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 motivation3 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:

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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 magnocellular 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 towards 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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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)\textsuperscript{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 fixing 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\textsuperscript{36} were not included because of relevant visual impairments. This left 13 patients (P) who were diagnosed with a craniopharyngioma (six female; age: mean \( \text{M}_p = 37.153 \), \( \text{SD}_p = 11.081 \); FrACT: \( \text{M}_p = 0.447 \), \( \text{SD}_p = 0.008 \)) and 23 healthy controls (HC) (11 female; age: \( \text{M}_{HC} = 36.826 \), \( \text{SD}_{HC} = 12.995 \); FrACT: \( \text{M}_{HC} = 0.447 \), \( \text{SD}_{HC} = 0.014 \)) to participate in the eye-tracking experiments. There was no significant difference in age or VA between the groups (\( t_{age} = 0.076, P_{age} = 0.940 \); \( t_{VA} = 0.166, P_{VA} = 0.869 \)).

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,\textsuperscript{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 (\( \Delta \% \text{oxytocin}: \text{M}_{p} = -7.898\%; \text{SD}_{p} = 20.600 \)) compared to healthy controls (\( \Delta \% \text{oxytocin}: \text{M}_{HC} = 21.256\%; \text{SD}_{HC} = 27.417 \)) \( U = 54.5, P < 0.001 \) (Figure 2A), but no significant difference in baseline levels (Oxy1: \( \text{M}_{HC} = 1.240 \) pg mL\(^{-1}\); \( \text{SD}_{HC} = 1.078 \); Oxy2: \( \text{M}_p = 1.903 \) pg mL\(^{-1}\); \( \text{SD}_p = 1.432 \)), \( U = 183, P = 0.865 \).

Patients’ degree of hypothalamic damage was assessed using an established grading system for classification,\textsuperscript{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\textsuperscript{50}), the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS\textsuperscript{51,52}) and the “Reading the Mind in the Eyes” test (RMET\textsuperscript{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.\textsuperscript{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...
BRANDI et al. (Kettler Ergometer TXI; Kettler, Ense, Germany) with stepwise increasing wattage difficulty. Lactate in capillary blood was measured repeatedly (Lactate Pro2®) aiming 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:

\[
\Delta\% - \text{oxytocin} = \left( \frac{\text{Oxy2} - \text{Oxy1}}{\text{Oxy1}} \right) \times 100
\]

**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 oestriadiol + 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 oestriadiol + oral progesterone are administered every 14 days for 10 days.
^aOf 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.

| 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)

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 Corp., 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 x 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 capabilities 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.\textsuperscript{12,41,42} The stimulus set included 24 different individuals (12 female) retrieved from the FACES database.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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 $2 \times 3$ 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.\textsuperscript{12,45}
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 (MP = 80.876%, SDp = 17.341) compared to healthy controls (MHC = 90.036%, SDHC = 6.104, t = −1.819, P = 0.046). The performance in the age categorisation task was not significantly different between patients (MP = 53.738%, SDp = 7.965) and healthy controls (MHC = 55.193%, SDHC = 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

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

| Measure                     | Levene’s test | Shapiro-Wilk test |
|-----------------------------|---------------|-------------------|
|                            | 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 |
| ox too cin                  | 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 |

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.
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, \eta^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 \times condition interaction (F_{1,34} = 0.31, P = 0.862, \eta^2 = 0.000), nor a significant effect for group differences (F_{1,34} = 0.844, P = 0.365, \eta^2 = 0.024).

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

| Table 4 | Descriptive statistic of self-report measures and test-statistical measures |
|---------|-------------|-------------|-------------|-------------|
| Group   | N  | Mean  | SD  | Test statistic |
|---------|----|--------|-----|---------------|
| 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 |
| 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.

**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.
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).

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).
The results somewhat contradict the previous findings reported by Daughters et al., 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. applied the 28-item short version), as well as differences in patient groups (we included craniopharyngioma patients with a defined hypothalamic damage, Daughters et al. 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.

Furthermore, similar to patients with autism, 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 Daughters et al., 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 demonstrating 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, such as by redirecting gaze towards...
informative regions of the face. 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 ∆% 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, responding to stimulation. Particularly in response to social and emotional cues, oxytocin pathways are likely to become activated, and not only trigger peripheral changes in oxytocin levels, but also simultaneously stimulate activity in specific central neural populations, in this way mediating complex social behaviour. 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. There is also evidence for oxytocin-mediated activity of the amygdala in humans: face perception and reflexive gaze behaviour during emotion recognition have been shown to be closely related to neural activation in the amygdala. The amygdala was also found to be strongly modulated by oxytocin administration and is assumed to have a key role in attentional processes reorienting to salient stimuli. 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. 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 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. 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 and improving self-evaluation in patients suffering from social anxiety. 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. 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 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. Second, this simultaneous release is likely triggered in response to social and emotional cues. Third, salivary oxytocin levels, in contrast to plasma levels, have been shown to correlate with cerebro-spinal fluid-levels in humans.

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.

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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.

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