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Research report

Hypothalamic tumors impact gray and white matter volumes in fronto-limbic brain areas☆

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ABSTRACT

Patients with hypothalamic involvement of a sellar/parasellar tumor often suffer from cognitive and social-emotional deficits that a lesion in the hypothalamus cannot fully explain. It is conceivable that these deficits are partly due to distal changes in hypothalamic networks, evolving secondary to a focal lesion. Focusing on childhood-onset craniopharyngioma patients, we aimed at investigating the impact of hypothalamic lesions on gray and white matter areas densely connected to the hypothalamus, and to relate structural changes to neuropsychological deficits frequently observed in patients.

We performed a voxel-based morphometric analysis based on data of 11 childhood-onset craniopharyngioma patients with hypothalamic tumor involvement, and 18 healthy controls (median age: 17.2 and 17.4 yrs.). Whole-brain analyses were used to test for volumetric differences between the groups (*T*-tests) and subsequent regression analyses were used to correlate neuropsychological performance with gray and white matter volumes within the patient group.

Patients compared to controls had significantly reduced gray matter volumes in areas of the anterior and posterior limbic subsystems which are densely connected with the hypothalamus. In addition, a reduction in white matter volumes was observed in tracts connecting the hypothalamus to other limbic areas. Worse long-term memory retrieval was correlated with smaller gray matter volumes in the posterior cingulate cortex.

Our data provide the first evidence that hypothalamic tumor involvement impacts gray and white matter volumes in limbic areas, outside the area of tumor growth. Notably, the functional range of the two limbic subsystems affected, strikingly parallels the two major domains of psychological complaints in patients i.e., deficits in episodic memory and in

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socio-emotional functioning. We suggest that focal hypothalamic lesions may trigger distal changes in connected brain areas, which then contribute to the impairments in cognitive, social and emotional performance often observable in patients, and not explicable by a hypothalamic lesion alone.

1. Introduction

The hypothalamus is a small multinuclear complex at the brain base (approx. .7 cm^3 in each side), located below and anteriorly to the thalamus. It regulates and coordinates a wide range of functions, which are of vital importance for survival, such as food and water intake, control of the cardiovascular system, temperature regulation, and control of pituitary function (Lemaire et al., 2011, 2013). Lesions to this region may result in profound endocrine and autonomic dysfunctions with potentially life-threatening outcomes. Accordingly, the often more subtle deficits in cognitive and socio-emotional outcomes after hypothalamic lesions have for long received less attention. In addition, isolated lesions of the hypothalamus are rare in humans and knowledge on its role in neurobehavioral functioning is mainly based on animal research and a few single-case studies in humans (Vann, 2010; Vann & Aggleton, 2004).

Craniopharyngiomas, however, as the most common tumors of the hypothalamic–pituitary region in children (Warmuth-Metz, Gnekow, Muller, & Solymosi, 2004), bear a high potential for investigating the effects of hypothalamic lesions on neurobehavioral functioning. These rare embryonal malformations have a low-grade histological malignancy and can be located anywhere along an axis extending from the sella turcica through the optic nerves, the pituitary stalk and the hypothalamus (Flitsch, Muller, & Burkhardt, 2011). Accordingly, the most frequent symptoms, which can seriously limit psychosocial functioning and quality of life, comprise visual field defects, loss of neurovegetative homeostasis, endocrine, and neurobehavioral disturbances. Long-term outcomes have been shown to be particular worse in case of hypothalamic involvement. Rates reported for hypothalamic involvement range from 60 to 92% for preoperative tumor involvement, and 59–71% for postoperative lesions (Fjalldal et al., 2013; Hoffmann et al., 2014; Laffond et al., 2012; Puget et al., 2007; de Vile et al., 1996). In most cases, craniopharyngiomas do not involve any other brain areas relevant for cognition or socio-emotional performance.

In patients with childhood-onset craniopharyngioma, the most consistent findings in the cognitive domain are impairments in learning and episodic memory, largely sparing other memory components (Ozyurt, Muller, & Thiel, 2015). This is in accordance with single case-studies and animal research, showing that isolated lesions of the mammillary bodies in the posterior part of the hypothalamus cause episodic memory deficits similar to those of patients with hippocampal lesions, but to a lesser degree (Vann & Aggleton, 2004). Patients with hypothalamic lesions may however also suffer from deficits in executive functioning, relying on the integrity of the prefrontal cortex along with its subcortical pathways, and deficits that indicate fronto-limbic dysfunctioning, such as emotional lability, and rage attacks (Garnett, Puget, Grill, & Sainte-Rose, 2007; Muller, 2008; Pierre-Kahn et al., 2005). Moreover, some patients complain about difficulties in social interactions and relations, and in social-cognitive skills such as understanding others' emotional states, thoughts and feelings (Hermann L. Müller, personal communication).

While lesions to the mammillary bodies of the hypothalamus were shown to be sufficient to cause clear deficits in episodic memory (Vann, 2010), impairments in executive or social-emotional skills do not appear to be fully explainable by a hypothalamic lesion. Such impairments may arise from several disease- and treatment-related factors associated with brain injury outside the region of tumor growth, including, e.g., surgical approaches, obstructive hydrocephalus, peri- and postoperative complications, and radiation effects. Alternatively, they may be due to distal effects, which relate to the long known finding that brain pathology is likely not confined to a discrete region but is propagated along its axonal pathways to affect connected areas. Pathological processes in disease propagation include diaschisis (interruption of function in distal regions due to functional connectivity changes) and transneuronal degeneration (structural degeneration of distal brain regions/pathways). In both cases, patterns of disease spread are shaped and constrained by the connectivity of the lesioned area (Fornito, Zalesky, & Breakspear, 2015).

Within a network supporting behavioral control, the hypothalamus has strong connections with major cortical and subcortical limbic areas, such as the orbitofrontal cortex, cingulum, insula, hippocampus, ventral striatum, amygdala, and thalamic nuclei. The dense hypothalamic projections to thalamic nuclei are of particular interest as they allow for substantial indirect influences of the hypothalamus on the ventral striatum and orbital/medial prefrontal cortex (Lemaire et al., 2011; Risold, Thompson, & Swanson, 1997; Toni, Malaguti, Benfenati, & Martini, 2004). The anatomical network of the hypothalamus is paralleled by resting state connectivity, showing significant functional connections with the same brain areas Kullmann et al. (2014). Notably, the notion of a single limbic system has been recently questioned in favor of at least two functionally distinct limbic sub-systems: a posterior subsystem that constitutes a neural system supporting episodic memory and an anterior subsystem supporting emotional, motivational and social functioning (Catani, Dell'acqua, & Thiebaut de Schotten, 2013; Rolls, 2015). Neurobehavioral deficits most frequently reported for craniopharyngioma patients (episodic memory and socio-emotional deficits) strikingly correspond to each of these two subsystems' functional range.

Cortical diaschisis after thalamic stroke is a well known phenomenon and cortical areas affected were shown to depend on areas of thalamo-cortical fiber loss (Baron et al.,