attenuated ability to empathize. Psychoneuroendocrinology 53, 223-232.
33. Lopatina, O.L., Komleva, Y.K., Gorina, Y.V., Higashida, H., and Salmina, A.B. (2018). Neurobiological Aspects of Face Recognition: The Role of Oxytocin. Frontiers in behavioral neuroscience 12, 195.
34. Labuschagne, I., Phan, K.L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., Stout, J.C., and Nathan, P.J. (2010). Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 35, 2403-2413.
35. Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., and Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience 25, 11489-11493.
36. Domes, G., Normann, C., and Heinrichs, M. (2016). The effect of oxytocin on attention to angry and happy faces in chronic depression. BMC psychiatry 16, 92.
37. Neumann, I.D., and Landgraf, R. (2012). Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends in neurosciences 35, 649-659.
38. Carson, D.S., Berquist, S.W., Trujillo, T.H., Garner, J.P., Hannah, S.L., Hyde, S.A., Sumiyoshi, R.D., Jackson, L.P., Moss, J.K., Strehlow, M.C., et al. (2015). Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. Molecular psychiatry 20, 1085-1090.
39. Guastella, A.J., Howard, A.L., Dadds, M.R., Mitchell, P., and Carson, D.S. (2009). A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34, 917-923.

40. Cataldo, I., Azhari, A., and Esposito, G. (2018). A Review of Oxytocin and Arginine-Vasopressin Receptors and Their Modulation of Autism Spectrum Disorder. Frontiers in molecular neuroscience 11, 27.
41. Servan, A., Brunelin, J., and Poulet, E. (2018). The effects of oxytocin on social cognition in borderline personality disorder. L'Encephale 44, 46-51.
42. Mitre, M., Minder, J., Morina, E.X., Chao, M.V., and Froemke, R.C. (2018). Oxytocin Modulation of Neural Circuits. Current topics in behavioral neurosciences 35, 31-53.
43. Ondruch, A., Maryniak, A., Kropiwnicki, T., Roszkowski, M., and Daszkiewicz, P. (2011). Cognitive and social functioning in children and adolescents after the removal of craniopharyngioma. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 27, 391-397.
44. Pereira, A.M., Schmid, E.M., Schutte, P.J., Voormolen, J.H., Biermasz, N.R., Van Thiel, S.W., Corssmit, E.P., Smit, J.W., Roelfsema, F., and Romijn, J.A. (2005). High prevalence of longâ€• term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. Clinical Endocrinology 62, 197-204.
45. Roemmler-Zehrer, J., Geigenberger, V., Störmann, S., Ising, M., Pfister, H., Sievers, C., Stalla, G.K., and Schopohl, J. Specific behaviour, mood and personality traits may contribute to obesity in patients with craniopharyngioma. Clinical Endocrinology 82, 106-114.
46. Zada, G., Kintz, N., Pulido, M., and Amezcua, L. (2013). Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: a systematic literature review. PloS one 8, e76562.
47. Cook, N., Miller, J., and Hart, J. (2016). Parent observed neuro-behavioral and pro-social improvements with oxytocin following surgical resection of craniopharyngioma. Journal of Pediatric Endocrinology and Metabolism.
48. Walker, E.R., McGee, R.E., and Druss, B.G. (2015). Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry 72, 334-341.
49. Churchland, P.S., and Winkielman, P. (2012). Modulating Social Behavior with Oxytocin: How does it work? What does it mean? Hormones and Behavior 61, 392-399.
50. Bartz, J.A., Zaki, J., Bolger, N., and Ochsner, K.N. (2011). Social effects of oxytocin in humans: context and person matter. Trends in cognitive sciences 15, 301-309.
51. Meyer-Lindenberg, A., Domes, G., Kirsch, P., and Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nature Reviews Neuroscience 12, 524-538.
52. Wotjak, C.T., Naruo, T., Muraoka, S., Simchen, R., Landgraf, R., and Engelmann, M. (2001). Forced swimming stimulates the expression of vasopressin and oxytocin in magnocellular neurons of the rat hypothalamic paraventricular nucleus. European Journal of Neuroscience 13, 2273-2281.
53. de Jong, T.R., Menon, R., Bludau, A., Grund, T., Biermeier, V., Klampfl, S.M., Jurek, B., Bosch, O.J., Hellhammer, J., and Neumann, I.D. (2015). Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. Psychoneuroendocrinology 62, 381-388.
54. Carter, C.S., Pournajafi-Nazarloo, H., Kramer, K.M., Ziegler, T.E., White-Traut, R., Bello, D., and Schwertz, D. (2007). Oxytocin: behavioral associations and potential as a salivary biomarker. Annals of the New York Academy of Sciences 1098, 312-322.
55. Månsson, K., Cortes, D., Lin, T., Horta, M., Frazier, I., Lussier, D., Feifel, D., Fischer, H., and Ebner, N. (2018). Neuroplasticity after acute and repeated exposure to oxytocin : a multi-site MRI analysis. In 24th Annual Meeting of the Organization for Human Brain Mapping, Singapore, June 17-21, 2018. (
56. Benner, S., Aoki, Y., Watanabe, T., Endo, N., Abe, O., Kuroda, M., Kuwabara, H., Kawakubo, Y., Takao, H., Kunimatsu, A., et al. (2018). Neurochemical evidence for differential effects of acute and repeated oxytocin administration. Molecular psychiatry.

57. Fujii, T., Schug, J., Nishina, K., Takahashi, T., Okada, H., and Takagishi, H. (2016). Relationship between Salivary Oxytocin Levels and Generosity in Preschoolers. Scientific Reports 6.
58. Grewen, K.M., Davenport, R.E., and Light, K.C. (2010). An investigation of plasma and salivary oxytocin responses in breast-and formula-feeding mothers of infants. Psychophysiology 47, 625-632.
59. Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wüllner, U., Maier, W., and Hurlemann, R. (2013). Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Scientific Reports 3, 3440.
60. Freeman, S.M., Samineni, S., Allen, P.C., Stockinger, D., Bales, K.L., Hwa, G.G., and Roberts, J.A. (2016). Plasma and CSF oxytocin levels after intranasal and intravenous oxytocin in awake macaques. Psychoneuroendocrinology 66, 185-194.
61. Heinrichs, M., and Domes, G. (2008). Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. Progress in brain research 170, 337-350.
62. Martin, J., Kagerbauer, S.M., Gempt, J., Podtschaske, A., Hapfelmeier, A., and Schneider, G. (2018). Oxytocin levels in saliva correlate better than plasma levels with concentrations in the cerebrospinal fluid of patients in neurocritical care. Journal of neuroendocrinology, e12596.
63. Kagerbauer, S.M., Martin, J., Schuster, T., Blobner, M., Kochs, E.F., and Landgraf, R. (2013). Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. Journal of neuroendocrinology 25, 668-673.
64. Leng, G., and Sabatier, N. (2016). Measuring Oxytocin and Vasopressin: Bioassays, Immunoassays and Random Numbers. Journal of neuroendocrinology 28.
65. Gebert, D., Auer, M.K., Stieg, M.R., Freitag, M.T., Lahne, M., Fuss, J., Schilbach, K., Schopohl, J., Stalla, G.K., and Kopczak, A. (2018). De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. Psychoneuroendocrinology 88, 61-69.
66. Happe, F., Cook, J.L., and Bird, G. (2017). The Structure of Social Cognition: In(ter)dependence of Sociocognitive Processes. Annual review of psychology 68, 243-267.
67. Perez-Rodriguez, M.M., Mahon, K., Russo, M., Ungar, A.K., and Burdick, K.E. (2015). Oxytocin and Social Cognition in Affective and Psychotic Disorders. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 25, 265-282.
68. Yao, S., Becker, B., Zhao, W., Zhao, Z., Kou, J., Ma, X., Geng, Y., Ren, P., and Kendrick, K.M. (2018). Oxytocin Modulates Attention Switching Between Interoceptive Signals and External Social Cues. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 43, 294-301.
69. Shahrestani, S., Kemp, A.H., and Guastella, A.J. (2013). The Impact of a Single Administration of Intranasal Oxytocin on the Recognition of Basic Emotions in Humans: A Meta-Analysis. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 38, 1929-1936.
70. Hovey, D., Henningsson, S., Cortes, D.S., Bänziger, T., Zettergren, A., Melke, J., Fischer, H., Laukka, P., and Westberg, L. (2018). Emotion recognition associated with polymorphism in oxytocinergic pathway gene ARNT2. Social cognitive and affective neuroscience 13, 173-181.
71. Rutigliano, G., Rocchetti, M., Paloyelis, Y., Gilleen, J., Sardella, A., Cappucciati, M., Palombini, E., Dell'Osso, L., Caverzasi, E., Politi, P., et al. (2016). Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. Psychiatry Res 241, 207-220.
72. Brandi, M.-L., Gebert, D., Kopczak, A., Auer, M.K., and Schilbach, L. (2020). Oxytocin release deficit and social cognition in craniopharyngioma patients. Journal of neuroendocrinology 32, e12842.
73. Kitzinger, J. (1995). Qualitative research. Introducing focus groups. BMJ (Clinical research ed) 311, 299-302.

74. Müller, H.L., Bruhnken, G., Emser, A., Faldum, A., Etavard-Gorris, N., Gebhardt, U., Kolb, R., and Sörensen, N. (2005). Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 21, 975-980.
75. Gesellschaft für Pädiatrische Onkologie und Hämatologie, G. (10/2001; überarbeitet 01/2019). S1-Leitlinie "Kraniopharyngeom im Kindes- und Jugendalter". AWMF-Reg._Nr. 025/026.
76. Kroll-Desrosiers, A.R., Nephew, B.C., Babb, J.A., Guilarte-Walker, Y., Moore Simas, T.A., and Deligiannidis, K.M. (2017). Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. Depression and anxiety 34, 137-146.
77. Mah, B.L. (2016). Oxytocin, Postnatal Depression, and Parenting: A Systematic Review. Harvard Review of Psychiatry 24, 1-13.
78. Parker, K.J., Kenna, H.A., Zeitzer, J.M., Keller, J., Blasey, C.M., Amico, J.A., and Schatzberg, A.F. (2010). Preliminary evidence that plasma oxytocin levels are elevated in major depression. Psychiatry research 178, 359-362.
79. Aoki, Y., Watanabe, T., Abe, O., Kuwabara, H., Yahata, N., Takano, Y., Iwashiro, N., Natsubori, T., Takao, H., and Kawakubo, Y. (2015). Oxytocin's neurochemical effects in the medial prefrontal cortex underlie recovery of task-specific brain activity in autism: a randomized controlled trial. Molecular psychiatry 20, 447-453.
80. Bourke, C., Douglas, K., and Porter, R. (2010). Processing of facial emotion expression in major depression: a review. Australian and New Zealand Journal of Psychiatry 44, 681-696.
81. Guastella, A.J., Einfeld, S.L., Gray, K.M., Rinehart, N.J., Tonge, B.J., Lambert, T.J., and Hickie, I.B. (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biological psychiatry 67, 692-694.
82. Kliemann, D., Dziobek, I., Hatri, A., Steimke, R., and Heekeren, H.R. (2010). Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. Journal of Neuroscience 30, 12281-12287.
83. Disner, S.G., Beevers, C.G., Haigh, E.A., and Beck, A.T. (2011). Neural mechanisms of the cognitive model of depression. Nature Reviews Neuroscience 12, 467-477.
84. Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., and Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. Journal of child psychology and psychiatry, and allied disciplines 42, 241-251.
85. Gooding, D.C., and Pflum, M.J. (2014). The assessment of interpersonal pleasure: introduction of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and preliminary findings. Psychiatry Res 215, 237-243.
86. Roiser, J.P., Elliott, R., and Sahakian, B.J. (2012). Cognitive mechanisms of treatment in depression. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 37, 117-136.
87. Hsu, E.A., Miller, J.L., Perez, F.A., and Roth, C.L. (2018). Oxytocin and Naltrexone Successfully Treat Hypothalamic Obesity in a Boy Post-Craniopharyngioma Resection. The Journal of clinical endocrinology and metabolism 103, 370-375.
88. Daubenbüchel, A.M.M., Hoffmann, A., Eveslage, M., Özyurt, J., Lohle, K., Reichel, J., Thiel, C.M., Martens, H., Geenen, V., and Müller, H.L. (2016). Oxytocin in survivors of childhood-onset craniopharyngioma. Endocrine 54, 524-531.
89. Hoffmann, A., Ozyurt, J., Lohle, K., Reichel, J., Thiel, C.M., and Muller, H.L. (2017). First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. Endocrine 56, 175-185.
90. Daughters, K., Manstead, A.S.R., and Rees, D.A. (2017). Hypopituitarism is associated with lower oxytocin concentrations and reduced empathic ability. Endocrine 57, 166-174.

91. Müller, H.L. (2019). MANAGEMENT OF ENDOCRINE DISEASE: Childhood-onset craniopharyngioma: state of the art of care in 2018. European journal of endocrinology 180, R159-R174.
92. Neumann, I.D., and Slattery, D.A. (2016). Oxytocin in general anxiety and social fear: a translational approach. Biological psychiatry 79, 213-221.
93. Domes, G., Heinrichs, M., Michel, A., Berger, C., and Herpertz, S.C. (2007). Oxytocin improves “mind-reading” in humans. Biological psychiatry 61, 731-733.
94. Ebert, A., and Brüne, M. (2017). Oxytocin and social cognition. In Behavioral pharmacology of neuropeptides: Oxytocin. (Springer), pp 375-388.
95. Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kästel, T., Schnell, K., Büchel, C., Domes, G., and Herpertz, S.C. (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. American Journal of Psychiatry 170, 1169-1177.
96. Platt, B., Cohen Kadosh, K., and Lau, J.Y. (2013). The role of peer rejection in adolescent depression. Depression and anxiety 30, 809-821.

8 Acknowledgements / Danksagung

Mein Dank gilt zu allererst meiner Mentorin und Betreuerin Dr Anna Kopczak. Gleichzeitig ein Haus zu bauen, zwei Kleinkinder aufzuziehen und als Vollzeit-Ärztin zu arbeiten hielt sie nicht davon ab, zusätzlich eine vollständige klinische Studie mit mir aufzusetzen, die die Basis nicht nur für meine sondern weitere Doktorarbeiten und PhDs geworden ist. Ich werde mich immer mit Freude an unsere spätabendlichen Paper-Diskussionen per Telefon erinnern, in deren Hintergrund man müdes Kindergeplapper von Kathi und Max hören konnte. Anna, mit deiner Stamina spielst du in einer eigenen Liga!

Mein Dank gilt des Weiteren dem wundervollen Team, mit dem ich am MPI-P München zusammen arbeiten durfte. Prof Stalla für die Unterstützung dieser Arbeit und Aufnahme in seine Arbeitsgruppe. Im einzelnen haben mich dort Dr Matthias Auer ("Vielleicht ist Oxytocin einfach nicht so wichtig..."), Dr Mareike Stieg ("Wie kann ich dich unterstützen?"), Dr Caroline Sievers ("Aber worauf basiert denn deine research rationale?") und Dr Johanna Faust ("Hast du deine Ausgaben eingereicht?") immer wieder großzügig gestützt und vorangetragen. Dr Marie-Luise Brandi ("Dieser *p*-Wert ist KEIN Trend!") war eine hervorragende Erstautorin der Publikation 2.

Mein ganz persönlicher Dank für jegliche Unterstützung in den Jahren dieser Doktorarbeit geht an meinen fantastischen Partner Ivo, der es immer wieder schafft, die perfekte Balance zwischen Gut-Zureden und Antreiben zu finden; an meinen wundervollen Stiefsohn *Joe-Poe* Jorin, der mich immer wieder aufs Neue stolz macht; an meine Freunde, die mich reihum im Laufe dieser Jahre bei sich aufgenommen, bekocht und mit hilfreichen Diskussionen vorangebracht haben: it-helps-talking-it-through Alexandra Clement, renaissance-man Dr Fabian Wadsworth, leidenschaftliche und eloquent-kritische Dr Susanne Thürigen, gleichermaßen leidenschaftlicher und eloquent-kritischer Dr Fabian Ochsenfeld, Pocahontas Maria Fischer, glamorous Monday-shark Luise Birgelen, und mein Bruder Friedrich, dessen unerbittlicher Drive und Charme mich immer wieder inspiriert.

Vor allem jedoch widme ich diese Arbeit meiner Mutter und meinem verstorbenen Vater. Dies hier ist nur eine winzige Anerkennung ihrer unermüdlichen Unterstützung und Führung durch die ersten Dekaden meines Lebens. In der Welt dieser beiden Menschen aufzuwachsen war ein Privileg.