# Socio-behavioral dysfunction in disorders of hypothalamic-pituitary involvement: The potential role of disease-induced oxytocin and vasopressin signaling deficits

Lauren Clarke [a], Olena Zyga [a], Psalm L. Pineo-Cavanaugh [a], Michael Jeng [b], Nancy J. Fischbein [c], Sonia Partap [d], Laurence Katznelson [e], Karen J. Parker [a,f,*]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University, 1201 Welch Road, MSLS P-104, Stanford, CA 94305, USA
[b] Department of Pediatrics (Hematology/Oncology Division), Stanford University, 1000 Welch Road, Suite 300, Palo Alto, CA 94304, USA
[c] Department of Radiology, Stanford University, 450 Quarry Rd, Suite 5659, Palo Alto, CA 94304, USA
[d] Department of Neurology and Neurological Sciences (Child Neurology Division), Stanford University, 750 Welch Road, Suite 317, Palo Alto, CA 94304, USA
[e] Departments of Neurosurgery and Medicine (Endocrinology Division), Stanford University, 875 Blake Wilbur Drive, Stanford, CA 94305, USA
[f] Department of Comparative Medicine, Stanford University, 300 Pasteur Drive, Stanford, CA 94305, USA

## ARTICLE INFO

## ABSTRACT

Disorders involving hypothalamic and pituitary (HPIT) structures—including craniopharyngioma, Langerhans cell histiocytosis, and intracranial germ cell tumors—can disrupt brain and endocrine function. An area of emerging clinical concern in patients with these disorders is the co-occurring socio-behavioral dysfunction that persists after standard hormone replacement therapy. Although the two neuropeptides most implicated in mammalian social functioning (oxytocin and arginine vasopressin) are of hypothalamic origin, little is known about how disease-induced damage to HPIT structures may disrupt neuropeptide signaling and, in turn, impact patients' socio-behavioral functioning. Here we provide a clinical primer on disorders of HPIT involvement and a review of neuropeptide signaling and socio-behavioral functioning in relevant animal models and patient populations. This collective evidence suggests that neuropeptide signaling disruptions contribute to socio-behavioral deficits experienced by patients with disorders of HPIT involvement. A better understanding of the biological underpinnings of patients' socio-behavioral symptoms is now needed to enable the development of the first targeted pharmacological strategies by which to manage patients' socio-behavioral dysfunction.

## 1. Introduction

Craniopharyngioma (CP), central nervous system Langerhans cell histiocytosis (CNS LCH), and intracranial germ cell tumors (IGCTs) frequently infiltrate and damage the hypothalamic-pituitary (HPIT) region of the brain and are therefore considered collectively here as disorders of HPIT involvement. The neuroanatomical presentation and clinical features of these conditions have been well-characterized, and treatments have been well-described for each disorder (Grois et al., 1998; Karavitaki et al., 2006; Crawford et al., 2007). There is, however, an emerging area of clinical concern for patients with these disorders that relates to impaired social and behavioral functioning. The pathogenesis of this co-occurring socio-behavioral dysfunction remains poorly understood, and the research findings in this domain have not been

comprehensively reviewed and synthesized.

Damage to the HPIT region can disrupt the production and release of oxytocin (OXT) and arginine vasopressin (AVP) (Sokol, 1970; Lang et al., 1983; Makara et al., 1995, 1996; Haller et al., 1996). OXT and AVP are closely-related neuropeptides that are predominantly produced by the hypothalamus and act as neurotransmitters when released directly into the brain and as hormones when released into the bloodstream via the posterior pituitary gland (Stoop, 2012). In the brain, OXT and AVP are important regulators of mammalian social behavior (Carter et al., 2008; Meyer-Lindenberg et al., 2011; Althammer, Eliava, and Grinevich, 2021). Disrupted hypothalamic OXT and/or AVP signaling may therefore contribute to socio-behavioral dysfunction in clinical populations. Because CP, CNS LCH, and IGCTs commonly involve the HPIT region, we hypothesize that the social and behavioral dysfunction often

experienced by patients with these disorders is related to HPIT damage and subsequent OXT/AVP dysregulation. To this end, the present review provides a clinical primer on disorders of HPIT involvement and subsequently examines the preclinical and clinical literature to assess and better understand the relationships between HPIT damage, OXT and AVP signaling pathways, and co-occurring socio-behavioral dysfunction in patients with CP, CNS LCH, and IGCTs.

## 2. Disorders of HPIT involvement

This section explores the epidemiology, pathogenesis, neuroanatomical presentation, clinical presentation, and common treatment strategies for the three aforementioned disorders of HPIT involvement: CP, CNS LCH, and IGCTs. We also review the available evidence for co-occurring socio-behavioral dysfunction in patients with these disorders. A summary of this section is included in Table 1.

### 2.1. Craniopharyngioma (CP)

#### 2.1.1. CP epidemiology and pathogenesis
The annual incidence of CP is 1.6 per million people in the United States (Momin et al., 2021). Of all brain and other CNS tumors, CP has been estimated to account for 4% in children and 0.7% in the overall population (Ostrom et al., 2015, 2021). CP exhibits a 1:1 sex ratio and a bimodal age distribution with incidence peaking between five to nine years and again between 50 and 69 years. In the United States, there was an increased incidence in Blacks compared to other races (Momin et al., 2021). These tumors arise from Rathke cleft cells or other embryonic epithelial cells (Gaston-Massuet et al., 2011). CP is usually categorized as adamantinomatous or papillary, though a few cases are classified as mixed (Bao et al., 2016; McCrea et al., 2016). Pediatric CP is almost exclusively adamantinomatous while the rarer papillary cases are more common among adults (McCrea et al., 2016). CP has characteristic radiologic findings of a suprasellar mass with both cystic and solid components and can be diagnosed with imaging alone when these findings are present. However, histological confirmation can also be used to make a definitive diagnosis, especially when these characteristic radiological findings are not present (Karavitaki et al., 2006; PDQ, 2020a).

#### 2.1.2. CP neuroanatomical presentation
Within the brain, CP commonly involves the sellar and hypothalamic areas, the third ventricle, and the adjacent vasculature (McCrea et al., 2016; Yano et al., 2016). CP infiltrates locally within the suprasellar and/or intrasellar regions, though recurrences in other regions have been reported (Ito, Jamshidi, and Yamanaka, 2001; Karavitaki et al., 2006; Karavitaki and Wass, 2008; PDQ, 2020a). Given its Rathke pouch origin, hypothalamic involvement is common, though not universal. According to a review of over 30 years of CP cases at a children's hospital, less than 6% (seven of 122) had no hypothalamic involvement. Of the remaining cases, 58% (67 of 115) had anterior hypothalamic involvement and 42% (48 of 115) had anterior and posterior hypothalamic involvement (Cohen et al., 2013). CP is also associated with the loss of the posterior pituitary "bright spot" on T1-weighted magnetic resonance imaging (MRI) (May et al., 2006). This "bright spot," an indication of the functional integrity of the posterior pituitary gland, is the result of local accumulation of AVP (Kilday et al., 2015). Characteristic CP features are shown in Fig. 1 and can be compared to typical features of the same neuroanatomic structures in Fig. S1.

#### 2.1.3. CP clinical presentation
Patients presenting with CP commonly report headache, visual impairment, weight gain, nausea/vomiting, and signs of pituitary insufficiency such as growth arrest or delayed puberty in children and hypopituitarism with central diabetes insipidus (DI) in adults (Bao et al., 2016; Capatina et al., 2018). Such pituitary dysfunction is common: In

one study, 35–95% of patients presenting with CP had growth hormone (GH) deficiency, 38–82% of patients had follicle-stimulating hormone/luteinizing hormone (FSH/LH) deficiency, 21–62% of patients had adrenocorticotropic hormone (ACTH) deficiency, 21–42% of patients had thyroid-stimulating hormone (TSH) deficiency, and six to 38% of patients central DI (Karavitaki et al., 2006). Hypopituitarism can be present at diagnosis or may occur following surgical intervention (Pratheesh et al., 2013). There is also a high degree of chronicity: At 20 years post-diagnosis, more than 85% of CP patients experience persistent deficiencies in GH, FSH/LH, ACTH, and TSH (Karavitaki et al., 2005). Despite undergoing full pituitary hormone replacement therapy, including GH replacement therapy, CP patients continue to report lower overall physical and mental health (Yano et al., 2016). There is therefore a need for the development of additional therapeutic options to improve the health of these patients.

#### 2.1.4. CP treatment options
While the therapeutic approach for CP often involves surgical resection with postoperative adjuvant radiation therapy, treatment plans may vary based on tumor localization. If tumors can be removed without damaging the optic pathway or HPIT region, the treatment of choice is complete resection. However, if the tumor involves or is immediately adjacent to these critical regions, the extensive surgery required for total resection has the potential to damage these vital structures. Such damage increases the likelihood that the patient will experience neuropsychological impairment and other postoperative complications that may leave them dependent on lifelong pituitary hormone replacement therapy. In these cases, limited resection followed by local irradiation is the favored treatment plan (Henderson and Schwartz, 2022; PDQ, 2020a).

Invasive surgery for CP has the potential to cause inadvertent damage to neighboring brain tissue; therefore, surgical techniques using endoscopy have been developed that provide a clearer view of the tumor site. These new techniques decrease the risk of inadvertent damage to neighboring structures and thus the risk of complications following resection (Yano et al., 2016; Qiao, 2019). For example, sparing the posterior hypothalamus during surgical resection of CP can improve health-related quality of life in CP patients (Bogusz et al., 2019). These surgical advances and other improvements in treatment options may have also contributed to the decreasing mortality of CP: While the mean standardized mortality ratio (the ratio of observed deaths in the study group to the expected deaths in the general population) was a pooled 6.2 before 2010, it declined to 2.9 after 2010 (Qiao, 2019).

#### 2.1.5. CP socio-behavioral functioning
A number of CP patients report the onset of social, emotional, and behavioral dysfunction at some point following their diagnosis. In a sample of 54 children and adults assessed 10 years post-diagnosis, 31% reported personality changes and 47% reported psychosocial morbidity (Pereira et al., 2005). Compared to healthy controls, CP patients also reported experiencing significantly higher levels of social isolation and decreased social functioning. Interestingly, the age of onset appears to influence the type of socio-behavioral disruptions associated with CP: While adult-onset CP patients had higher levels of anxiety and depression, younger patients saw more impact in the domains of social isolation and social functioning (Dekkers et al., 2006).

Multiple studies have endeavored to further quantify the impact these socio-behavioral disruptions have on quality of life in children with CP. Among other issues, parents reported that children with CP experienced significant problems in school, rejection by their peers, high levels of aggression, and challenges with depression and anxiety (Poretti et al., 2004; Ondruch et al., 2011). A systematic review of individuals with child-onset CP found that 57% experienced neurobehavioral dysfunction, 41% reported social impairment, and 40% had difficulties maintaining relationships (Zada et al., 2013). Children with hypothalamic CP involvement also experienced challenges performing

**Table 1**
Clinical overview of the disorders of HPIT involvement and associated OXT/AVP alterations.

| | Craniopharyngioma (CP) | Langerhans cell histiocytosis (LCH) | Intracranial germ cell tumors (IGCT) |
|---|---|---|---|
| Disease description | • Low-grade brain tumor<br>• Arising from ectodermal remnants, rathke cleft, or other embryonal epithelium<br>(PDQ, 2020a) | • Low-grade tumor that can occur throughout the body, including the CNS<br>• Arising from dendritic cells<br>(PDQ, 2020b) | • High-grade brain tumor<br>• Arising from germ cells (ovarian and testicular) which fail to leave the CNS during fetal development<br>(PDQ, 2020c) |
| Epidemiology | • 1.6 per million people<br>• Peak incidence: 5–9 years; 50–69 years<br>• No male/female predominance (1:1)<br>(Momin et al., 2021) | • 4–5 per million people<br>• Peak incidence: 5.9 years<br>• Male predominance (1.2:1 – 1.5:1)<br>(Guyot-Goubin et al., 2008; Salotti et al., 2009) | • 0.8 per million people<br>• Peak incidence: 10–19 years<br>• Male predominance (3:1)<br>(Fujimaki, 2009; Takami et al., 2019; PDQ, 2020a;Ostrom et al., 2021) |
| Neuroanatomical presentation | • Sellar & hypothalamic area, third ventricle, adjacent vasculature<br>(McCrea et al., 2016; Yano et al., 2016) | • Pituitary stalk, hypothalamus, dura, leptomeninges<br>• Accompanying abnormalities in the cerebellum, pons, and basal ganglia<br>(Grois et al., 1998; Imashuku et al., 2015; Yeh et al., 2018) | • Pineal gland, suprasellar region within the pituitary stalk<br>• Less commonly, tumors can be found in the basal ganglia or other sites in the third ventricle<br>(McCarthy et al., 2012; McCrea et al., 2016; Takami et al., 2019) |
| Clinical presentation (if CNS involvement) | • Nonspecific symptoms: headache, visual impairment, weight gain, nausea/vomiting<br>• Pituitary insufficiency: growth arrest or delayed puberty in children, hypopituitarism with DI in adults<br>• DI and other hormone deficiencies (GH, FSH/LH, ACTH, TSH)<br>(Karavitaki et al., 2006; Bao et al., 2016; Capatina et al., 2018) | • Nonspecific symptoms: fever, weight loss, diarrhea, edema, polydipsia, and polyuria<br>• Mild symptoms: headache, dizziness, general malaise<br>• Severe symptoms: decreased verbal intelligence; deficits in attention, memory, and learning; LCH-ND<br>• Pituitary insufficiency: DI, hormone deficiency (GH, FSH/LH, TSH, ACTH), thyroid disorders<br>(Modan-Moses et al., 2001; Laurencikas et al., 2010; Yeh et al., 2018; PDQ, 2020c) | • Endocrine disturbances<br>• 50–60% of all patients have at least one endocrine abnormality<br>• Patients with suprasellar tumors: DI, low growth rates, and delayed sexual development or precocious puberty<br>• Other symptoms depend on location and type<br>• Patients with suprasellar tumors: headache, vomiting, visual field loss, and hormonal disturbances<br>• Patients with pineal tumors: headache, vomiting, and upward gaze palsy<br>(Crawford et al., 2007; Fujimaki, 2009; Sethi et al., 2013; Chang et al., 2021) |
| Treatment | • Surgical resection if appropriate<br>• Limited resection followed by local irradiation<br>• Intracystic chemotherapy<br>(Henderson and Schwartz, 2022; PDQ, 2020b) | • Curettage<br>• Adjuvant radiation therapy<br>• Vinblastine<br>• Prednisone<br>• Intravenous immunoglobulin may benefit patients with LCH-ND<br>(Ouyang et al., 2006; Imashuku et al., 2015; Yeh et al., 2018) | • Radiotherapy<br>• Chemotherapy depending on tumor subtype<br>(Kim and Park, 2015; Phi, Wang, and Kim, 2018) |
| Socio-behavioral dysfunction | • Personality changes, increased social isolation, decreased social functioning, aggression, depression, and anxiety<br>(Poretti et al., 2004; Pereira et al., 2005; Dekkers et al., 2006; Hammond and Hall, 2011; Ondruch et al., 2011) | • Aggression, depression, delinquent behavior, immaturity, social ineptness, behavioral and sleep disturbances, and intellectual impairment<br>(Whitsett et al., 1999; Nanduri et al., 2003; Fahrner et al., 2012) | • Challenges organizing leisure time, decreased social functioning, emotional disturbances, and psycho-organic syndrome<br>(Haupt et al., 1996; Strojan et al., 2006; Lo et al., 2018) |
| OXT alterations assessed via endogenous OXT measurement | • Tumors localized to anterior and posterior hypothalamus caused lower baseline salivary OXT concentrations compared to tumors with no HPIT involvement<br>• Patients had blunted salivary OXT release in response to exercise; blunted salivary OXT was also linked to higher level of autistic traits, lower hedonia, and worse emotional recognition<br>• Fasting salivary OXT levels were not related to social functioning | • No direct measurement of endogenous OXT signaling | • No known OXT measurement studies |
| OXT alterations and links with behavior as assessed via exogenous OXT administration | • Repeated intranasal OXT administration improved social function<br>(Cook, Miller, and Hart, 2016; Gebert et al., 2018; Hoffmann et al., 2018; Brandi et al., 2020; Özyurt et al., 2020) | • Challenges with pregnancy suggest OXT deficiency: OXT administered third stage of labor to enhance uterine contractions, lack of milk let-down<br>(Shinar, Many, and Maslovitz, 2016) | • No known OXT administration studies |
| AVP alterations assessed via rates of central DI or endogenous AVP measurement | • Central DI in 8–35% of patients pre-operatively, 70–90% post-operatively<br>• Low AVP concentration in 3.4% of patients pre-operatively, 8.7% post-operatively | • 10-year risk of DI was 23% in multisystem patients and 7% in single system patients<br>• Pituitary damage linked to development of DI | • Tumors in the suprasellar region, pineal region, and pituitary stalk have all been associated with the development of DI |
| AVP alterations and links with behavior as assessed via exogenous AVP administration | • No known AVP administration studies<br>(Ghirardello et al., 2006; Shi et al., 2017) | • No known AVP administration studies<br>(Tien, Kucharczyk, and Kucharczyk, 1991; Grois et al., 2006; Liu et al., 2013) | • No known AVP administration studies<br>(Wang, Zou, and Gao, 2010; Liu et al., 2013; Patti et al., 2022) |

Abbreviations: Central Nervous System (CNS); Diabetes Insipidus (DI); Growth Hormone (GH); Follicle-Stimulating Hormone/Luteinizing Hormone (FSH/LH); Adrenocorticotropic Hormone (ACTH); Thyroid-Stimulating Hormone (TSH); Neurodegenerative Langerhans Cell Histiocytosis (LCH-ND); Hypothalamic-Pituitary (HPIT); Oxytocin (OXT); Arginine Vasopressin (AVP).
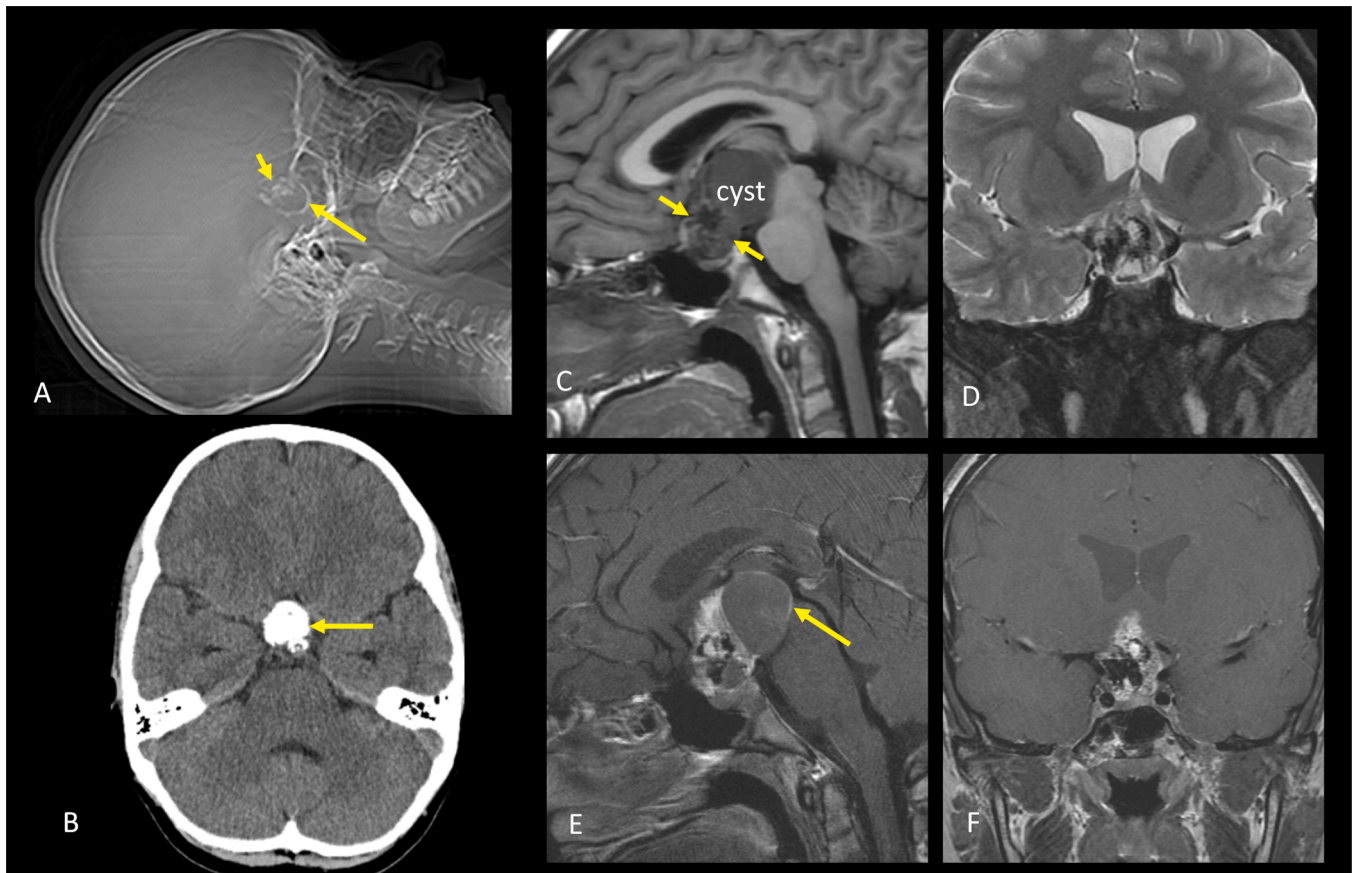
**Fig. 1.** Computerized tomography (CT) and magnetic resonance imaging (MRI) of a 13-year-old male with biopsy-confirmed adamantinomatous craniopharyngioma. A: Lateral digital scout view from a CT scan demonstrates enlargement of the sella turcica (long arrow) and a calcified suprasellar mass (short arrow). B: Axial slice from the non-contrast head CT shows the densely calcified suprasellar mass lesion (arrow). C: Sagittal T1-weighted MRI shows an absence of the posterior pituitary "bright spot". (See Fig. S1 for an example of the normal "bright spot".) A large lobulated sellar and suprasellar lesion is present, with a more anteroinferior solid/calcified portion (arrows) and a more posterosuperior cystic component ("cyst"). D: Coronal T2-weighted MRI demonstrates the mixed signal intensity solid/calcified portion of the mass. E: Sagittal T1-weighted MRI post-gadolinium demonstrates enhancement of the solid portion of the mass. There is also enhancement of the cyst wall (arrow). F: Coronal T1-weighted MRI post-gadolinium demonstrates heterogeneous enhancement of the sellar and suprasellar calcified and solid components of the mass. The calcified areas appear dark while the enhancing soft tissue is bright post gadolinium.

age-appropriate activities of daily living (Poretti et al., 2004). Fortunately, as discussed previously, clinical outcomes have improved as surgical interventions for CP have become less invasive (Cohen et al., 2013).

As alluded to above, surgical resection of CP may affect socio-behavioral functioning. For instance, one case study reported sudden-onset aggression in a typically-developing six-year-old female following surgical resection of her CP (Hammond and Hall, 2011). Significant postoperative behavioral changes have also been reported in larger study populations. One group found that 15 out of 20 (75%) children who underwent partial or gross tumor resection to treat their CP experienced mild, moderate, or severe socio-behavioral impairments following surgery (Anderson et al., 1997). Another study involving 20 patients found that 15 (75%) of the individuals who had undergone surgery for CP in childhood reported spending less than half of their free time with others (Clopper et al., 1977). CP patients with hypothalamic lesions were significantly less likely to correctly identify the emotional content of vocal expressions and the mental state of another person (Özyurt et al., 2020). While surgical resection does seem to be somewhat contributory to patients' behavioral symptoms, there is also a case report of a man with CP localizing to the pituitary who presented with a 24-month history of personality and behavior change, indicating that CP may cause alterations to socio-behavioral functioning prior to medical intervention (Bowers and Hughes, 2021). This provides further evidence that damage to the HPIT region, whether by the disease itself or by

iatrogenic causes, plays a key role in the development of socio-behavioral dysfunction in CP patients.

### 2.2. Langerhans cell histiocytosis (LCH)

#### 2.2.1. LCH epidemiology and pathogenesis

LCH has an established incidence rate of four to five per million children (Guyot-Goubin et al., 2008). LCH can also occur in adulthood, but there has been less research on its incidence in this population. Nevertheless, one study reported the incidence rate of LCH in adults as one to two per million (Baumgartner et al., 1997). LCH occurs more often in males than females and has a median age at diagnosis of 5.9 years (Guyot-Goubin et al., 2008; Salotti et al., 2009). LCH originates from the clonal proliferation of dendritic cells, a type of mononuclear phagocyte (Willman et al., 1994; Yu et al., 1994; PDQ, 2020b). Over 50% of LCH cases may also be linked to somatic mutations in *BRAF* (Berres et al., 2014; Monsereenusorn and Rodriguez-Galindo, 2015). Because LCH may be systemic, it is categorized as unifocal, multifocal unisystem (multiple tumors confined to a single organ), or multifocal multisystem (multiple tumors involving multiple organs) based on the level of disease spread (PDQ, 2020b). LCH most commonly originates in the bone and skin (Guyot-Goubin et al., 2008; Salotti et al., 2009), but the CNS can also be affected. Estimates of CNS involvement in LCH patients vary widely and are reported to range from 3.4% to 57% (Yeh et al., 2018). CNS LCH most commonly affects the HPIT region (Grois

et al., 1998; Fahrner et al., 2012). While a confirmatory biopsy is required to make a definitive diagnosis of LCH, tumor location may make performing a biopsy difficult and/or clinically contraindicated in some patients. In these cases, a thorough history and physical examination, radiologic tests such as computed tomography (CT) and MRI, blood tests, and urine tests can be utilized to make a clinical diagnosis of LCH. In patients with suspected multisystem LCH, the diagnosis can be made by identifying a more readily accessible biopsy site elsewhere in the body (PDQ, 2020b).

### 2.2.2. LCH neuroanatomical presentation

CNS LCH most commonly presents as an infiltrative mass lesion in the HPIT axis though other areas of the CNS, including the dura and leptomeninges, may also be affected (Grois et al., 1998; Yeh et al., 2018). Many radiologic studies reveal thickening of the pituitary stalk with loss of the posterior pituitary "bright spot." Accompanying abnormalities in the cerebellum, pons, and basal ganglia have also been described (Grois et al., 1998; Imashuku et al., 2015; Yeh et al., 2018). Reported rates of HPIT involvement vary: In one study, 31% of CNS LCH patients had HPIT involvement (Laurencikas et al., 2010), while another found pituitary stalk thickening in 50% of CNS LCH patients. Pituitary stalk lesions appear to be more common than hypothalamic lesions, the latter of which were cited by the same study to be present in only 10% of CNS LCH patients (Prayer et al., 2004). Characteristic CNS LCH features are shown in Fig. 2 and can be compared to typical features of the same neuroanatomic structures in Fig. S1.

### 2.2.3. LCH clinical presentation

Clinical features of LCH vary depending on the disease severity and the extent of organ involvement. The initial clinical presentation often includes numerous non-specific symptoms such as fever, weight loss, diarrhea, edema, polydipsia, and polyuria (PDQ, 2020b). The majority of CNS LCH patients do not present with clinically significant neurological abnormalities (Grois et al., 1998). When neurological



**Fig. 2.** MRI of a 28-year-old female with biopsy-confirmed Langerhans cell histiocytosis. A: Sagittal T1-weighted MRI shows a mass at the level of the tuber cinereum and hypothalamus (arrow). The pituitary gland is small and there is absence of the posterior pituitary "bright spot". (See Fig. S1 for an example of normal sellar imaging.) B: The suprasellar soft tissue mass (arrow) is also seen in the coronal plane of this T1-weighted MRI. C and D: Sagittal and coronal T1-weighted MRI, respectively, post gadolinium demonstrate homogeneous enhancement of the mass (long arrows). The short arrow in C indicates the optic chiasm situated anterior and immediately adjacent to the hypothalamic mass.

abnormalities are detected, symptoms may include headache, dizziness, and general malaise. However, some CNS LCH patients experience more severe symptoms such as decreased verbal intelligence and deficits in attention, memory, and learning (Laurencikas et al., 2010; Yeh et al., 2018). In rare cases, CNS LCH may also cause a neurodegenerative (ND) syndrome, LCH-ND. The onset of LCH-ND may occur at the time of diagnosis but may also occur more than five years after initial presentation. HPIT involvement is also associated with endocrine disturbances. Pituitary LCH lesions constitute a strong risk factor for central DI, GH deficiency, and thyroid disorders. Central DI is actually the most common initial sign of CNS involvement and it occurs in up to 50% of CNS LCH patients with HPIT involvement (Modan-Moses et al., 2001; Yeh et al., 2018). In a study of seven CNS LCH patients, all patients with HPIT involvement had deficiencies in either GH, FSH/LH, TSH, or ACTH (Modan-Moses et al., 2001). As a result of hormonal dysregulation, children diagnosed with LCH often present with a decreased growth rate as well as disturbances in sexual development, delayed bone age, hypothyroidism, and hypocortisolism. Additionally, FSH/LH deficiency in adult LCH patients is associated with hypogonadism, which may be permanent (Fahrner et al., 2012; Yavropoulou, Tsoli, and Kaltsas, 2021).

### 2.2.4. LCH treatment options

If surgical resection is feasible, LCH lesions isolated to a single organ system may be treated with surgery alone. However, multisystem disease typically demands a multimodal treatment plan (Monsereenusorn and Rodriguez-Galindo, 2015). Common clinical practice for treating mass CNS LCH lesions involves curettage and adjuvant radiation therapy for isolated lesions or a combination of vinblastine and prednisone for multifocal lesions (Ouyang et al., 2006; Yeh et al., 2018). Bone lesions in locations that confer additional risk for progression into the CNS (orbit, mastoid, sphenoid, or temporal bones), parenchymal brain lesions, and pituitary lesions are treated with systemic chemotherapy (Yeh et al., 2018). Patients with LCH-ND may also benefit from the addition of intravenous immunoglobulin to their chemotherapy regimen due to its immune-modulatory effects (Imashuku et al., 2015; Yeh et al., 2018). Radiation therapy has also proven to be an effective method of treatment, especially in central DI. And while radiation therapy in patients with central DI has been shown to decrease desmopressin requirements (Ouyang et al., 2006), CNS LCH patients with endocrine sequelae must undergo long-term hormone replacement therapy (Vaiani et al., 2021). BRAF inhibitors are also currently being evaluated as potential therapeutics as mutations in this gene are present in over half of LCH cases (Berres et al., 2014; Monsereenusorn and Rodriguez-Galindo, 2015).

### 2.2.5. LCH socio-behavioral functioning

Because LCH is not inherently confined to the brain, only a subset of patients experience socio-behavioral dysfunction. In one cohort of 28 patients who were long-term survivors of multisystem LCH, seven (25%) reported behavioral abnormalities such as increased aggression and depression (Nanduri et al., 2003). A case study involving two adolescent CNS LCH patients reported clinically significant evidence of social problems and delinquent behavior in both individuals. A follow-up interview with one of the patients also revealed high levels of immaturity and social ineptness that did not show improvement following social-skills training (Whitsett et al., 1999). Another study found that children with LCH have a higher rate of internalizing problems such as anxiety and depression when compared to children without LCH, and these problems were more common in patients with CNS involvement (Vrijmoet-Wiersma et al., 2009).

It is important to note that many of the studies on socio-behavioral deficits in patients with CNS LCH focus on people who have already undergone surgical intervention. As is the case with CP, it is unknown whether LCH itself, surgical resection, or a combination of the two influence the development of socio-behavioral dysfunction. Many of these studies nevertheless demonstrate a clear link between damage to the HPIT region (whether organically or iatrogenically) and socio-
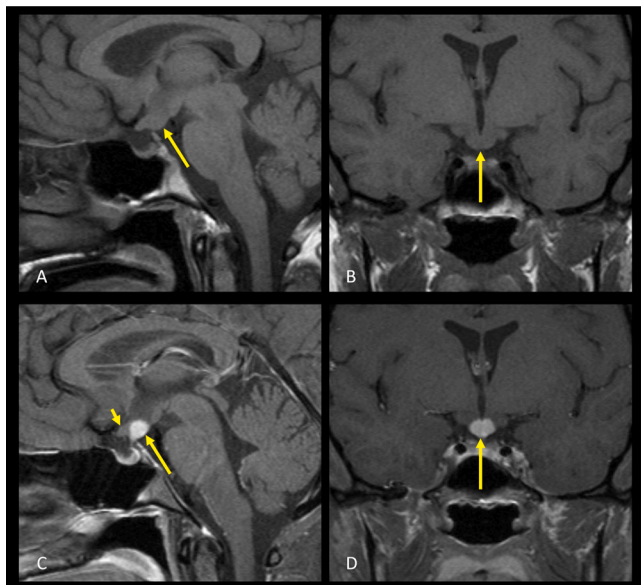
behavioral dysfunction. For example, while the patient with immaturity and social challenges in the aforementioned case study did not have evidence of HPIT involvement, the other patient did (Whitsett et al., 1999). In another example, out of the seven patients with multisystem LCH and behavioral abnormalities in the Nanduri et al. (2003) study, three had evidence of HPIT damage. This subset of patients reported additional behavioral disruptions, such as rage attacks and abnormal eating patterns, that were not seen in the CNS LCH patients whose disease lacked HPIT involvement. In a study of 22 CNS LCH patients with HPIT involvement and LCH-ND, it was found that five patients reported overt clinical symptoms of the neurogenerative disease. It is thus evident that while HPIT involvement may not explain all of the socio-behavioral disruptions experienced by CNS LCH patients, there is likely a causal relationship between damage to this region and the onset of these behavioral changes.

### 2.3. Intracranial germ cell tumors (IGCT)

#### 2.3.1. IGCT epidemiology and pathogenesis

In the United States, IGCTs have an annual incidence rate of 1.2 cases per million men and 0.4 cases per million women (Ostrom et al., 2021). IGCTs constitute 3.7% percent of all primary pediatric brain tumors in the United States but up to 16.9% of pediatric brain tumors in Japan (Ostrom et al., 2015; Takami et al., 2019). IGCTs occur most often in 10- to 19-year-old patients but can be seen with some frequency in patients less than 10 years of age and during young adulthood (Fujimaki, 2009; Takami et al., 2019; PDQ, 2020c). Germ cell tumors originate from fetal or neonatal germ cells and therefore usually occur in the gonads. However, one to five percent of germ cell tumors exist in extragonadal sites such as the brain, where they typically affect midline structures (De Felici et al., 2021).

IGCTs may be broadly classified as germinomas or non-germinomatous (including mixed germ cell tumors, malignant teratomas, choriocarcinomas, embryonal carcinomas, and yolk sac tumors). Germinomas are associated with significantly longer survival when compared to nongerminomatous IGCTs (Fujimaki, 2009; McCrea et al., 2016; PDQ, 2020c). IGCTs are also classified as being unifocal, bifocal, or multifocal. However, it is unclear whether bifocal lesions represent synchronous development of tumors in different locations or metastatic spread from a single location (Phi et al., 2013). IGCTs can be diagnosed based on symptoms, neuroimaging, and/or the presence of elevated α-fetoprotein (AFP) and β-human chorionic gonadotropin (hCG) in serum or lumbar cerebral spinal fluid (CSF) (McCrea et al., 2016; Yang et al., 2016; Phi, Wang, and Kim, 2018; PDQ, 2020c). In cases where tumor markers (AFP and hCG) are unrevealing, histology is required to confirm a diagnosis; however, tumor localization to high-risk anatomical regions can limit tissue sampling for biopsy (Yang et al., 2016).

#### 2.3.2. IGCT neuroanatomical presentation

IGCTs occur most frequently in the pineal gland, followed by the suprasellar region within the pituitary stalk. Less commonly, tumors can be found in the basal ganglia or other sites in the third ventricle (McCarthy et al., 2012; McCrea et al., 2016; Takami et al., 2019). Bifocal tumors originating in the suprasellar and pineal regions reportedly occur in six to 41% of patients, and a recent study reported that 97% (34 of 35) of bifocal germ cell tumors were germinomas (Phi et al., 2013; Takami et al., 2019). The pituitary is the primary tumor site in an estimated eight percent of cases (McCarthy et al., 2012), and 11% of IGCTs infiltrate the hypothalamus (Jennings, Gelman, and Hochberg, 1985). Interestingly, the strongest predictor of tumor location for single-site cases is sex. Compared to female IGCT patients, male patients not only have higher rates of IGCTs but also have a significantly higher ratio of pineal to suprasellar tumor localization (Goodwin, Sainani, and Fisher, 2009). IGCTs can also be associated with the loss of the pituitary "bright spot" on MRI (Morana et al., 2018). Characteristic IGCT features are shown in Fig. 3 and can be compared to typical features of the same

neuroanatomic structures in Fig. S1.

#### 2.3.3. IGCT clinical presentation

Tumor location, type, and secretory status determine the clinical features of IGCTs. For example, tumors that produce hCG in the neurohypophyseal or pineal regions may initiate precocious puberty, basal ganglia tumors may cause hemiparesis, and choriocarcinomas are linked to sudden intracranial bleeding. Tumors confined to the pineal region commonly present with obstructive hydrocephalus leading to increased intracranial pressure, which can cause headache, vomiting, and diplopia from Parinaud syndrome (upward gaze palsy) (Crawford et al., 2007; Fujimaki, 2009; Sethi et al., 2013). Suprasellar tumors can also present with headache, vomiting, and visual field loss in addition to hormonal disturbances including adrenal insufficiency, hypogonadotropic hypogonadism, central hypothyroidism, and low levels of GH (Crawford et al., 2007; Sethi et al., 2013; Chang et al., 2021). As a result, patients with suprasellar tumors often experience endocrinopathies. One study involving 24 patients with suprasellar IGCTs found that 50% of patients presented central DI, 26% with GH deficiency, 19% with central hypothyroidism, and 19% with central adrenal insufficiency. Patients with suprasellar tumors also reported low growth rates and delayed sexual development or precocious puberty. Another study of 30 IGCT patients with a variety of tumor localizations found that 57% had signs of endocrine dysfunction at presentation, further strengthening the relationship between IGCTs and endocrine disturbances (Crawford et al., 2007; Sethi et al., 2013).
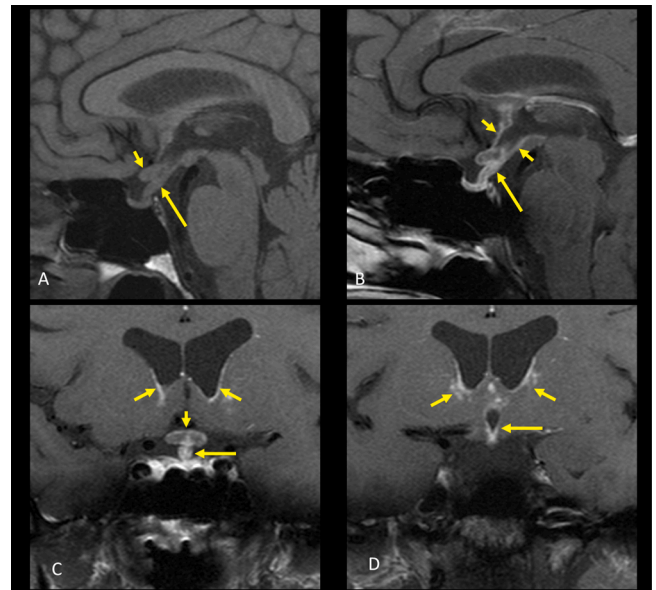


**Fig. 3.** MRI of a 49-year-old male with a biopsy-confirmed intracranial germinoma. A: Sagittal T1-weighted MRI shows the absence of the posterior pituitary "bright spot" (see Fig. S1 for comparison). The pituitary gland is small. The pituitary stalk is diffusely thickened (long arrow) as is the immediately adjacent anterosuperior optic chiasm (short arrow). B: Sagittal T1-weighted MRI post-gadolinium shows diffuse enhancement of the thickened pituitary stalk (long arrow), as well as peripheral enhancement of the optic chiasm. There is an additional periventricular enhancement (short arrows) along the margins of the third ventricle. C: Coronal T1-weighted MRI post-gadolinium demonstrates the thickened pituitary stalk (long arrow), peripherally enhancing optic chiasm (short arrow), and linear enhancement around the margins of the frontal horns of the lateral ventricles (obliquely angled arrows). D: Coronal T1-weighted MRI post-gadolinium, slightly posterior to C, again demonstrates linear and nodular periventricular enhancement along the margins of the lateral ventricles (obliquely angled arrows), but also of the third ventricle (long arrow) and adjacent hypothalamus.

### 2.3.4. IGCT treatment options

Treatment for IGCTs can incorporate both chemotherapy and radiation. Focal irradiation is associated with a high relapse rate for IGCTs, whereas whole-brain or whole-ventricular radiation is associated with lower rates of recurrence and improved survival (Calaminus et al., 2013). Radiotherapy over a large volume encompassing the ventricular space with a boost dosage to the primary tumor site is therefore the standard of care for IGCTs (Kim and Park, 2015). The extent of radiation therapy does, however, vary with tumor type: Germinomas can be treated with whole-ventricular radiation for survival rates of > 90%, whereas nongerminomatous germ cell tumors may require craniospinal radiation for improved survival (Fangusaro et al., 2019; Koh et al., 2021). A short course of chemotherapy may also be added prior to the initiation of radiation therapy (Phi, Wang, and Kim, 2018). Intensity-modulated or proton-beam radiotherapies can be utilized in the treatment of IGCTs to minimize the irradiated volume in some cases, thereby decreasing toxicity and limiting neurocognitive impairment resulting from radiation (Kim and Park, 2015). Gamma knife radiosurgery is another treatment option available for patients with IGCTs, and the 5-year survival rate for gamma knife radiosurgery was similar to the survival rate for chemotherapy and radiation (Yang et al., 2016). Endoscopic procedures are also utilized to manage the acute hydrocephalus seen in some IGCT patients and to enable tissue biopsy for suprasellar and pineal IGCTs (Phi, Wang, and Kim, 2018).

### 2.3.5. IGCT socio-behavioral functioning

A number of studies have examined the socio-behavioral deficits experienced by adult survivors of pediatric IGCTs. In one study, over half of these adult survivors had challenges organizing their leisure time and keeping up with the speed of daily activities (Haupt et al., 1996). Another study involving adult survivors of pediatric IGCTs also found evidence of decreased social functioning (Lo et al., 2018). Additionally, out of five long-term IGCT survivors who underwent psychological evaluation for research purposes, emotional disturbances were found in four individuals and psycho-organic syndrome (a progressive disease caused by organic brain damage that leads to cognitive and memory deficits) was found in three individuals (Strojan et al., 2006). There also appears to be a link between age at diagnosis and the level of social functioning impairment: IGCT patients diagnosed during childhood had more deficits in psychosocial functioning compared to IGCT patients diagnosed at over 18 years of age (Sands et al., 2001).

As discussed previously for both CP and CNS LCH, it is difficult to determine whether socio-behavioral deficits in patients with IGCTs were influenced by medical intervention or related to the disease process itself. In contrast to CNS LCH, there is limited and contradictory evidence related to the impact of tumor localization on the development of socio-behavioral dysfunction in IGCT patients (Liang et al., 2013; Park et al., 2017), which makes identifying the etiology of these symptoms even more challenging. Despite these challenges, it is clear that neuroanatomic damage, whether from the disease process or treatment, leads to alterations in the socio-behavioral function of IGCT patients.

## 3. Overview of oxytocin (OXT) and arginine vasopressin (AVP) biology and their impact on socio-behavioral functioning

OXT and AVP are closely related "sister" neuropeptides. These nonapeptides differ by only two amino acids, are synthesized and secreted in overlapping neural regions, and both regulate mammalian social behavior (Stoop, 2012; Baribeau and Anagnostou, 2015; Rae, Duarte, Gomes, Camarini & Devi, 2022). OXT and AVP are thought to have originated during a gene duplication event involving the ancestral nonapeptide vasotocin (Gruber, 2014). The oxytocin receptor (OXTR) and five AVP receptor (AVPR) subtypes (AVPR1a, AVPR1b, AVPR2a, AVPR2b, and AVPR2c; two of which, AVPR2b and AVPR2c, have been lost in mammals) are also ancestrally related (Lagman et al., 2013). Because of the high degree of structural homology between OXT and

AVP and the close evolutionary relationship between OXTR and AVPR subtypes, there is significant cross-talk between the two neuropeptides and their receptors (Sala et al., 2011; Song et al., 2016; Song, and Albers, 2018; Rae et al., 2022). To better understand how these neuropeptides may be implicated in the socio-behavioral dysfunction of patients with disorders of HPIT involvement, below we review the basic biology of OXT and AVP signaling and summarize the impact these neuropeptides have on socio-behavioral functioning.

### 3.1. Overview of oxytocin (OXT)

#### 3.1.1. OXT biology and preclinical models of socio-behavioral functioning

OXT is predominantly synthesized by magnocellular neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus. OXT is transported along the median eminence and released into the peripheral circulation by the posterior pituitary. In the periphery, OXT acts as a classic hormone to regulate a variety of physiological and reproductive processes (e.g., smooth muscle contractions during parturition; milk letdown during lactation) at distal target sites (Yang, Wang, Han and Wang, 2013). OXT is also secreted centrally from dendrites of magnocellular neurons into extracellular fluid and from axonal projections of hypothalamic parvocellular neurons in the PVN (which also synthesize OXT). These hypothalamic OXT fibers project to diverse regions of the vertebrate forebrain including the prefrontal cortex, anterior olfactory nucleus, nucleus accumbens, lateral septum, hippocampus, and medial and central amygdala (Jurek and Neumann, 2018). In the brain, OXT acts as a neurotransmitter to regulate a variety of species-specific behavioral functions, including social behavior (Althammer, Eliava and Grinevich, 2021; Baribeau and Anagnostou, 2015), as discussed in greater detail below. A general mammalian overview of OXT neurophysiology is presented in Fig. 4.

OXT regulates its physiological and behavioral functions primarily by binding to OXTRs, which are G-protein coupled receptors (Jurek and
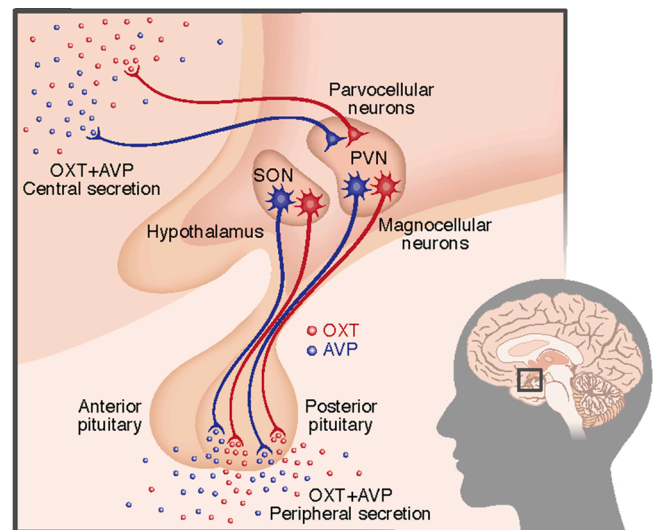


**Fig. 4.** Generalized mammalian oxytocin and arginine vasopressin synthesis and release. OXT; depicted in red and AVP; depicted in blue are primarily synthesized in neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus. Parvocellular PVN neurons (depicted as smaller circles) secrete OXT and AVP throughout widely distributed axonal projections, where these neuropeptides act as neurotransmitters in the brain to regulate a variety of behavioral functions. Magnocellular PVN and SON neurons (depicted as larger circles) project axons down through the posterior pituitary and release OXT and AVP from secretory vesicles into the peripheral circulation, where these neuropeptides act as hormones to regulate a variety of endocrine functions. Brain inset with black square shows the neuroanatomical region depicted in the magnified image to its left.

Neumann, 2018). There are large variations in OXTR localization both within (Parker et al., 2001a; Parker et al., 2001b; King et al., 2016) and between (Insel, Gelhard and Shapiro, 1991; Insel and Shapiro, 1992; Althammer, Eliava and Grinevich, 2021) species. In humans, OXTRs are found in a variety of tissues including the myometrium, mammary glands, endometrium, ovary, testis, and brain (Kimura et al., 2003). More specifically, immunohistochemical staining of postmortem human brain tissue reveals high levels of OXTR expression within the cingulate cortex, uncus, ventrolateral septal nucleus, central amygdala, posterior cortical nucleus amygdala, tuberomammillary nucleus, and solitary nucleus: All of which are regions that have been implicated in human social motivation, behavior, and emotion (Boccia et al., 2013). The expression of OXTR in these brain regions is therefore likely responsible for the neuropeptide's impact on social functioning (Jurek and Neumann, 2018).

Much of the recent research on OXT has focused on its role as a critical regulator of social, maternal, and aggressive behaviors. For example, central OXT administration causes female prairie voles to spend more time with their partner (Williams et al., 1994) and promotes the initiation of maternal behavior in female rats (Pedersen and Prange, 1979). Exogenous OXT administration also induces anxiolytic-like effects in male mice (Ring et al., 2006) and in male and female rats (Sabihi, Durosko, Dong and Leuner, 2014). It is likely that OXT exerts this anxiolytic effect at least in part by modulating the activity of the hypothalamic-pituitary-adrenal (HPA)-axis: Specifically, the peripheral secretion of ACTH and corticosterone (Neumann et al., 2000). Low-dose central OXT administration in male rats also improves social memory (Benelli et al., 1995), reverses defeat-induced social avoidance after exposure to an unfamiliar aggressive male rat (Lukas et al., 2011), and decreases anxiety levels in valproate-induced autism models (László et al., 2022). Intranasal OXT administration has similarly been found to decrease aggressive behaviors in a male mouse model of callousness (Zoratto et al., 2018) and exert anti-aggressive and pro-affiliative effects in male rats (Calcagnoli et al., 2015). Intranasal OXT administration also diminishes the neuroendocrine response to social isolation stress in female squirrel monkeys (Parker et al., 2005) and leads to decreased vigilance towards potential social threats in male rhesus macaques, which, in turn, could lead to the induction of prosocial behaviors (Ebitz, Watson, and Platt, 2013).

There is also an increasingly large body of literature supporting the role of hypothalamic OXT signaling in moderating these behaviors. For example, the number of cells expressing OXT in the hypothalamus has been found to increase during the critical window of postnatal development that overlaps with the acquisition of social skills (Soumier et al., 2021). Additionally, hypothalamic OXT neurons were found to project to the majority of rat forebrain regions: Many of which are associated with social behavior (Knobloch et al., 2012). These collective findings provide additional support not only for OXT's role in social behavior but also for the unique role HPIT structures play in the hormone's impact on social behavior.

### 3.1.2. An overview of OXT and human socio-behavioral functioning

In addition to the strong evidence implicating OXT signaling in various non-human species, evidence also suggests that OXT signaling plays a role in regulating human social behavior. For example, male research participants who received intranasal OXT increased their level of trust in interpersonal interactions (Kosfeld et al., 2005). Intranasal OXT administration in men was also found to not only increase in-group trust and cooperation but also promote defensive aggression towards competing out-groups. This suggests that OXT plays a role in both promoting sociability and protecting individuals against social threats (De Dreu et al., 2010). A study involving 45 female college students also found that serum OXT levels were negatively correlated with depressive symptomatology (Veiga et al., 2022). Another study similarly found that depressed females had lower plasma OXT concentrations than healthy controls; however, the same study found that depressed males had

higher plasma OXT concentrations than healthy controls. This suggests that the relationship between OXT and depression may be mediated by sex (Yuen et al., 2014).

OXT signaling has also been implicated in the maintenance of romantic relationships through improving conflict resolution and increasing the perceived attractiveness of romantic partners (Ditzen et al., 2009; Scheele et al., 2013). High blood OXT concentrations were also predictive of maternal bonding behaviors including gaze, vocalizations, positive affect, and affectionate touch (Feldman et al., 2007). Recent research also suggests that OXT shapes the development of socio-behavioral neural circuits (Baribeau and Anagnostou, 2015; Caldwell et al., 2017), indicating that alterations to OXT signaling could have widespread impacts on social functioning.

*3.1.2.1. Central and peripheral OXT.* When delineating OXT's influence on human social behavior, central OXT needs to be differentiated from peripheral OXT (e.g., blood). In addition to its hormonal actions via peripheral release through the systemic circulation, OXT exerts effects on behavior via focal release from axonal terminals and accumulation in the extracellular fluid of the brain. CSF concentrations of OXT are therefore more likely to be related to the neuropeptide's behavioral effects than blood concentrations (Landgraf and Neumann, 2004; Ludwig and Leng, 2006). However, peripheral measures such as blood are easier to obtain. Studies therefore have sought to assess whether blood OXT concentration can serve as a surrogate for CSF OXT concentration. While some studies have suggested that blood OXT concentration can be used as a proxy for CSF OXT concentration and the neuropeptide's impact on social behavior (Parker et al., 2014; Carson, Berquist et al., 2015), others have called into question the accuracy of blood OXT as a measure of the neuropeptide's central effects (Kagerbauer et al., 2013; Lefevre et al., 2017). It is also possible to measure OXT concentrations in saliva, but data on the validity of measuring OXT in saliva and its relationship to plasma and/or CSF OXT concentrations remains unresolved (Martin et al., 2018; Martins et al., 2020).

### 3.2. Arginine vasopressin (AVP)

### 3.2.1. AVP biology and preclinical models of socio-behavioral functioning

AVP is primarily synthesized in the magnocellular neurons of the hypothalamic PVN and SON but is also synthesized in the accessory nuclei situated between the PVN and SON, the parvocellular neurons of the PVN and suprachiasmatic nucleus, the bed nucleus of the stria terminalis, and the medial amygdala (Caldwell et al., 2008; Stoop, 2012; Baribeau and Anagnostou, 2015). In the periphery, AVP is released into the blood from the posterior pituitary and regulates water homeostasis by influencing the kidneys' ability to concentrate urine (Baribeau and Anagnostou, 2015). Impairments in AVP synthesis or release, which can be caused by surgeries or traumatic brain injuries that damage the hypothalamus or posterior pituitary, will result in central DI due to a lack of AVP signaling (Kalra et al., 2016). AVP signaling occurs centrally through multiple mechanisms, including synaptic secretion from hypothalamic parvocellular neurons and somato-dendritic release from AVP-synthesizing neurons (Landgraf and Neumann, 2004; Stoop, 2012; Bichet, 2014). One notable vasopressinergic hypothalamic axonal projection is to the amygdala, where AVP release increases aggression, anxiety, stress, and memory consolidation (Huber, Veinante, and Stoop, 2005). Other projections include the ventral pallidum, lateral septum, retrosplenial cortex, and anterior hypothalamus: Regions that facilitate pair bonding in prairie voles and potentially in humans (Bichet, 2014). A general mammalian overview of AVP neurophysiology is presented in Fig. 4.

As noted above, there are three major AVPR subtypes in mammals: AVPR1A (V1a), AVPR1B (V1b), and AVPR2 (V2). Like OXTR, the 3 AVPR subtypes are all G protein-coupled receptors. V1a is predominantly found in the liver, kidney, vasculature, and brain; V1b is

primarily found in the ACTH-producing cells of the anterior pituitary; and V2 is found in the kidney (Caldwell et al., 2008). There is a large amount of intra- and inter-species variation in regards to the expression pattern of V1a in the brain (Parker et al., 2001b; Charles et al., 2014). One study utilizing rats found V1a in the lateral septum, thalamus, hypothalamus, substantia nigra, ventral tegmental area, regions of the olfactory system, and parts of the cortex (Johnson et al., 1993). A similar study involving mice found high levels of V1b in the CA2 pyramidal neurons of the hippocampus and low levels of V1b in the PVN, amygdala, piriform cortex, caudate-putamen, septum, midbrain, pons, cerebellum, and medulla (Young et al., 2006). In humans and chimpanzees, microsatellite variations upstream of the V1a gene that are predicted to influence neural expression patterns of the receptor have been linked to relationship quality, personality traits, and the development of autism spectrum disorder (Barrett et al., 2013). While there has been less research on V1b, mouse models have implicated the receptor as a moderator of aggression, social memory, social motivation, and the HPA-mediated stress response (Stevenson and Caldwell, 2012). These collective studies provide further evidence for the relationship between AVP signaling and social behavior.

AVP has been shown to influence a wide variety of mammalian social behaviors including social recognition, cooperation, and competition. For example, central administration of exogenous AVP in rats led to improved social recognition (Engelmann and Landgraf, 1994) and decreased maternal aggression (Nephew, Byrnes, and Bridges, 2010). AVP signaling is also implicated in the development of pair bonding in monogamous male prairie voles (Winslow et al., 1993). Specifically, the AVP pathway in male prairie voles is altered after three days of cohabitation with a female, suggesting that AVP plays a role in mating-induced behavior changes (Wang and Aragona, 2004). However, in contrast to OXT-expressing cells, AVP-expressing cells in hypothalamic nuclei do not change across postnatal development, suggesting an alternate route of influence on social development (Soumier et al., 2021). Centrally administered AVP also led to increased affiliative behavior in prairie voles (Young et al., 1999) and the onset of paternal care in related vole species (Parker and Lee, 2001). Like OXT signaling, AVP signaling has also been linked to altered levels of aggression; however, the impact of AVP on aggression is more mixed. While increased AVP signaling has been associated with an increase in aggressive behaviors in both hamsters and dogs (Ferris et al., 1997; MacLean et al., 2017), decreased AVP signaling has alternatively been shown to be required for the development of aggressive behaviors in a female rat model of enhanced aggression (Oliveira et al., 2021). One potential explanation for these contrasting results is that the impact of AVP may be region-specific. For example, a study found that while septal AVP facilitates inter-male aggression, the release of AVP from the bed nucleus of the stria terminalis inhibits inter-male aggression (Veenema, Beiderbeck, Lukas and Neumann, 2010). Another possible explanation for these discrepant findings is that instead of being directly involved in aggression, AVP may modulate ancillary social and anxiety-related behaviors, leading to the appearance of altered levels of aggression (Beiderbeck, Neumann and Veenema, 2007).

### 3.2.2. An overview of AVP and human socio-behavioral functioning

While strong data exist for the role of AVP signaling in animal behavior, there is also research that shows a role for AVP signaling in human social functioning. Following a single dose of intranasal AVP, male research participants were more likely to engage in risky but mutually beneficial cooperative behavior compared to those administered a placebo. This AVP-mediated behavior change was found to be driven by downregulation of the left dorsolateral prefrontal cortex and increased connectivity between the left dorsolateral prefrontal cortex and the ventral pallidum: A region rich in AVPRs that has been associated with AVP-mediated social reward processing (Brunnlieb et al., 2016). Additionally, when compared to single-dose administration of intranasal OXT, single-dose administration of intranasal AVP was found

to lead to a higher increase in the reciprocity of cooperation in men (Rilling et al., 2012).

In contrast to the aforementioned results, other studies have shown that increased AVP signaling can lead to amplified perceptions of aggression. For example, single-dose intranasal AVP led male participants to have similar levels of corrugator EMG activity (a measure that is elevated in repose to adverse stimuli, including angry/threatening facial expressions) after exposure to emotionally neutral and angry facial expressions (Thompson et al., 2004). A different study showed that intranasal AVP administration also caused men to perceive unfamiliar faces as less friendly. However, intranasal AVP administration alternatively caused women to view unfamiliar faces as more friendly, suggesting that AVP may have sex-specific effects on human social behavior (Thompson et al., 2006). One potential explanation for the seemingly contradictory relationship between AVP and cooperativity/aggression is that these studies investigate the effect of exogenous AVP administration on individuals who already have 'normal' endogenous concentrations of the neuropeptide. Administering AVP to these individuals likely results in supranormal AVP concentrations. This is markedly different from administering the neuropeptide to an individual who is deficient in AVP, and this difference could explain why exogenous AVP administration leads to an increased perception of aggression in healthy volunteers (Thompson et al., 2004, 2006) but no increase in aggressive behaviors in individuals with autism (Parker et al., 2019): A condition shown to be related to impaired AVP signaling (Parker et al., 2018; Oztan et al., 2018, 2020).

AVP signaling has also been shown to have a contradictory impact on anxiety- and depression-like symptoms. While postmortem analysis of human brain tissue found a 60% increase in AVP signal in the SON of depressed individuals (Meynen et al., 2006), another study found no difference in CSF AVP levels between depressed patients and healthy controls (Brunner et al., 2002). Additionally, intranasal AVP administration to children with autism led to reduced anxiety, particularly in individuals with the highest pretreatment blood AVP concentrations (Parker et al., 2019). These collective data suggest that while AVP signaling may play a role in negative arousal and depression, it also plays a role in affiliative behavior. Research is clearly warranted to gain a more nuanced understanding of AVP's regulation of socio-behavioral functioning.

### 3.2.2.1. Central and peripheral AVP.

CSF AVP concentration may have the most utility for understanding social behavior since it has the closest relationship to the biologically active neuropeptide in the brain parenchyma (Landgraf and Neumann, 2004; El-Farhan, Hampton, and Penney, 2013). However, it is again important to note that CSF is more difficult to obtain than blood. While one study did show that blood AVP concentrations positively correlated with interpersonal functioning (Gouin et al., 2012), the relationship between blood and CSF AVP concentrations remains unresolved (Kagerbauer et al., 2013; Carson et al., 2014; Carson, Garner et al., 2015; Parker et al., 2018). The concentration of AVP in urine was also found to correlate with the concentration of AVP in the blood; however, AVP's concentration in urine is influenced by many factors including osmolar clearance, urine specific gravity, and renal metabolism (El-Farhan, Hampton, and Penney, 2013), making it difficult to validate clinically.

### 3.2.2.2. DDAVP and human socio-behavioral functioning.

Patients with central DI or other disorders of AVP deficiency are often prescribed desmopressin (DDAVP), which acts as a synthetic version of AVP (Robinson, 1976). It is important to note that DDAVP does not cross the blood-CSF barrier (Stegner et al., 1983) and is thus unable to induce any of AVP's central effects that might otherwise be restored via intranasal AVP administration (Pietrowsky et al., 1996). DDAVP also acts selectively on V2, while the behavioral effects of AVP have been shown to be due to the neuropeptide's action on the V1a receptor (Donaldson,

Spiegel, and Young, 2010; Parker and Lee, 2001; Robben, Knoers, and Deen, 2004). DDAVP is therefore not predicted to alter socio-behavioral functioning in an experimental setting or to increase the CNS concentration of this neuropeptide in a clinical setting.

## 4. OXT and AVP signaling disruptions in disorders of HPIT involvement: preclinical findings

Given that OXT and AVP are made/secreted in the HPIT region and play a critical role in socio-behavioral functioning, we advance for consideration the possibility that a connection exists between the OXT/AVP systems and the social and behavioral deficits experienced by patients with disorders of HPIT involvement. Indeed, preclinical research has shown that OXT and AVP disruption can negatively impact social functioning. Further, work in animal models with HPIT damage and in patients with disorders of HPIT involvement point to a potential link between OXT/AVP disruption and socio-behavioral dysfunction. These findings are reviewed below to further support a framework that implicates OXT and AVP signaling in the etiology of socio-behavioral dysfunction in patients with CP, CNS LCH, and IGCTs.

### 4.1. OXT-deficient models and socio-behavioral functioning

As discussed thus far, OXT signaling is implicated in the social behaviors of both animals and humans. To further determine the impact that OXT has on socio-behavioral functioning, it is important to review findings from studies involving preclinical models with disrupted OXT signaling. Various techniques have been used to knock out the OXT gene in these models, including the utilization of homologous recombination in embryonic stem cells to remove the first exon of the OXT gene (Nishimori et al., 1996) and to similarly remove most of the first exon and all of the second and third exons of the OXT gene (Young et al., 1996). Both of these techniques result in a complete lack of OXT release (Nishimori et al., 1996; Young et al., 1996).

OXT knockout (OXTKO) models have been studied in an effort to identify aspects of social functioning that are altered in the absence of OXT signaling. Findings from these models have generally implicated an impairment in the ability to form social memories. One study found that male OXTKO mice did not become familiarized to an ovariectomized female and did not show the expected decline in olfactory investigation following repeated presentation of identical stimuli. Other non-social forms of memory in the OXTKO mice were spared, suggesting that OXT has a specific impact on social memory formation (Ferguson et al., 2000). These results were substantiated by an additional study, which found that centrally administered OXT rescued social recognition in OXTKO mice (Ferguson et al., 2001). Another study utilizing male OXTKO mice found that wild type (wt) mice spent more time investigating female mice compared to the OXTKO mice. Additionally, when presented with female mice of the same strain, male wt mice were able to discriminate between novel and familiar mice whereas male OXTKO mice failed to discriminate between different mice of the same strain in two of the three strains included in the study (Macbeth et al., 2009). While social memory and recognition appear to be impaired in OXTKO mice, not all aspects of social functioning decline in the OXTKO models. For example, one study showed that two strains of OXTKO mice had the same level of sociability as control mice (Crawley et al., 2007). These results suggest that central OXT signaling may be involved in more nuanced aspects of social memory formation that then contribute to deficits in socio-behavioral functioning: A possibility that warrants further investigation.

OXTKO models also show altered levels of aggression and anxiety. Compared to wt mice, a group of female OXTKO mice initiated more intense aggressive behaviors when deprived of food (Ragnauth et al., 2005). However, the relationship between OXT signaling and the development of aggression is likely more complex than initially expected. In contrast to the study above, male OXTKO mice have also been

shown to have shorter bouts of aggression compared to wt mice (DeVries, Young, and Nelson, 1997). Another study found that male OXTKO mice raised by dams homozygous for the OXT gene deletion (OXT$^{-/-}$) had higher levels of aggression than male OXTKO mice raised by dams heterozygous for the OXT gene deletion (OXT$^{-/+}$) (Takayanagi et al., 2005). This suggests that environmental factors may influence the impact of OXT signaling on aggression. OXT-deficient female mice have also been found to have higher levels of anxiety-related behaviors that were improved following central OXT administration (Mantella et al., 2003). These preclinical models therefore support the relationship between OXT signaling and behavioral functioning and therefore offer additional evidence for the hypothesis that altered OXT signaling contributes to the socio-behavioral deficits experienced by patients with disorders of HPIT involvement.

### 4.2. AVP deficient models and socio-behavioral functioning

Studying preclinical models of AVP deficiency has similarly provided insight into AVP's impact on social functioning, and Brattleboro rats are commonly utilized in these studies as a model of AVP deficiency. These rats have a mutation that results in the production of a dysfunctional AVP precursor that cannot be released by the hypothalamus, resulting in a complete lack of AVP signaling in the CNS (Bohus and de Wied, 1998). Brattleboro rats are therefore commonly used as a substitute for AVP knockout models, as these rats are unable to survive without the peripheral administration of AVP (Zelena, 2017).

Adolescent Brattleboro rats have been shown to play less, emit fewer ultrasonic vocalizations (a measure of social interaction), be less active in an open field, and spend more time huddling than rats with wt AVP signaling. This atypical social profile, with more passive and less active social behaviors, suggests that AVP signaling in the CNS may facilitate social arousal (Schatz et al., 2018). The same trends (decreased playing, reduced social behaviors, and lower frequency of ultrasonic vocalizations) have also been observed in juvenile (P34 and P44) Brattleboro rats (Paul et al., 2016). A different study showed that while changes in sociability between AVP-deficient rats and those with wt AVP signaling were not present at P7, they had become present by P10 (Schank, 2009). These results suggest that AVP deficiency does not affect sociability during the very early stages of development, implying that early AVP-based interventions may have the ability to rescue social functioning if administered during this critical period.

Preclinical models have also linked AVP deficiency to depression, anxiety, increased aggression, and impaired social memory. Both male and female Brattleboro rats showed reduced levels of anxiety- and depressive-like symptoms (Fodor et al., 2016; Mlynarik et al., 2007; Bielsky, Hu, Szegda, Westphal and Young, 2004), but some of the social effects of decreased AVP signaling show sex-specificity. For example, while disruptions in AVP signaling led to decreased aggressiveness in lactating female rats and decreased intensity of aggression in male rats who had not reproduced, it had no effect on the levels of aggression in male rats who had reproduced (Fodor et al., 2014). Brattleboro rats also showed reduced social memory formation, but the administration of AVP rescued this ability (Engelmann and Landgraf, 1994). The results of another study suggest that AVP exerts these effects on social memory by modulating emotionality, motivation, and/or attention rather than modulating the actual retrieval and consolidation of information (Williams, Carey and Miller, 1983). The alterations in social functioning observed in these preclinical studies further strengthen the link between AVP signaling and socio-behavioral dysfunction and thus offer additional support for our hypothesis that alterations to AVP signaling may be contributing to the development of socio-behavioral dysfunction seen in some patients with disorders of HPIT involvement.

### 4.3. Damage to the HPIT region

Preclinical models with damage to the HPIT region provide

additional insight into the potential impact that HPIT involvement in CP, CNS LCH, and IGCTs could have on OXT/AVP signaling. For example, one study utilized lesioning electrodes to bilaterally ablate the PVN (with varying degrees of success) in male and female rats with central DI. Subsequent histological assessment revealed a direct correlation between PVN cell number and the amount of stored neurosecretory material in the pituitary (which was presumed to be OXT due to subjects' central DI status) (Sokol, 1970). This suggests that HPIT damage can cause a decrease in the synthesis of OXT. This finding was substantiated by a different study utilizing male rats, which found that complete ablation of the PVN led to a more than 90% reduction in OXT peptide concentration within the brainstem and spinal cord. Complete ablation of the PVN also impacted AVP peptide concentration, which was reduced by 50% in the brainstem and by more than 80% in the spinal cord (Lang et al., 1983). This evidence confirms that damage to the HPIT region disrupts both OXT and AVP production; therefore, it is reasonable to propose that HPIT damage caused by CP, CNS LCH, or IGCTs could similarly lead to disruptions in OXT and/or AVP signaling. Because of the strong link these neuropeptides have to social behavior, this provides further evidence that HPIT damage and subsequent AVP/OXT abnormalities may be the root cause of the socio-behavioral dysfunction seen in some patients with disorders of HPIT involvement.

### 4.4. Models of disorders of HPIT involvement

A literature review was conducted to investigate the impact that disorders of HPIT involvement have on the production of OXT/AVP and on the socio-behavioral functioning of preclinical animal models. While there are mouse models that mimic LCH (Steiner et al., 2008; Berres et al., 2014), there are no available models to study CNS LCH. Models of IGCTs could also not be identified. And while various models of CP have been developed (Gaston-Massuet et al., 2011; Martinez-Barbera, 2015; Apps and Martinez-Barbera, 2017), much of the phenotypic analysis of these models involves only endocrine disturbances and does not investigate alterations to socio-behavioral functioning (Roth et al., 2011). To gain a better understanding of the impact that CP, CNS LCH, and IGCTs have on behavior, appropriate animal models need to be developed and more research needs to be conducted regarding the presence and neurobiological etiology of socio-behavioral deficits in these models.

### 5. OXT and AVP signaling disruptions in disorders of HPIT involvement: clinical findings

Thus far we have not only presented evidence that disorders of HPIT involvement can lead to impairments in socio-behavioral functioning but have also provided support for the hypothesis that alterations in OXT and/or AVP signaling may be responsible for these impairments. To this end, we reviewed OXT and AVP's roles in socio-behavioral functioning and presented evidence that OXT- and AVP-deficient preclinical animal models show social and behavioral deficits similar to those reported for patients with disorders of HPIT involvement. A summary of the clinical features of CP, CNS LCH, and IGCTs—including their impact on socio-behavioral functioning—is presented in Table 1. We also discussed how preclinical models with HPIT damage have alterations in OXT and AVP signaling, further strengthening the argument that the socio-behavioral dysfunction experienced by patients with disorders of HPIT involvement may be due to alterations in OXT and AVP signaling. While limited in comparison to the preclinical data, we next review clinical findings that implicate OXT and AVP signaling deficits in the altered social and behavioral functioning observed in CP, CNS LCH, and IGCT patients.

### 5.1. OXT and AVP signaling in CP

#### 5.1.1. OXT

Studies have linked variations in CP patients' OXT concentrations with altered cognitive, emotional, social, behavioral, and physiological functioning. One study that compared CP patients to healthy controls found that while baseline salivary OXT concentrations did not differ between groups, CP patients experienced blunted OXT release in response to stimulation (exercise). Additionally, CP patients with damage to both the anterior and posterior hypothalamus had significantly lower baseline salivary OXT concentrations compared to CP patients with no hypothalamic involvement (Gebert et al., 2018), further implicating damage to the HPIT region in the OXT dysregulation seen in patients with disorders of HPIT involvement.

The above study found that CP patients' blunted salivary OXT release correlated with higher state anxiety scores (Gebert et al., 2018). Another study found that CP patients who showed impaired salivary OXT release following physical stress also had higher levels of self-reported autistic traits (specifically in the domains of social skills and attention switching as measured by the Autism-Spectrum Quotient), lower levels of hedonia when socializing, and worse scores on an emotional recognition task than healthy controls (Brandi et al., 2020). While the aforementioned studies support the link between salivary OXT levels and social functioning deficits in CP patients, another found no relationship between the two even when the HPIT region was implicated (Özyurt et al., 2020). More research is therefore needed to further characterize the relationship between OXT signaling and socio-behavioral deficits in CP patients.

Because of OXT's known role in regulating social functioning, some researchers have investigated the effects of administering exogenous OXT to CP patients. One case study of this novel treatment focused on a six-year-old female diagnosed with CP involving the infundibulum and pituitary stalk. Following surgical resection of the tumor, the patient developed physiologic signs of hypothalamic damage and experienced personality changes including increased social isolation, decreased interest in physical contact with family members, and the development of obsessive-compulsive behaviors. However, following treatment with intranasal OXT, the patient began to re-engage in play with family members and in positive social interactions with family and peers (Cook, Miller, and Hart, 2016). In another study involving 10 patients who had CP with HPIT involvement, the administration of a single dose of intranasal OXT led not only to stable or improved mood in all but one patient but also to improved emotion recognition among the patients with damage restricted to the anterior hypothalamus (Hoffmann et al., 2018). These results further implicate OXT signaling disruptions in the socio-behavioral dysfunction experienced by a subset of CP patients and suggest that OXT administration may be a potential therapeutic intervention for these patients.

#### 5.1.2. AVP

AVP deficiency is common among CP patients. However, unlike the studies investigating OXT deficiencies that measure the concentrations of the neuropeptide directly, many of the studies investigating AVP deficiencies report rates of central DI, a condition that results from a lack of AVP (Kalra et al., 2016). The presence of central DI can therefore be interpreted as an indication of AVP dysregulation, and the studies that report rates of DI among CP patients allow us to indirectly infer the effect of CP on patients' AVP signaling. Rates of DI in CP vary widely, ranging from eight to 35% of patients pre-operatively and 70–90% post-operatively (Ghirardello et al., 2006). The one study we identified that directly measured AVP concentrations found that 3.4% of CP patients had low concentrations of AVP prior to undergoing tumor resection for their CP, but this percentage increased significantly to 8.7% after surgery. The same study found that 29.7% of CP patients who did not have DI prior to surgery were diagnosed with the condition post-operatively. Existing DI also worsened for 70.4% of patients after surgery (Shi et al., 2017). This suggests that while AVP signaling may be altered by CP, there may also be iatrogenic causes to the AVP dysregulation seen in some of these patients. And while the study that found that there was no correlation between central DI and OXT levels (Gebert et al., 2018), no studies published to date have directly studied the link

between AVP deficiency/central DI and socio-behavioral dysfunction in patients with CP.

Without studies that assess the socio-behavioral impact of altered AVP signaling in CP patients, we cannot state with certainty what impact the neuropeptide has on the social and behavioral dysfunction experienced by these individuals. However, with both the preclinical and clinical literature suggesting a strong association between AVP and social behavior, it is reasonable to hypothesize that the two are related.

### 5.2. OXT and AVP signaling in CNS LCH

#### 5.2.1. OXT

While a literature search was performed, we could not identify any studies that have systematically evaluated OXT concentrations among CNS LCH patients. However, some reports of women with childhood CNS LCH have attempted to link challenges with aspects of parturition and lactation to disrupted OXT signaling. One woman with CNS LCH was included in a case report of four females with HPIT damage and presumed OXT deficiency. While the pregnancy was uneventful, OXT had to be administered during the third stage of labor to enhance uterine contractions in order to control postpartum hemorrhage. Following delivery, milk let-down did not occur and thus breastfeeding was not possible (Shinar, Many, and Maslovitz, 2016). These observations suggest that there was at least some amount of OXT dysregulation in this individual with childhood CNS LCH. In another case study, a woman with known central DI and presumed CNS LCH and OXT deficiency underwent normal delivery and spontaneous lactation (Clark and Houlden, 2018). In addition to the fact that both involved single case studies, another limitation to these examples is that OXT was not measured directly but was rather assumed to be deficient. Future studies involving patients with CNS LCH that directly measure OXT concentrations and concomitantly assess social functioning are needed to gain a better understanding of the relationship between potential OXT signaling disruptions and socio-behavioral dysfunction in these patients.

#### 5.2.2. AVP

AVP deficiency in patients with CNS LCH, like in patients with CP, was only captured indirectly via a diagnosis of central DI. The prevalence of DI among patients with LCH varies depending on the location of disease involvement and on the presence of multisystem disease. In one study involving 1741 patients with biopsy-proven LCH, DI was present in 6% of individuals at the time of diagnosis and in 12% of individuals at the time the study was conducted. The 10-year risk of DI was 23% in multisystem LCH patients and 7% in single system patients (Grois et al., 2006). The neuroanatomical distribution of LCH also seems to influence the development of DI (and, therefore, of AVP dysregulation). One study reported that nine of 12 (75%) patients with LCH and DI had a thickened pituitary stalk (Liu et al., 2013), while another found pituitary stalk thickening in all of the patients with co-occurring LCH and DI (Tien, Kucharczyk, and Kucharczyk, 1991).

Like the data on AVP deficiency in patients with CP, the aforementioned studies have significant limitations in regards to their application to this review, the two primary ones being the lack of direct quantification of AVP and no accompanying reports of behavioral data. Further research is therefore needed before drawing conclusions on the impact that AVP dysregulation has on social and behavioral dysfunction in this patient population.

### 5.3. OXT and AVP signaling in IGCTs

#### 5.3.1. OXT

A search of the literature revealed no studies that investigated OXT concentrations in patients with IGCTs, highlighting the need for more research into how IGCTs impact this neuropeptide.

#### 5.3.2. AVP

As with CP and LCH, AVP dysregulation in patients with IGCTs is captured through the development central DI. The prevalence of DI varies widely based on germ cell tumor location and subtype. Tumors in the suprasellar region, pineal region, and pituitary stalk have all been associated with the development of DI (Wang, Zou, and Gao, 2010; Liu et al., 2013; Patti et al., 2022). Tumor localization plays a large role in the likelihood of a patient developing DI. One study showed that while 86% of patients with neurohypophyseal tumors developed DI, only three percent of those with pineal lesions developed the condition (Matsutani, 2004). Surgical intervention may also cause alterations in AVP signaling. A study of sixteen patients with IGCTs reported that while twelve (75%) had DI prior to surgical intervention, the remaining four (25%) developed DI after surgical intervention (Saeki et al., 2000). It is again important to note that none of these studies measured AVP directly or evaluated the behavioral impacts of neuropeptide dysregulation, thereby highlighting the urgent need to conduct further research into the impact IGCTs have on AVP signaling and subsequent alterations in socio-behavioral functioning.

## 6. Discussion

There is robust clinical evidence for the development of socio-behavioral dysfunction across disorders of HPIT involvement. Additionally, the majority of CP and CNS LCH patients, as well as a smaller fraction of IGCT patients, develop pathology in the hypothalamus and/or pituitary: Structures implicated in OXT/AVP production and signaling. Given OXT and AVP's roles in regulating social behaviors across mammalian species and the evidence suggesting that HPIT damage disrupts the signaling of these neuropeptides, socio-behavioral dysfunction observed in some patients with CP, CNS LCH, and IGCTs may be due to OXT and AVP processing impairments via damaged HPIT structures in the brain. This hypothesis presents an acquired model of social disruption: One that is due to the presence of a developed disorder rather than a congenital defect. Under this model, damage to the hypothalamus and pituitary in disorders of HPIT involvement leads to disrupted OXT and AVP production (hypothalamus) and/or release (hypothalamus/pituitary). Such injuries may then, via the dysregulation of OXT and AVP, impact downstream social behaviors and cause the socio-behavioral dysfunction seen in some patients with CP, CNS LCH, and IGCTs. This model therefore offers the hope that targeting these pathways with early therapeutic interventions may prevent or reverse socio-behavioral dysfunction in patients with these disorders.

## 7. Gaps in knowledge and future research directions

While the preclinical research provides a strong argument for the role of OXT and AVP in socio-behavioral functioning and the potential for these neuropeptides to become altered following damage to the HPIT region, there have not been any preclinical studies investigating the impact of CP, CNS LCH, and IGCTs on OXT/AVP signaling or on socio-behavioral functioning. Animal models have not yet been developed for CNS LCH or IGCTs, and while models exist for CP, they have not been utilized to study OXT/AVP signaling or socio-behavioral functioning. One important area for future research therefore is the development of appropriate animal models of CNS LCH and IGCTs and the subsequent utilization of these models, along with the pre-existing models of CP, to study OXT/AVP signaling and socio-behavioral functioning. These models will allow for more tractable experiments than are possible in humans and will thus have the ability to greatly increase our understanding of the relationship between disorders of HPIT involvement, OXT/AVP signaling, and socio-behavioral functioning. The results of these experiments can then guide future research involving human subjects, providing the foundation for studies that could impact the clinical management and outcomes of patients with disorders of HPIT involvement and co-occurring socio-behavioral dysfunction. These

animal models would also facilitate future research on the impact that disorders of HPIT involvement may have on other neurotransmitters, such as serotonin and dopamine, which are influenced by OXT signaling and also modulate social behavior (Lefevre et al., 2018; Nunes et al., 2021).

The clinical evidence for the relationship between disorders of HPIT involvement, OXT/AVP signaling, and socio-behavioral deficits is similarly lacking in critical areas. Due to the limited clinical evidence investigating the presence of dysregulated OXT/AVP signaling and socio-behavioral dysfunction among patients with disorders of HPIT involvement, more research needs to be conducted to better characterize the deficits evidenced in the biochemical and behavioral phenotypes of CP, CNS LCH, and IGCTs. While there have been a few studies that directly measure the impact of CP on OXT signaling (Gebert et al., 2018; Brandi et al., 2020), there have not been studies that investigate the direct effect of CNS LCH or IGCTs on OXT signaling. And while clinical evidence among pregnant women with childhood LCH show mixed effects regarding the condition's potential impact on OXT signaling (Shinar, Many, and Maslovitz, 2016; Clark and Houlden, 2018), without directly measuring neuropeptide concentrations it is difficult, if not impossible, to capture the disease's direct impact on behaviorally-relevant OXT production and release. To this end, future research should measure baseline and stimulated OXT concentrations in CNS LCH and IGCT patients to evaluate general OXT dysregulation as well as whether these putative OXT production/signaling deficits correlate with social and behavioral functional impairments.

Future research must also directly measure the impact that CP, CNS LCH, and IGCTs have on AVP signaling. We were only able to identify one clinical study that directly measured AVP concentrations in a cohort of patients with CP (Shi et al., 2017); we otherwise had to utilize a diagnosis of central DI to estimate AVP dysregulation in all other studies included in this review. While a diagnosis of central DI is reflective of reduced AVP concentrations (Di Iorgi et al., 2012), it does not allow for the direct quantification of AVP. Without measuring the concentration of AVP in patients with CP, CNS LCH, or IGCTs, researchers are unable to fully capture the effect that these disorders of HPIT involvement have on the neuropeptide's production and signaling. Further, while there is some evidence suggesting alterations to socio-behavior functioning in patients with central DI (Nabe et al., 2007), future studies that quantify AVP concentrations in patients with disorders of HPIT involvement must also collect social and behavioral data. This will facilitate an improved understanding of the relationship between AVP disruption and changes in the socio-behavioral functioning in patients with disorders of HPIT involvement.

## 8. Conclusions

The present synthesis of the disease characteristics, relevant preclinical research, and clinical studies of CP, CNS LCH, and IGCTs provides ample evidence to suggest that the socio-behavioral deficits experienced by a subset of patients with these disorders of HPIT involvement may be caused in part by OXT and/or AVP signaling disruptions that occur due to hypothalamic and/or pituitary damage. The co-occurring socio-behavioral dysfunction experienced by patients with CP, CNS LCH, or IGCTs can be debilitating, and there is currently no standardized treatment available to lessen the social and behavioral impact of these diseases. Gaining a better understanding of the biological underpinnings of the socio-behavioral dysfunction frequently observed in patients with disorders of HPIT involvement will help inform clinical care and guide the development of best practices in treating these patients. By proposing the aforementioned hypothesis that these socio-behavioral deficits are due to a neurohormonal imbalance and calling for further preclinical and clinical research on the subject, we are one step closer to providing these patients with effective, evidence-based pharmacological interventions that will lead to improvements in their socio-behavioral functioning and quality of life.

## References

Althammer, F., Eliava, M., Grinevich, V., 2021. Central and peripheral release of oxytocin: Relevance of neuroendocrine and neurotransmitter actions for physiology and behavior. Handb. Clin. Neurol. 180, 25–44. https://doi.org/10.1016/B978-0-12-820107-7.00003-3.

Anderson, C.A., Wilkening, G.N., Filley, C.M., Reardon, M.S., Kleinschmidt-DeMasters, B. K., 1997. Neurobehavioral outcome in pediatric craniopharyngioma. Pediatr. Neurosurg. 26 (5), 255–260. https://doi.org/10.1159/000121200.

Apps, J.R., Martinez-Barbera, J.P., 2017. Genetically engineered mouse models of craniopharyngioma: an opportunity for therapy development and understanding of tumor biology. Brain Pathol. 27 (3), 364–369. https://doi.org/10.1111/bpa.12501.

Bao, Y., Pan, J., Qi, S., Lu, Y., Peng, J., 2016. Origin of craniopharyngiomas: Implications for growth pattern, clinical characteristics, and outcomes of tumor recurrence. J. Neurosurg. 125 (1), 24–32. https://doi.org/10.3171/2015.6.jns141883.

Baribeau, D.A., Anagnostou, E., 2015. Oxytocin and vasopressin: linking pituitary neuropeptides and their receptors to social neurocircuits. Front. Neurosci. 9, 335. https://doi.org/10.3389/fnins.2015.00335.

Barrett, C.E., Keebaugh, A.C., Ahern, T.H., Bass, C.E., Terwilliger, E.F., Young, L.J., 2013. Variation in vasopressin receptor (Avpr1a) expression creates diversity in behaviors related to monogamy in prairie voles. Horm. Behav. 63 (3), 518–526. https://doi.org/10.1016/j.yhbeh.2013.01.005.

Baumgartner, I., von Hochstetter, A., Baumert, B., Luetolf, U., Follath, F., 1997. Langerhans'-cell histiocytosis in adults. Med. Pediatr. Oncol. 28 (1), 9–14. https://doi.org/10.1002/(sici)1096-911x(199701)28:1<9::aid-mpo3>3.0.co;2-p.

Beiderbeck, D.I., Neumann, I.D., Veenema, A.H., 2007. Differences in intermale aggression are accompanied by opposite vasopressin release patterns within the septum in rats bred for low and high anxiety. Eur. J. Neurosci. 26 (12), 3597–3605. https://doi.org/10.1111/j.1460-9568.2007.05974.x.

Benelli, A., Bertolini, A., Poggioli, R., Menozzi, B., Basaglia, R., Arletti, R., 1995. Polymodal dose-response curve for oxytocin in the social recognition test. Neuropeptides 28, 251–255. https://doi.org/10.1016/0143-4179(95)90029-2.

Berres, M.L., Lim, K.P., Peters, T., Price, J., Takizawa, H., Salmon, H., Idoyaga, J., Ruzo, A., Lupo, P.J., Hicks, M.J., Shih, A., Simko, S.J., Abhyankar, H., Chakraborty, R., Leboeuf, M., Beltrāo, M., Lira, S.A., Heym, K.M., Bigley, V., Collin, M., Allen, C.E., 2014. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J. Exp. Med. 211 (4), 669–683. https://doi.org/10.1084/jem.20130977.

Bichet, D.G., 2014. Central vasopressin: dendritic and axonal secretion and renal actions. Clin. Kidney J. 7 (3), 242–247. https://doi.org/10.1093/ckj/sfu050.

Bielsky, I.F., Hu, S.B., Szegda, K.L., Westphal, H., Young, L.J., 2004. Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 29 (3), 483–493. https://doi.org/10.1038/sj.npp.1300360.

Boccia, M.L., Petrusz, P., Suzuki, K., Marson, L., Pedersen, C.A., 2013. Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience 253 (s.), 155–164. https://doi.org/10.1016/j.neuroscience.2013.08.048.

Bogusz, A., Boekhoff, S., Warmuth-Metz, M., Calaminus, G., Eveslage, M., Müller, H.L., 2019. Posterior hypothalamus-sparing surgery improves outcome after childhood craniopharyngioma. Endocr. Connect. 8 (5), 481–492. https://doi.org/10.1530/ec-19-0074.

Bohus, B., de Wied, D., 1998. The vasopressin deficient Brattleboro rats: a natural knockout model used in the search for CNS effects of vasopressin. Prog. brain Res. 119, 555–573. https://doi.org/10.1016/s0079-6123(08)61593-9.

Bowers, A.R., Hughes, L., 2021. Craniopharyngioma presenting with psychiatric symptoms: a case report. Prog. Neurol. Psychiatry 25 (3), 18–20. https://doi.org/10.1002/pnp.715.

Brandi, M., Gebert, D., Kopczak, A., Auer, M.K., Schilbach, L., 2020. Oxytocin release deficit and social cognition in craniopharyngioma patients. J. Neuroendocrinol. 32 (5) https://doi.org/10.1111/jne.12842.

Brunner, J., Keck, M.E., Landgraf, R., Uhr, M., Namendorf, C., Bronisch, T., 2002. Vasopressin in CSF and plasma in depressed suicide attempters: preliminary results. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 12 (5), 489–494. https://doi.org/10.1016/s0924-977x(02)00071-8.

Brunnlieb, C., Nave, G., Camerer, C.F., Schosser, S., Vogt, B., Münte, T.F., Heldmann, M., 2016. Vasopressin increases human risky cooperative behavior. Proc. Natl. Acad. Sci. USA 113 (8), 2051–2056. https://doi.org/10.1073/pnas.1518825113.

Calaminus, G., Kortmann, R., Worch, J., Nicholson, J.C., Alapetite, C., Garrè, M.L., Patte, C., Ricardi, U., Saran, F., Frappaz, D., 2013. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. Neuro-Oncol. 15 (6), 788–796. https://doi.org/10.1093/neuonc/not019.

Calcagnoli, F., Kreutzmann, J.C., de Boer, S.F., Althaus, M., Koolhaas, J.M., 2015. Acute and repeated intranasal oxytocin administration exerts anti-aggressive and pro-affiliative effects in male rats. Psychoneuroendocrinology 51, 112–121. https://doi.org/10.1016/j.psyneuen.2014.09.019.

Caldwell, H.K., Lee, H.J., Macbeth, A.H., Young 3rd, W.S., 2008. Vasopressin: behavioral roles of an "original" neuropeptide. Prog. Neurobiol. 84 (1), 1–24. https://doi.org/10.1016/j.pneurobio.2007.10.007.

Caldwell, H.K., Aulino, E.A., Freeman, A.R., Miller, T.V., Witchey, S.K., 2017. Oxytocin and behavior: lessons from knockout mice. Dev. Neurobiol. 77 (2), 190–201. https://doi.org/10.1002/dneu.22431.

Capatina, C., Vintila, M., Gherlan, I., Dumitrașcu, A., Caragheorgheopol, A., Procopiuc, C., Ciubotaru, V., Poiana, C., 2018. Craniopharyngioma - Clinical And Therapeutic Outcome Data in a Mixed Cohort of Adult and Paediatric Cases. Acta Endocrinol. (Buchar.) 14 (4), 549–555. https://doi.org/10.4183/aeb.2018.549.

Carson, D.S., Howerton, C.L., Garner, J.P., Hyde, S.A., Clark, C.L., Hardan, A.Y., Penn, A.A., Parker, K.J., 2014. Plasma vasopressin concentrations positively predict cerebrospinal fluid vasopressin concentrations in human neonates. Peptides 61, 12–16. https://doi.org/10.1016/j.peptides.2014.08.003.

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 (9), 1085–1090. https://doi.org/10.1038/mp.2014.132.

Carson, D.S., Garner, J.P., Hyde, S.A., Libove, R.A., Berquist, S.W., Hornbeak, K.B., Jackson, L.P., Sumiyoshi, R.D., Howerton, C.L., Hannah, S.L., Partap, S., Phillips, J.M., Hardan, A.Y., Parker, K.J., 2015. Arginine vasopressin is a blood-based biomarker of social functioning in children with autism. PloS One 10 (7), e0132224. https://doi.org/10.1371/journal.pone.0132224.

Carter, C., Grippo, A., Pournajafinazarloo, H., Ruscio, M., Porges, S., 2008. Oxytocin, vasopressin and sociality. Adv. Vasopressin Oxytocin — Genes Behav. Dis. Prog. Brain Res. 331–336. https://doi.org/10.1016/s0079-6123(08)00427-5.

Chang, H.-Y., Chiu, C.-F., Jung, S.-M., Wong, A.M.-C., Wu, C.-T., Lo, F.-S., 2021. Neurological and endocrinological manifestations of 49 children with intracranial pure germinoma at initial diagnosis in Taiwan. Pediatr. Neonatol. 62 (1), 106–112. https://doi.org/10.1016/j.pedneo.2020.07.017.

Charles, R., Sakurai, T., Takahashi, N., Elder, G.A., Gama Sosa, M.A., Young, L.J., Buxbaum, J.D., 2014. Introduction of the human AVPR1A gene substantially alters brain receptor expression patterns and enhances aspects of social behavior in transgenic mice. Dis. Models Mech. 7 (8), 1013–1022. https://doi.org/10.1242/dmm.017053.

Clark, A., Houlden, R.L., 2018. Oxytocin deficiency and spontaneous onset of labor and lactation in langerhans cell histiocytosis. AACE Clin. Case Rep. 4 (5) https://doi.org/10.4158/accr-2018-0085.

Clopper, R.R., Meyer 3rd, W.J., Udvarhelyi, G.B., Money, J., Aarabi, B., Mulvihill, J.J., Piasio, M., 1977. Postsurgical IQ and behavioral data on twenty patients with a history of childhood craniopharyngioma. Psychoneuroendocrinology 2 (4), 365–372. https://doi.org/10.1016/0306-4530(77)90006-3.

Cohen, M., Bartels, U., Branson, H., Kulkarni, A.V., Hamilton, J., 2013. Trends in treatment and outcomes of pediatric craniopharyngioma, 1975-2011. Neuro-Oncol. 15 (6), 767–774. https://doi.org/10.1093/neuonc/not026.

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 (8) https://doi.org/10.1515/jpem-2015-0445.

Crawford, J.R., Santi, M.R., Vezina, G., Myseros, J.S., Keating, R.F., LaFond, D.A., Rood, B.R., MacDonald, T.J., Packer, R.J., 2007. CNS germ cell tumor (CNSGCT) of childhood: presentation and delayed diagnosis. Neurology 68 (20), 1668–1673. https://doi.org/10.1212/01.wnl.0000261908.36803.ac.

Crawley, J.N., Chen, T., Puri, A., Washburn, R., Sullivan, T.L., Hill, J.M., Young, N.B., Nadler, J.J., Moy, S.S., Young, L.J., Caldwell, H.K., Young, W.S., 2007. Social approach behaviors in oxytocin knockout mice: comparison of two independent lines tested in different laboratory environments. Neuropeptides 41 (3), 145–163. https://doi.org/10.1016/j.npep.2007.02.002.

De Dreu, C.K.W., Greer, L.L., Handgraaf, M.J.J., Shalvi, S., Van Kleef, G.A., Baas, M., Ten Velden, F.S., Van Dijk, E., Feith, S.W.W., 2010. The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. Science 328 (5984), 1408–1411. https://doi.org/10.1126/science.1189047.

De Felici, M., Klinger, F.G., Campolo, F., Balistreri, C.R., Barchi, M., Dolci, S., 2021. To be or not to be a germ cell: the extragonadal germ cell tumor paradigm. Int. J. Mol. Sci. 22 (11), 5982. https://doi.org/10.3390/ijms22115982.

Dekkers, O.M., Biermasz, N.R., Smit, J.W., Groot, L.E., Roelfsema, F., Romijn, J.A., Pereira, A.M., 2006. Quality of life in treated adult craniopharyngioma patients. Eur. J. Endocrinol. 154 (3), 483–489. https://doi.org/10.1530/eje.1.02114.

DeVries, A.C., Young 3rd, W.S., Nelson, R.J., 1997. Reduced aggressive behaviour in mice with targeted disruption of the oxytocin gene. J. Neuroendocrinol. 9 (5), 363–368. https://doi.org/10.1046/j.1365-2826.1997.t01-1-00589.x.

Di Iorgi, N., Napoli, F., Allegri, A.E.M., Olivieri, I., Bertelli, E., Gallizia, A., Rossi, A., Maghnie, M., 2012. Diabetes insipidus - diagnosis and management. Horm. Res. Paediatr. 77 (2), 69–84. https://doi.org/10.1159/000336333.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry 65 (9), 728–731. https://doi.org/10.1016/j.biopsych.2008.10.011.

Donaldson, Z.R., Spiegel, L., Young, L.J., 2010. Central vasopressin V1a receptor activation is independently necessary for both partner preference formation and expression in socially monogamous male prairie voles. Behav. Neurosci. 124 (1), 159–163. https://doi.org/10.1037/a0018094.

Ebitz, R.B., Watson, K.K., Platt, M.L., 2013. Oxytocin blunts social vigilance in the rhesus macaque. Proc. Natl. Acad. Sci. USA 110 (28), 11630–11635. https://doi.org/10.1073/pnas.1305230110.

El-Farhan, N., Hampton, D., Penney, M., 2013. Measurement of arginine vasopressin. Methods in Molecular Biology. Methods in Molecular Biology,, pp. 129–139. https://doi.org/10.1007/978-1-62703-616-0_8.

Engelmann, M., Landgraf, R., 1994. Microdialysis administration of vasopressin into the septum improves social recognition in Brattleboro rats. Physiol. Behav. 55 (1), 145–149. https://doi.org/10.1016/0031-9384(94)90022-1.

Fahrner, B., Prosch, H., Minkov, M., Krischmann, M., Gadner, H., Prayer, D., Grois, N., 2012. Long-term outcome of hypothalamic pituitary tumors in Langerhans cell histiocytosis. Pediatr. Blood Cancer 58 (4), 606–610. https://doi.org/10.1002/pbc.24042.

Fangusaro, J., Wu, S., MacDonald, S., Murphy, E., Shaw, D., Bartels, U., Khatua, S., Souweidane, M., Lu, H.M., Morris, D., Panigrahy, A., Onar-Thomas, A., Fouladi, M., Gajjar, A., Dhall, G., 2019. Phase II trial of response-based radiation therapy for patients with localized CNS nongerminomatous germ cell tumors: a children's oncology group study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 37 (34), 3283–3290. https://doi.org/10.1200/JCO.19.00701.

Feldman, R., Weller, A., Zagoory-Sharon, O., Levine, A., 2007. Evidence for a neuroendocrinological foundation of human affiliation. Psychol. Sci. 18 (11), 965–970. https://doi.org/10.1111/j.1467-9280.2007.02010.x.

Ferguson, J.N., Young, L.J., Hearn, E.F., Matzuk, M.M., Insel, T.R., Winslow, J.T., 2000. Social amnesia in mice lacking the oxytocin gene. Nat. Genet. 25 (3), 284–288. https://doi.org/10.1038/77040.

Ferguson, J.N., Aldag, J.M., Insel, T.R., Young, L.J., 2001. Oxytocin in the medial amygdala is essential for social recognition in the mouse. J. Neurosci.: Off. J. Soc. Neurosci. 21 (20), 8278–8285. https://doi.org/10.1523/JNEUROSCI.21-20-08278.2001.

Ferris, C.F., Melloni Jr., R.H., Koppel, G., Perry, K.W., Fuller, R.W., Delville, Y., 1997. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J. Neurosci.: Off. J. Soc. Neurosci. 17 (11), 4331–4340. https://doi.org/10.1523/JNEUROSCI.17-11-04331.1997.

Fodor, A., Barsvari, B., Aliczki, M., Balogh, Z., Zelena, D., Goldberg, S.R., Haller, J., 2014. The effects of vasopressin deficiency on aggression and impulsiveness in male and female rats. Psychoneuroendocrinology 47, 141–150. https://doi.org/10.1016/j.psyneuen.2014.05.010.

Fodor, A., Kovács, K.B., Balázsfi, D., Klausz, B., Pintér, O., Demeter, K., Daviu, N., Rabasa, C., Rotllant, D., Nadal, R., Zelena, D., 2016. Depressive- and anxiety-like behaviors and stress-related neuronal activation in vasopressin-deficient female Brattleboro rats. Physiol. Behav. 158, 100–111. https://doi.org/10.1016/j.physbeh.2016.02.041.

Fujimaki, T., 2009. Central nervous system germ cell tumors: classification, clinical features, and treatment with a historical overview. J. Child Neurol. 24 (11), 1439–1445. https://doi.org/10.1177/0883073809342127.

Gaston-Massuet, C., Andoniadou, C.L., Signore, M., Jayakody, S.A., Charolidi, N., Kyeyune, R., Vernay, B., Jacques, T.S., Taketo, M.M., Le Tissier, P., Dattani, M.T., Martinez-Barbera, J.P., 2011. Increased Wingless (Wnt) signaling in pituitary progenitor/stem cells gives rise to pituitary tumors in mice and humans. Proc. Natl. Acad. Sci. USA 108 (28), 11482–11487. https://doi.org/10.1073/pnas.1101553108.

Gebert, D., Auer, M.K., Stieg, M.R., Freitag, M.T., Lahne, M., Fuss, J., Schilbach, K., Schopohl, J., Stalla, G.K., Kopczak, A., 2018. De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. Psychoneuroendocrinology 88, 61–69. https://doi.org/10.1016/j.psyneuen.2017.11.006.

Ghirardello, S., Hopper, N., Albanese, A., Maghnie, M., 2006. Diabetes insipidus in craniopharyngioma: postoperative management of water and electrolyte disorders. J. Pediatr. Endocrinol. Metab.: JPEM 19 (Suppl 1), 413–421.

Goodwin, T.L., Sainani, K., Fisher, P.G., 2009. Incidence patterns of central nervous system germ cell tumors: a SEER Study. J. Pediatr. Hematol. /Oncol. 31 (8), 541–544. https://doi.org/10.1097/MPH.0b013e3181983af5.

Gouin, J.P., Carter, C.S., Pournajafi-Nazarloo, H., Malarkey, W.B., Loving, T.J., Stowell, J., Kiecolt-Glaser, J.K., 2012. Plasma vasopressin and interpersonal functioning. Biol. Psychol. 91 (2), 270–274. https://doi.org/10.1016/j.biopsycho.2012.07.003.

Grois, N., Pötschger, U., Prosch, H., Minkov, M., Arico, M., Braier, J., Henter, J.-I., Janka-Schaub, G., Ladisch, S., Ritter, J., Steiner, M., Unger, E., Gadner, H., 2006. Risk factors for diabetes insipidus in langerhans cell histiocytosis. Pediatr. Blood Cancer 46 (2), 228–233. https://doi.org/10.1002/pbc.20425.

Grois, N., Favara, B.E., Mostbeck, G.H., Prayer, D., 1998. Central nervous system disease in Langerhans cell histiocytosis. Hematol. /Oncol. Clin. North Am. 12 (2), 287–305. https://doi.org/10.1016/s0889-8588(05)70511-6.

Gruber, C.W., 2014. Physiology of invertebrate oxytocin and vasopressin neuropeptides. Exp. Physiol. 99 (1), 55–61. https://doi.org/10.1113/expphysiol.2013.072561.

Guyot-Goubin, A., Donadieu, J., Barkaoui, M., Bellec, S., Thomas, C., Clavel, J., 2008. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr. Blood Cancer 51 (1), 71–75. https://doi.org/10.1002/pbc.21498.

Haller, J., Makara, G., Barna, I., Kovács, K., Nagy, J., Vecsernyés, M., 1996. CompressioN Of The Pituitary Stalk Elicits Chronic Increases in CSF Vasopressin, Oxytocin As Well As In Social Investigation And Aggressiveness. J. Neuroendocrinol. 8 (5), 361–365. https://doi.org/10.1046/j.1365-2826.1996.04654.x.

Hammond, J.L., Hall, S.S., 2011. Functional analysis and treatment of aggressive behavior following resection of a craniopharyngioma. Dev. Med. Child Neurol. 53 (4), 369–374. https://doi.org/10.1111/j.1469-8749.2010.03887.x.

Haupt, C., Ancker, U., Muller, M., Herrmann, H.D., Schulte, F.J., 1996. Intracranial germ-cell tumours–treatment results and residuals. Eur. J. Pediatr. 155 (3), 230–236. https://doi.org/10.1007/BF01953944.

Henderson Jr., F., Schwartz, T.H., 2022. Update on management of craniopharyngiomas. J. neuro-Oncol. 156 (1), 97–108. https://doi.org/10.1007/s11060-021-03906-4.

Hoffmann, A., Özyurt, J., Thiel, C., Müller, H.L., 2018. Cran-04. Oxytocin in childhood-onset craniopharyngioma - first experiences with neuropsychological effects of oxytocin administration. Neuro-Oncol. 20 (Suppl_2) https://doi.org/10.1093/neuonc/noy059.041.

Huber, D., Veinante, P., Stoop, R., 2005. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Sci. (N. Y., N. Y.) 308 (5719), 245–248. https://doi.org/10.1126/science.1105636.

Imashuku, S., Fujita, N., Shioda, Y., Noma, H., Seto, S., Minato, T., Sakashita, K., Ito, N., Kobayashi, R., Morimoto, A., Japan LCH Study Group (JLSG), 2015. Follow-up of pediatric patients treated by IVIG for Langerhans cell histiocytosis (LCH)-related neurodegenerative CNS disease. Int. J. Hematol. 101 (2), 191–197. https://doi.org/10.1007/s12185-014-1717-5.

Insel, T.R., Shapiro, L.E., 1992. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc. Natl. Acad. Sci. 89 (13), 5981–5985. https://doi.org/10.1073/pnas.89.13.5981.

Insel, T.R., Gelhard, R., Shapiro, L.E., 1991. The comparative distribution of forebrain receptors for neurohypophyseal peptides in monogamous and polygamous mice. Neuroscience 43 (2–3), 623–630. https://doi.org/10.1016/0306-4522(91)90321-e.

Ito, M., Jamshidi, J., Yamanaka, K., 2001. Does craniopharyngioma metastasize? Case report and review of the literature. Neurosurgery 48 (4), 933–936. https://doi.org/10.1097/00006123-200104000-00050.

Jennings, M.T., Gelman, R., Hochberg, F., 1985. Intracranial germ-cell tumors: natural history and pathogenesis. J. Neurosurg. 63 (2), 155–167. https://doi.org/10.3171/jns.1985.63.2.0155.

Johnson, A.E., Audigier, S., Rossi, F., Jard, S., Tribollet, E., Barberis, C., 1993. Localization and characterization of vasopressin binding sites in the rat brain using an iodinated linear AVP antagonist. Brain Res. 622 (1–2), 9–16. https://doi.org/10.1016/0006-8993(93)90795-o.

Jurek, B., Neumann, I.D., 2018. The oxytocin receptor: from intracellular signaling to behavior. Physiol. Rev. 98 (3), 1805–1908. https://doi.org/10.1152/physrev.00031.2017.

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. Neuroendocrinol. 25 (7), 668–673. https://doi.org/10.1111/jne.12038.

Kalra, S., Zargar, A.H., Jain, S.M., Sethi, B., Chowdhury, S., Singh, A.K., Thomas, N., Unnikrishnan, A.G., Thakkar, P.B., Malve, H., 2016. Diabetes insipidus: The other diabetes. Indian J. Endocrinol. Metab. 20 (1), 9–21. https://doi.org/10.4103/2230-8210.172273.

Karavitaki, N., Wass, J.A., 2008. Craniopharyngiomas. Endocrinol. Metab. Clin. North Am. 37 (1) https://doi.org/10.1016/j.ecl.2007.10.012.

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. 62 (4), 397–409. https://doi.org/10.1111/j.1365-2265.2005.02231.x.

Karavitaki, N., Cudlip, S., Adams, C.B., Wass, J.A., 2006. Craniopharyngiomas. Endocr. Rev. 27 (4), 371–397. https://doi.org/10.1210/er.2006-0002.

Kilday, J.P., Laughlin, S., Urbach, S., Bouffet, E., Bartels, U., 2015. Diabetes insipidus in pediatric germinomas of the suprasellar region: characteristic features and significance of the pituitary bright spot. J. Neuro Oncol. 121 (1), 167–175. https://doi.org/10.1007/s11060-014-1619-7.

Kim, J.Y., Park, J., 2015. Understanding the treatment strategies of intracranial germ cell tumors: focusing on radiotherapy. J. Korean Neurosurg. Soc. 57 (5), 315–322. https://doi.org/10.3340/jkns.2015.57.5.315.

Kimura, T., Saji, F., Nishimori, K., Ogita, K., Nakamura, H., Koyama, M., Murata, Y., 2003. Molecular regulation of the oxytocin receptor in peripheral organs. J. Mol. Endocrinol. 30 (2), 109–115. https://doi.org/10.1677/jme.0.0300109.

King, L.B., Walum, H., Inoue, K., Eyrich, N.W., Young, L.J., 2016. Variation in the oxytocin receptor gene predicts brain region–specific expression and social attachment. Biol. Psychiatry 80 (2), 160–169. https://doi.org/10.1016/j.biopsych.2015.12.008.

Knobloch, H.S., Charlet, A., Hoffmann, L.C., Eliava, M., Khrulev, S., Cetin, A.H., Osten, P., Schwarz, M.K., Seeburg, P.H., Stoop, R., Grinevich, V., 2012. Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73 (3), 553–566. https://doi.org/10.1016/j.neuron.2011.11.030.

Koh, K.N., Wong, R.X., Lee, D.E., Han, J.W., Byun, H.K., Yoon, H.I., Kim, D.S., Lyu, C.J., Kang, H.J., Hong, K.T., Lee, J.H., Kim, I.H., Phi, J.H., Kim, S.K., Wong, T.T., Lee, H. L., Lai, I.C., Kang, Y.M., Ra, Y.S., Ahn, S.D., Kim, J.Y., 2021. Outcomes of intracranial germinoma-a retrospective multinational Asian study on effect of clinical presentation and differential treatment strategies. Neuro Oncol. https://doi.org/10.1093/neuonc/noab295.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435 (7042), 673–676. https://doi.org/10.1038/nature03701.

Lagman, D., Ocampo Daza, D., Widmark, J., Abalo, X.M., Sundström, G., Larhammar, D., 2013. The vertebrate ancestral repertoire of visual opsins, transducin alpha subunits and oxytocin/vasopressin receptors was established by duplication of their shared genomic region in the two rounds of early vertebrate genome duplications. BMC Evolut. Biol. 13 (1), 238. https://doi.org/10.1186/1471-2148-13-238.

Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25 (3–4), 150–176. https://doi.org/10.1016/j.yfrne.2004.05.001.

Lang, R.E., Heil, J., Ganten, D., Hermann, K., Rascher, W., Unger, T., 1983. Effects of lesions in the paraventricular nucleus of the hypothalamus on vasopressin and oxytocin contents in brainstem and spinal cord of rat. Brain Res. 260 (2), 326–329. https://doi.org/10.1016/0006-8993(83)90690-x.

László, K., Kiss, O., Vörös, D., Mintál, K., Ollmann, T., Péczely, L., Kovács, A., Zagoracz, O., Kertes, E., Kállai, V., László, B., Hormay, E., Berta, B., Tóth, A., Karádi, Z., Lénárd, L., 2022. Intraamygdaloid oxytocin reduces anxiety in the valproate-induced autism rat model. Biomedicines 10 (2), 405. https://doi.org/10.3390/biomedicines10020405.

Laurencikas, E., Gavhed, D., Stålemark, H., Hooft, I.V., Prayer, D., Grois, N., Henter, J., 2010. Incidence and pattern of radiological central nervous system Langerhans cell histiocytosis in children: a population based study. Pediatr. Blood Cancer 56 (2), 250–257. https://doi.org/10.1002/pbc.22791.

Lefevre, A., Mottolese, R., Dirheimer, M., Mottolese, C., Duhamel, J.R., Sirigu, A., 2017. A comparison of methods to measure central and peripheral oxytocin concentrations in human and non-human primates. Sci. Rep. 7 (1), 17222. https://doi.org/10.1038/s41598-017-17674-7.

Lefevre, A., Mottolese, R., Redouté, J., Costes, N., Le Bars, D., Geoffray, M.M., Leboyer, M., Sirigu, A., 2018. OxytoCin Fails To Recruit Serotonergic Neurotransmission In The Autistic Brain. Cereb. Cortex 28 (12), 4169–4178. https://doi.org/10.1093/cercor/bhx272.

Liang, S.Y., Yang, T.F., Chen, Y.W., Liang, M.L., Chen, H.H., Chang, K.P., Shan, I.K., Chen, Y.S., Wong, T.T., 2013. Neuropsychological functions and quality of life in survived patients with intracranial germ cell tumors after treatment. Neuro Oncol. 15 (11), 1543–1551. https://doi.org/10.1093/neuonc/not127.

Liu, S.Y., Tung, Y.C., Lee, C.T., Liu, H.M., Peng, S.F., Wu, M.Z., Kuo, M.F., Tsai, W.Y., 2013. Clinical characteristics of central diabetes insipidus in Taiwanese children. J. Formos. Med. Assoc.Taiwan yizhi 112 (10), 616–620. https://doi.org/10.1016/j.jfma.2013.06.019.

Lo, A., Laperriere, N., Hodgson, D., Goddard, K., 2018. GERM-26. Long-term health-related quality of life in adult survivors of pediatric intracranial germ cell tumor. Neuro-Oncol. 20 (Suppl 2), i88–i89. https://doi.org/10.1093/neuonc/noy059.272.

Ludwig, M., Leng, G., 2006. Dendritic peptide release and peptide-dependent behaviours. Nat. Rev. Neurosci. 7 (2), 126–136. https://doi.org/10.1038/nrn1845.

Lukas, M., Toth, I., Reber, S.O., Slattery, D.A., Veenema, A.H., Neumann, I.D., 2011. The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. Neuropsychopharmacology 36 (11), 2159–2168. https://doi.org/10.1038/npp.2011.95.

Macbeth, A.H., Lee, H.-J., Edds, J., Young, W.S., 2009. Oxytocin and the oxytocin receptor underlie intrastrain, but not interstrain, social recognition. Genes Brain Behav. 8 (5), 558–567. https://doi.org/10.1111/j.1601-183x.2009.00506.x.

MacLean, E.L., Gesquiere, L.R., Gruen, M.E., Sherman, B.L., Martin, W.L., Carter, C.S., 2017. Endogenous oxytocin, vasopressin, and aggression in domestic dogs. Front. Psychol. 8, 1613. https://doi.org/10.3389/fpsyg.2017.01613.

Makara, G.B., Sutton, S., Otto, S., Plotsky, P.M., 1995. Marked changes of arginine vasopressin, oxytocin, and corticotropin-releasing hormone in hypophysial portal plasma after pituitary stalk damage in the rat. Endocrinology 136 (5), 1864–1868. https://doi.org/10.1210/endo.136.5.7720631.

Makara, G.B., Kiss, A., Lolait, S.J., Aguilera, G., 1996. Hypothalamic-pituitary corticotroph function after shunting of magnocellular vasopressin and oxytocin to the hypophyseal portal circulation. Endocrinology 137 (2), 580–586. https://doi.org/10.1210/endo.137.2.8593805.

Mantella, R.C., Vollmer, R.R., Li, X., Amico, J.A., 2003. Female oxytocin-deficient mice display enhanced anxiety-related behavior. *Endocrinolog*y 144 (6), 2291–2296. https://doi.org/10.1210/en.2002-0197.

Martin, J., Kagerbauer, S.M., Gempt, J., Podtschaske, A., Hapfelmeier, A., Schneider, G., 2018. Oxytocin levels in saliva correlate better than plasma levels with concentrations in the cerebrospinal fluid of patients in neurocritical care. J. Neuroendocrinol. 30 (5), e12596 https://doi.org/10.1111/jne.12596.

Martinez-Barbera, J.P., 2015. 60 years of neuroendocrinology: Biology of human craniopharyngioma: lessons from mouse models. J. Endocrinol. 226 (2), T161–T172. https://doi.org/10.1530/JOE-15-0145.

Martins, D., Gabay, A.S., Mehta, M., Paloyelis, Y., 2020. Salivary and plasmatic oxytocin are not reliable trait markers of the physiology of the oxytocin system in humans. Elife *9*. https://doi.org/10.7554/elife.62456.

Matsutani, M., 2004. Clinical management of primary central nervous system germ cell tumors. Semin. Oncol. 31 (5), 676–683. https://doi.org/10.1053/j.seminoncol.2004.07.010.

May, J., Krieger, M.D., Bowen, I., Geffner, M.E., 2006. Craniopharyngioma in childhood. Adv. Pediatr. 53, 183–209. https://doi.org/10.1016/j.yapd.2006.04.013.

McCarthy, B.J., Shibui, S., Kayama, T., Miyaoka, E., Narita, Y., Murakami, M., Matsuda, A., Matsuda, T., Sobue, T., Palis, B.E., Dolecek, T.A., Kruchko, C., Engelhard, H.H., Villano, J.L., 2012. Primary CNS germ cell tumors in Japan and the

United States: an analysis of 4 tumor registries. Neuro Oncol. 14 (9), 1194–1200. https://doi.org/10.1093/neuonc/nos155.

McCrea, H.J., George, E., Settler, A., Schwartz, T.H., Greenfield, J.P., 2016. Pediatric suprasellar tumors. J. Child Neurol. 31 (12), 1367–1376. https://doi.org/10.1177/0883073815620671.

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 (9), 524–538. https://doi.org/10.1038/nrn3044.

Meynen, G., Unmehopa, U.A., van Heerikhuize, J.J., Hofman, M.A., Swaab, D.F., Hoogendijk, W.J., 2006. Increased arginine vasopressin mRNA expression in the human hypothalamus in depression: a preliminary report. Biol. Psychiatry 60 (8), 892–895. https://doi.org/10.1016/j.biopsych.2005.12.010.

Mlynarik, M., Zelena, D., Bagdy, G., Makara, G.B., Jezova, D., 2007. Signs of attenuated depression-like behavior in vasopressin deficient Brattleboro rats. Horm. Behav. 51 (3), 395–405. https://doi.org/10.1016/j.yhbeh.2006.12.007.

Modan-Moses, D., Weintraub, M., Meyerovitch, J., Segal-Lieberman, G., Bielorai, B., Shimon, I., 2001. Hypopituitarism in Langerhans cell histiocytosis: seven cases and literature review. J. Endocrinol. Investig. 24 (8), 612–617. https://doi.org/10.1007/bf03343902.

Momin, A.A., Recinos, M.A., Cioffi, G., Patil, N., Soni, P., Almeida, J.P., Kruchko, C., Barnholtz-Sloan, J.S., Recinos, P.F., Kshettry, V.R., 2021. Descriptive epidemiology of craniopharyngiomas in the United States. Pituitary 24 (4), 517–522. https://doi.org/10.1007/s11102-021-01127-6.

Monsereenusorn, C., Rodriguez-Galindo, C., 2015. Clinical characteristics and treatment of langerhans cell histiocytosis. Hematol. /Oncol. Clin. North Am. 29 (5), 853–873. https://doi.org/10.1016/j.hoc.2015.06.005.

Morana, G., Alves, C.A., Tortora, D., Finlay, J.L., Severino, M., Nozza, P., Ravegnani, M., Pavanello, M., Milanaccio, C., Maghnie, M., Rossi, A., Garrè, M.L., 2018. T2*-based MR imaging (gradient echo or susceptibility-weighted imaging) in midline and off-midline intracranial germ cell tumors: a pilot study. Neuroradiology 60 (1), 89–99. https://doi.org/10.1007/s00234-017-1947-3.

Nabe, K., Honjo, S., Ikeda, H., Wada, Y., Nomura, K., Hamamoto, Y., Koh, T., Tatsuoka, Y., Koshiyama, H., 2007. Diabetes insipidus and cognitive function. Med. Hypotheses 69 (4), 764–766. https://doi.org/10.1016/j.mehy.2007.01.081.

Nanduri, V.R., Lillywhite, L., Chapman, C., Parry, L., Pritchard, J., Vargha-Khadem, F., 2003. Cognitive outcome of long-term survivors of multisystem Langerhans cell histiocytosis: a single-institution, cross-sectional study. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 21 (15), 2961–2967. https://doi.org/10.1200/JCO.2003.05.048.

Nephew, B.C., Byrnes, E.M., Bridges, R.S., 2010. Vasopressin mediates enhanced offspring protection in multiparous rats (s.). Neuropharmacology 58 (1), 102–106. https://doi.org/10.1016/j.neuropharm.2009.06.032.

Neumann, I.D., Wigger, A., Torner, L., Holsboer, F., Landgraf, R., 2000. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. J. Neuroendocrinol. 12 (3), 235–243. https://doi.org/10.1046/j.1365-2826.2000.00442.x.

Nishimori, K., Young, L.J., Guo, Q., Wang, Z., Insel, T.R., Matzuk, M.M., 1996. Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. Proc. Natl. Acad. Sci. USA 93 (21), 11699–11704. https://doi.org/10.1073/pnas.93.21.11699.

Nunes, A.R., Gliksberg, M., Varela, S., Teles, M., Wircer, E., Blechman, J., Petri, G., Levkowitz, G., Oliveira, R.F., 2021. Developmental Effects of Oxytocin Neurons on Social Affiliation and Processing of Social Information. J. Neurosci.: Off. J. Soc. Neurosci. 41 (42), 8742–8760. https://doi.org/10.1523/JNEUROSCI.2939-20.2021.

Oliveira, V., Lukas, M., Wolf, H.N., Durante, E., Lorenz, A., Mayer, A.L., Bludau, A., Bosch, O.J., Grinevich, V., Egger, V., de Jong, T.R., Neumann, I.D., 2021. Oxytocin and vasopressin within the ventral and dorsal lateral septum modulate aggression in female rats. Nat. Commun. 12 (1), 2900. https://doi.org/10.1038/s41467-021-23064-5.

Ondruch, A., Maryniak, A., Kropiwnicki, T., Roszkowski, M., Daszkiewicz, P., 2011. Cognitive and social functioning in children and adolescents after the removal of craniopharyngioma. Child'S. Nerv. Syst. 27 (3), 391–397. https://doi.org/10.1007/s00381-010-1301-0.

Ostrom, Q.T., de Blank, P.M., Kruchko, C., Petersen, C.M., Liao, P., Finlay, J.L., Stearns, D.S., Wolff, J.E., Wolinsky, Y., Letterio, J.J., Barnholtz-Sloan, J.S., 2015. Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007-2011. Neuro Oncol. 16 (Suppl 10), x1–x36. https://doi.org/10.1093/neuonc/nou327.

Ostrom, Q.T., Cioffi, G., Waite, K., Kruchko, C., Barnholtz-Sloan, J.S., 2021. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united states in 2014-2018. Neuro Oncol. 23 (12 Suppl 2), iii1–iii105. https://doi.org/10.1093/neuonc/noab200.

Ouyang, D.L., Roberts, B.K., Gibbs, I.C., Katznelson, L., 2006. Isolated langerhans cell histiocytosis in an adult with central diabetes insipidus: case report and review of literature. Endocr. Pract. 12 (6), 660–663. https://doi.org/10.4158/ep.12.6.660.

Oztan, O., Garner, J.P., Partap, S., Sherr, E.H., Hardan, A.Y., Farmer, C., Thurm, A., Swedo, S.E., Parker, K.J., 2018. Cerebrospinal fluid vasopressin and symptom severity in children with autism. Ann. Neurol. 84 (4), 611–615. https://doi.org/10.1002/ana.25314.

Oztan, O., Garner, J.P., Constantino, J.N., Parker, K.J., 2020. Neonatal CSF vasopressin concentration predicts later medical record diagnoses of autism spectrum disorder. Proc. Natl. Acad. Sci. USA 117 (19), 10609–10613. https://doi.org/10.1073/pnas.1919050117.

Özyurt, J., Mehren, A., Boekhoff, S., Müller, H.L., Thiel, C.M., 2020. Social cognition in patients with hypothalamic-pituitary tumors. Front. Oncol. 10, 1014. https://doi.org/10.3389/fonc.2020.01014.

Park, Y., Yu, E.S., Ha, B., Park, H.J., Kim, J.H., Kim, J.Y., 2017. Neurocognitive and psychological functioning of children with an intracranial germ cell tumor. Cancer Res. Treat.: Off. J. Korean Cancer Assoc. 49 (4), 960–969. https://doi.org/10.4143/crt.2016.204.

Parker, K.J., Lee, T.M., 2001. Central vasopressin administration regulates the onset of facultative paternal behavior in microtus pennsylvanicus (meadow voles). Horm. Behav. 39 (4), 285–294. https://doi.org/10.1006/hbeh.2001.1655.

Parker, K.J., Phillips, K.M., Kinney, L.F., Lee, T.M., 2001a. Day length and sociosexual cohabitation alter central oxytocin receptor binding in female meadow voles (Microtus pennsylvanicus). Behav. Neurosci. 115 (6), 1349–1356.

Parker, K.J., Kinney, L.F., Phillips, K.M., Lee, T.M., 2001b. Paternal behavior is associated with central neurohormone receptor binding patterns in meadow voles (Microtus pennsylvanicus). Behav. Neurosci. 115 (6), 1341–1348. https://doi.org/10.1037//0735-7044.115.6.1341.

Parker, K.J., Buckmaster, C.L., Schatzberg, A.F., Lyons, D.M., 2005. Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. Psychoneuroendocrinology 30 (9), 924–929. https://doi.org/10.1016/j.psyneuen.2005.04.002.

Parker, K.J., Garner, J.P., Libove, R.A., Hyde, S.A., Hornbeak, K.B., Carson, D.S., Liao, C.P., Phillips, J.M., Hallmayer, J.F., Hardan, A.Y., 2014. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. Proc. Natl. Acad. Sci. USA 111 (33), 12258–12263. https://doi.org/10.1073/pnas.1402236111.

Parker, K.J., Garner, J.P., Oztan, O., Tarara, E.R., Li, J., Sclafani, V., Del Rosso, L.A., Chun, K., Berquist, S.W., Chez, M.G., Partap, S., Hardan, A.Y., Sherr, E.H., Capitanio, J.P., 2018. Arginine vasopressin in cerebrospinal fluid is a marker of sociality in nonhuman primates. Sci. Transl. Med. 10 (439), eaam9100. https://doi.org/10.1126/scitranslmed.aam9100.

Parker, K.J., Oztan, O., Libove, R.A., Mohsin, N., Karhson, D.S., Sumiyoshi, R.D., Summers, J.E., Hinman, K.E., Motonaga, K.S., Phillips, J.M., Carson, D.S., Fung, L.K., Garner, J.P., Hardan, A.Y., 2019. A randomized placebo-controlled pilot trial shows that intranasal vasopressin improves social deficits in children with autism. Sci. Transl. Med. 11 (491), eaau7356. https://doi.org/10.1126/scitranslmed.aau7356.

Patti, G., Napoli, F., Fava, D., Casalini, E., Di Iorgi, N., Maghnie, M., 2022. Approach to the pediatric patient: central diabetes insipidus. J. Clin. Endocrinol. Metab. dgab930 https://doi.org/10.1210/clinem/dgab930 (Advance online publication).

Paul, M.J., Peters, N.V., Holder, M.K., Kim, A.M., Whylings, J., Terranova, J.I., De Vries, G.J., 2016. Atypical social development in vasopressin-deficient brattleboro rats. Eneuro 3 (2). https://doi.org/10.1523/eneuro.0150-15.2016. ENEURO.0150–15.

PDQ Pediatric Treatment Editorial Board, 2020a. Childhood Craniopharyngioma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. National Cancer Institute, US.

PDQ Pediatric Treatment Editorial Board, 2020b. Langerhans Cell Histiocytosis Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. National Cancer Institute, US.

PDQ Pediatric Treatment Editorial Board, 2020c. Childhood central nervous system germ cell tumors treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. National Cancer Institute, US.

Pedersen, C.A., Prange, A.J., 1979. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. Proc. Natl. Acad. Sci. 76 (12), 6661–6665. https://doi.org/10.1073/pnas.76.12.6661.

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. 62 (2), 197–204. https://doi.org/10.1111/j.1365-2265.2004.02196.x.

Phi, J.H., Kim, S.K., Lee, J., Park, C.K., Kim, I.H., Ahn, H.S., Shin, H.Y., Kim, I.O., Jung, H.W., Kim, D.G., Paek, S.H., Wang, K.C., 2013. The enigma of bifocal germ cell tumors in the suprasellar and pineal regions: synchronous lesions or metastasis? J. Neurosurg. Pediatr. 11 (2), 107–114. https://doi.org/10.3171/2012.10.PEDS11487.

Phi, J.H., Wang, K.C., Kim, S.K., 2018. Intracranial germ cell tumor in the molecular era. J. Korean Neurosurg. Soc. 61 (3), 333–342. https://doi.org/10.3340/jkns.2018.0056.

Pietrowsky, R., Strüben, C., Mölle, M., Fehm, H.L., Born, J., 1996. Brain potential changes after intranasal vs. intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. Biol. Psychiatry 39 (5), 332–340. https://doi.org/10.1016/0006-3223(95)00180-8.

Poretti, A., Grotzer, M.A., Ribi, K., Schönle, E., Boltshauser, E., 2004. Outcome of craniopharyngioma in children: long-term complications and quality of life. Dev. Med. Child Neurol. 46 (4), 220–229. https://doi.org/10.1017/s0012162204000374.

Pratheesh, R., Swallow, D.M., Rajaratnam, S., Jacob, K.S., Chacko, G., Joseph, M., Chacko, A.G., 2013. Incidence, predictors and early post-operative course of diabetes insipidus in paediatric craniopharyngioma: a comparison with adults. Child'S. Nerv. Syst.: ChNS: Off. J. Int. Soc. Pediatr. Neurosurg. 29 (6), 941–949. https://doi.org/10.1007/s00381-013-2041-8.

Prayer, D., Grois, N., Prosch, H., Gadner, H., Barkovich, A.J., 2004. MR imaging presentation of intracranial disease associated with Langerhans cell histiocytosis. AJNR Am. J. Neuroradiol. 25 (5), 880–891.

Qiao, N., 2019. Excess mortality after craniopharyngioma treatment: are we making progress. Endocrine 64 (1), 31–37. https://doi.org/10.1007/s12020-018-1830-y.

Rae, M., Lemos Duarte, M., Gomes, I., Camarini, R., Devi, L.A., 2022. Oxytocin and vasopressIN: Signalling, behavioural modulation and potential therapeutic effects. Br. J. Pharmacol. 179 (8), 1544–1564. https://doi.org/10.1111/bph.15481.

Ragnauth, A.K., Devidze, N., Moy, V., Finley, K., Goodwillie, A., Kow, L.M., Muglia, L.J., Pfaff, D.W., 2005. Female oxytocin gene-knockout mice, in a semi-natural environment, display exaggerated aggressive behavior. Genes brain, Behav. 4 (4), 229–239. https://doi.org/10.1111/j.1601-183X.2005.00118.x.

Rilling, J.K., DeMarco, A.C., Hackett, P.D., Thompson, R., Ditzen, B., Patel, R., Pagnoni, G., 2012. Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. Psychoneuroendocrinology 37 (4), 447–461. https://doi.org/10.1016/j.psyneuen.2011.07.013.

Ring, R.H., Malberg, J.E., Potestio, L., Ping, J., Boikess, S., Luo, B., Schechter, L.E., Rizzo, S., Rahman, Z., Rosenzweig-Lipson, S., 2006. Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications. Psychopharmacology 185 (2), 218–225. https://doi.org/10.1007/s00213-005-0293-z.

Robben, J.H., Knoers, N.V., Deen, P.M., 2004. Regulation of the vasopressin V2 receptor by vasopressin in polarized renal collecting duct cells. Mol. Biol. Cell 15 (12), 5693–5699. https://doi.org/10.1091/mbc.e04-04-0337.

Robinson, A.G., 1976. DDAVP in the treatment of central diabetes insipidus. N. Engl. J. Med. 294 (10), 507–511. https://doi.org/10.1056/NEJM197603042941001.

Roth, C.L., Blevins, J.E., Ralston, M., Elfers, C., Ogimoto, K., Kaiyala, K.J., Morton, G.J., 2011. A novel rodent model that mimics the metabolic sequelae of obese craniopharyngioma patients. Pediatr. Res. 69 (3), 230–236. https://doi.org/10.1203/PDR.0b013e3182083b67.

Sabihi, S., Durosko, N.E., Dong, S.M., Leuner, B., 2014. Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. Psychoneuroendocrinology 45, 31–42. https://doi.org/10.1016/j.psyneuen.2014.03.009.

Saeki, N., Tamaki, K., Murai, H., Kubota, M., Yamaura, A., Uchida, D., Noguchi, Y., Nakamura, S., Tatsuno, I., Wada, K., Minagawa, M., Yasuda, T., 2000. Long-TERM OUTCOME OF ENDOCRINE FUNCTION IN PATIENTS WITH NEUROHYPOPHYSEAL GERminomas. Endocr. J. 47 (1), 83–89. https://doi.org/10.1507/endocrj.47.83.

Sala, M., Braida, D., Lentini, D., Busnelli, M., Bulgheroni, E., Capurro, V., Finardi, A., Donzelli, A., Pattini, L., Rubino, T., Parolaro, D., Nishimori, K., Parenti, M., Chini, B., 2011. Pharmacologic rescue of impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: a neurobehavioral model of autism. Biol. Psychiatry 69 (9), 875–882. https://doi.org/10.1016/j.biopsych.2010.12.022.

Salotti, J.A., Nanduri, V., Pearce, M.S., Parker, L., Lynn, R., Windebank, K.P., 2009. Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. Arch. Dis. Child. 94 (5), 376–380. https://doi.org/10.1136/adc.2008.144527.

Sands, S.A., Kellie, S.J., Davidow, A.L., Diez, B., Villablanca, J., Weiner, H.L., Pietanza, M.C., Balmaceda, C., Finlay, J.L., 2001. Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: from the First International CNS Germ-Cell Tumor Study. Neuro-Oncol. 3 (3), 174–183. https://doi.org/10.1093/neuonc/3.3.174.

Schank, J., 2009. Early locomotor and social effects in vasopressin deficient neonatal rats. Behav. Brain Res. 197 (1), 166–177. https://doi.org/10.1016/j.bbr.2008.08.019.

Schatz, K.C., Kyne, R.F., Parmeter, S.L., Paul, M.J., 2018. Investigation of social, affective, and locomotor behavior of adolescent Brattleboro rats reveals a link between vasopressin's actions on arousal and social behavior. Horm. Behav. 106, 1–9. https://doi.org/10.1016/j.yhbeh.2018.08.015.

Scheele, D., Wille, A., Kendrick, K.M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., Maier, W., Hurlemann, R., 2013. Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proc. Natl. Acad. Sci. USA 110 (50), 20308–20313. https://doi.org/10.1073/pnas.1314190110.

Sethi, R.V., Marino, R., Niemierko, A., Tarbell, N.J., Yock, T.I., MacDonald, S.M., 2013. Delayed diagnosis in children with intracranial germ cell tumors. J. Pediatr. 163 (5), 1448–1453. https://doi.org/10.1016/j.jpeds.2013.06.024.

Shi, X., Zhou, Z., Wu, B., Zhang, Y., Qian, H., Sun, Y., Yang, Y., Yu, Z., Tang, Z., Lu, S., 2017. Outcome of radical surgical resection for craniopharyngioma with hypothalamic preservation: a single-center retrospective study of 1054 patients. World Neurosurg. 102, 167–180. https://doi.org/10.1016/j.wneu.2017.02.095.

Shinar, S., Many, A., Maslovitz, S., 2016. Questioning the role of pituitary oxytocin in parturition: spontaneous onset of labor in women with panhypopituitarism – a case series. Eur. J. Obstet. Gynecol. Reprod. Biol. 197, 83–85. https://doi.org/10.1016/j.ejogrb.2015.11.028.

Sokol, H.W., 1970. Evidence for oxytocin synthesis after electrolytic destruction of the paraventricular nucleus in rats with hereditary hypothalamic diabetes insipidus. Neuroendocrinology 6 (2), 90–97. https://doi.org/10.1159/000121911.

Song, Z., Albers, H.E., 2018. Cross-talk among oxytocin and arginine-vasopressin receptors: relevance for basic and clinical studies of the brain and periphery. Front. Neuroendocrinol. 51, 14–24. https://doi.org/10.1016/j.yfrne.2017.10.004.

Song, Z., Larkin, T.E., Malley, M.O., Albers, H.E., 2016. Oxytocin (OT) and arginine-vasopressin (AVP) act on OT receptors and not AVP V1a receptors to enhance social recognition in adult Syrian hamsters (Mesocricetus auratus). Horm. Behav. 81, 20–27. https://doi.org/10.1016/j.yhbeh.2016.02.004.

Soumier, A., Habart, M., Lio, G., Demily, C., Sirigu, A., 2021. Differential fate between oxytocin and vasopressin cells in the developing mouse brain. iScience 25 (1), 103655. https://doi.org/10.1016/j.isci.2021.103655.

Stegner, H., Artman, H.G., Leake, R.D., Fisher, D.A., 1983. Does DDAVP (1-desamino-8-D-arginine-vasopressin) cross the blood-CSF barrier? Neuroendocrinology 37 (4), 262–265. https://doi.org/10.1159/000123555.

Steiner, Q.-G., Otten, L.A., Hicks, M.J., Kaya, G., Grosjean, F., Saeuberli, E., Lavanchy, C., Beermann, F., Mcclain, K.L., Acha-Orbea, H., 2008. In vivo transformation of mouse conventional CD8α+ dendritic cells leads to progressive multisystem histiocytosis. Blood 111 (4), 2073–2082. https://doi.org/10.1182/blood-2007-06-097576.

Stevenson, E.L., Caldwell, H.K., 2012. The vasopressin 1b receptor and the neural regulation of social behavior. Horm. Behav. 61 (3), 277–282. https://doi.org/10.1016/j.yhbeh.2011.11.009.

Stoop, R., 2012. Neuromodulation by oxytocin and vasopressin. Neuron 76 (1), 142–159. https://doi.org/10.1016/j.neuron.2012.09.025.

Strojan, P., Zadravec, L.Z., Anzic, J., Korenjak, R., Jereb, B., 2006. The role of radiotherapy in the treatment of childhood intracranial germinoma: long-term survival and late effects. Pediatr. Blood Cancer 47 (1), 77–82. https://doi.org/10.1002/pbc.20507.

Takami, H., Fukuoka, K., Fukushima, S., Nakamura, T., Mukasa, A., Saito, N., Yanagisawa, T., Nakamura, H., Sugiyama, K., Kanamori, M., Tominaga, T., Maehara, T., Nakada, M., Kanemura, Y., Asai, A., Takeshima, H., Hirose, Y., Iuchi, T., Nagane, M., Yoshimoto, K., Ichimura, K., 2019. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neuro Oncol. 21 (12), 1565–1577. https://doi.org/10.1093/neuonc/noz139.

Takayanagi, Y., Yoshida, M., Bielsky, I.F., Ross, H.E., Kawamata, M., Onaka, T., Yanagisawa, T., Kimura, T., Matzuk, M.M., Young, L.J., Nishimori, K., 2005. Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. Proc. Natl. Acad. Sci. USA 102 (44), 16096–16101. https://doi.org/10.1073/pnas.0505312102.

Thompson, R., Gupta, S., Miller, K., Mills, S., Orr, S., 2004. The effects of vasopressin on human facial responses related to social communication. Psychoneuroendocrinology 29 (1), 35–48. https://doi.org/10.1016/s0306-4530(02)00133-6.

Thompson, R.R., George, K., Walton, J.C., Orr, S.P., Benson, J., 2006. Sex-specific influences of vasopressin on human social communication. Proc. Natl. Acad. Sci. 103 (20), 7889–7894. https://doi.org/10.1073/pnas.0600406103.

Tien, R., Kucharczyk, J., Kucharczyk, W., 1991. MR imaging of the brain in patients with diabetes insipidus. AJNR Am. J. Neuroradiol. 12 (3), 533–542.

Vaiani, E., Felizzia, G., Lubieniecki, F., Braier, J., Belgorosky, A., 2021. Paediatric langerhans cell histiocytosis disease: long-term sequelae in the hypothalamic endocrine system. Horm. Res. Paediatr. 94 (1–2), 9–17. https://doi.org/10.1159/000517040.

Veenema, A.H., Beiderbeck, D.I., Lukas, M., Neumann, I.D., 2010. Distinct correlations of vasopressin release within the lateral septum and the bed nucleus of the stria terminalis with the display of intermale aggression. Horm. Behav. 58 (2), 273–281. https://doi.org/10.1016/j.yhbeh.2010.03.006.

Veiga, L., Carolino, E., Santos, I., Veríssimo, C., Almeida, A., Grilo, A., Brito, M., Santos, M.C., 2022. Depressive symptomatology, temperament and oxytocin serum levels in a sample of healthy female university students. BMC Psychol. 10 (1), 36. https://doi.org/10.1186/s40359-022-00744-5.

Vrijmoet-Wiersma, C.M., Kooloos, V.M., Koopman, H.M., Kolk, A.M., van der Laan, I., Grootenhuis, M.A., Egeler, R.M., 2009. Health-related quality of life, cognitive functioning and behaviour problems in children with Langerhans cell histiocytosis. Pediatr. blood Cancer 52 (1), 116–122. https://doi.org/10.1002/pbc.21740.

Wang, Y., Zou, L., Gao, B., 2010. Intracranial germinoma: clinical and MRI findings in 56 patients. Child's. Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg. 26 (12), 1773–1777. https://doi.org/10.1007/s00381-010-1247.

Wang, Z., Aragona, B.J., 2004. Neurochemical regulation of pair bonding in male prairie voles. Physiol. Behav. 83 (2), 319–328. https://doi.org/10.1016/j.physbeh.2004.08.024.

Whitsett, S.F., Kneppers, K., Coppes, M.J., Egeler, R.M., 1999. Neuropsychologic deficits in children with Langerhans cell histiocytosis. Med. Pediatr. Oncol. 33 (5), 486–492. https://doi.org/10.1002/(sici)1096-911x(199911)33:53.0.co;2-j.

Williams, A.R., Carey, R.J., Miller, M., 1983. Behavioral differences between vasopressin-deficient (Brattleboro) and normal Long-Evans Rats. Peptides 4 (5), 711–716. https://doi.org/10.1016/0196-9781(83)90023-2.

Williams, J.R., Insel, T.R., Harbaugh, C.R., Carter, C.S., 1994. Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (Microtus ochrogaster). J. Neuroendocrinol. 6 (3), 247–250. https://doi.org/10.1111/j.1365-2826.1994.tb00579.x.

Willman, C.L., Busque, L., Griffith, B.B., Favara, B.E., McClain, K.L., Duncan, M.H., Gilliland, D.G., 1994. Langerhans'-cell histiocytosis (histiocytosis X)–a clonal proliferative disease. New Engl. J. Med. 331 (3), 154–160. https://doi.org/10.1056/NEJM199407213310303.

Winslow, J.T., Hastings, N., Carter, C.S., Harbaugh, C.R., Insel, T.R., 1993. A role for central vasopressin in pair bonding in monogamous prairie voles. Nat., 365(6446), S. 545–548. https://doi.org/10.1038/365545a0.

Yang, H.P., Wang, L., Han, L., Wang, S.C., 2013. Nonsocial functions of hypothalamic oxytocin. ISRN Neurosci. 2013, 179272 https://doi.org/10.1155/2013/179272.

Yang, Q.Y., Guo, C.C., Deng, M.L., Wang, J., Wang, J., Lin, F.H., Zhang, J., Jiang, X.B., Mou, Y.G., Chen, Z.P., 2016. Treatment of primary intracranial germ cell tumors: single center experience with 42 clinically diagnosed cases. Oncotarget 7 (37), 60665–60675. https://doi.org/10.18632/oncotarget.10218.

Yano, S., Kudo, M., Hide, T., Shinojima, N., Makino, K., Nakamura, H., Kuratsu, J., 2016. Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma. World Neurosurg. 85, 153–162. https://doi.org/10.1016/j.wneu.2015.08.059.

Yavropoulou, M.P., Tsoli, M., Kaltsas, G., 2021. Neuroendocrine manifestations of Langerhans cell histiocytosis. Handb. Clin. Neurol. 181, 127–135. https://doi.org/10.1016/B978-0-12-820683-6.00009-9.

Yeh, E.A., Greenberg, J., Abla, O., Longoni, G., Diamond, E., Hermiston, M., Tran, B., Rodriguez-Galindo, C., Allen, C.E., McClain, K.L., North American Consortium for Histiocytosis, 2018. Evaluation and treatment of Langerhans cell histiocytosis patients with central nervous system abnormalities: current views and new vistas. Pediatr. Blood Cancer 65 (1). https://doi.org/10.1002/pbc.26784.

Young, L.J., Nilsen, R., Waymire, K.G., Macgregor, G.R., Insel, T.R., 1999. Increased affiliative response to vasopressin in mice expressing the V1a receptor from a monogamous vole. Nature 766–768. https://doi.org/10.1038/23475.

Young 3rd, W.S., Shepard, E., Amico, J., Hennighausen, L., Wagner, K.U., LaMarca, M.E., McKinney, C., Ginns, E.I., 1996. Deficiency in mouse oxytocin prevents milk ejection, but not fertility or parturition. J. Neuroendocrinol. 8 (11), 847–853. https://doi.org/10.1046/j.1365-2826.1996.05266.x.

Young, W.S., Li, J., Wersinger, S.R., Palkovits, M., 2006. The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy. Neuroscience 143 (4), 1031–1039. https://doi.org/10.1016/j.neuroscience.2006.08.040.

Yu, R.C., Chu, C., Buluwela, L., Chu, A.C., 1994. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 343 (8900), 767–768. https://doi.org/10.1016/s0140-6736(94)91842-2.

Yuen, K.W., Garner, J.P., Carson, D.S., Keller, J., Lembke, A., Hyde, S.A., Kenna, H.A., Tennakoon, L., Schatzberg, A.F., Parker, K.J., 2014. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. J. Psychiatr. Res. 51, 30–36. https://doi.org/10.1016/j.jpsychires.2013.12.012.

Zada, G., Kintz, N., Pulido, M., Amezcua, L., 2013. Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: a systematic literature review. PLoS One 8 (11), e76562. https://doi.org/10.1371/journal.pone.0076562.

Zelena, D., 2017. Comparison of natural and artificial vasopressin deficiency: why is the latter lethal. Russ. J. Genet. Appl. Res. 7 (3), 243–248. https://doi.org/10.1134/s2079059717030157.

Zoratto, F., Sbriccoli, M., Martinelli, A., Glennon, J.C., Macrì, S., Laviola, G., 2018. Intranasal oxytocin administration promotes emotional contagion and reduces aggression in a mouse model of callousness. Neuropharmacology 143, 250–267. https://doi.org/10.1016/j.neuropharm.2018.09.010.
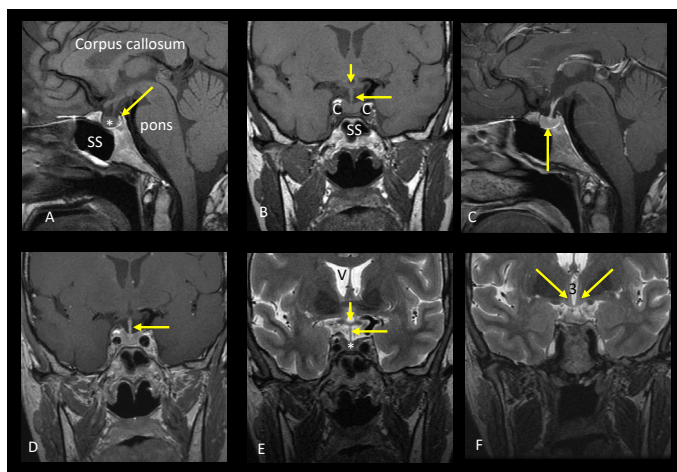
**Figure S1. MRI of a 60-year-old female with a normal hypothalamic-pituitary axis.**

**A:** Sagittal T1-weighted MRI without gadolinium-based contrast agent demonstrates the sella turcica superior to the sphenoid sinus (SS) and housing the normal pituitary gland, with anterior lobe (asterisk) and posterior lobe (arrow) indicated. Note the characteristic high signal of the posterior lobe of the gland ("bright spot"), situated immediately anterior to the dorsum sella. **B:** Coronal T1-weighted MRI without gadolinium demonstrates the normal anterior lobe of the pituitary in the sella turcica superior to the sphenoid sinus (SS). The cavernous segment of the internal carotid artery [C] is seen on either side of the gland. The infundibulum (pituitary stalk, long arrow) and optic chiasm (short arrow) are indicated. **C:** Sagittal T1-weighted MRI post-gadolinium shows homogeneous enhancement of the adenohypophysis (arrow). The posterior pituitary cannot be clearly appreciated on the post-contrast image as it is similar in signal intensity to the enhancing anterior lobe. Note that the normal and slender pituitary stalk also demonstrates enhancement. **D:** Coronal T1-weighted MRI post-gadolinium, with the enhancing pituitary stalk indicated (arrow). **E:** Coronal T2-weighted MRI indicates the pituitary gland (asterisk), stalk (long arrow), and optic chiasm (short arrow). The frontal horn of the right lateral ventricle is indicated (V). **F:** Coronal T2-weighted image slightly posterior to E. indicates the hypothalamus (arrows) on either side of the anteroinferior third ventricle (3).