Cell Metabolism
Perspective

# Metabolic and Non-Cognitive Manifestations of Alzheimer's Disease: The Hypothalamus as Both Culprit and Target of Pathology

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**Alzheimer's disease (AD) is increasingly recognized as a complex neurodegenerative disease beginning decades prior to the cognitive decline. While cognitive deficits remain the cardinal manifestation of AD, metabolic and non-cognitive abnormalities, such as alterations in body weight and neuroendocrine functions, are also present, often preceding the cognitive decline. Furthermore, hypothalamic dysfunction can also be a driver of AD pathology. Here we offer a brief appraisal of hypothalamic dysfunction in AD and provide insight into an underappreciated dual role of the hypothalamus as both a culprit and target of AD pathology, as well as into new opportunities for therapeutic interventions and biomarker development.**

## Introduction

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is an incurable and devastating disease that has emerged as one of the major public health threats of our times (Alzheimer's Association, 2015). The pathogenesis of AD remains elusive, but the abnormal accumulation in the brain of amyloid-beta (Aβ), a peptide derived from the amyloid precursor protein (APP), and of the microtubule-associated protein tau is believed to lead to the synaptic dysfunction and neurodegeneration underlying the dementia (Musiek and Holtzman, 2015). AD pathology develops decades prior to the initial cognitive symptoms in a preclinical or presymptomatic stage, in which Aβ and tau start to accumulate in brain as amyloid plaques and neurofibrillary tangles (Sperling et al., 2011). Cerebrovascular function is also impaired in patients with early AD or at risk for AD, leading to a mismatch between the delivery of oxygen and glucose through blood flow and the energy demands of the active brain (Iadecola, 2013). In addition, cerebrovascular dysfunction may impair the vascular clearance of Aβ and promote AD pathology (Gupta and Iadecola, 2015). Therefore, AD is now believed to be a continuum with gradually worsening pathological changes in the brain that are the consequences of Aβ, tau, vascular dysfunctions, and other changes that take several years to decades before manifesting with clinical symptoms. Thus, an early preclinical stage is followed by mild cognitive symptoms (minimal cognitive impairment [MCI]) before progressing to symptomatic AD and eventually terminal dementia (Albert et al., 2011; McKhann et al., 2011).

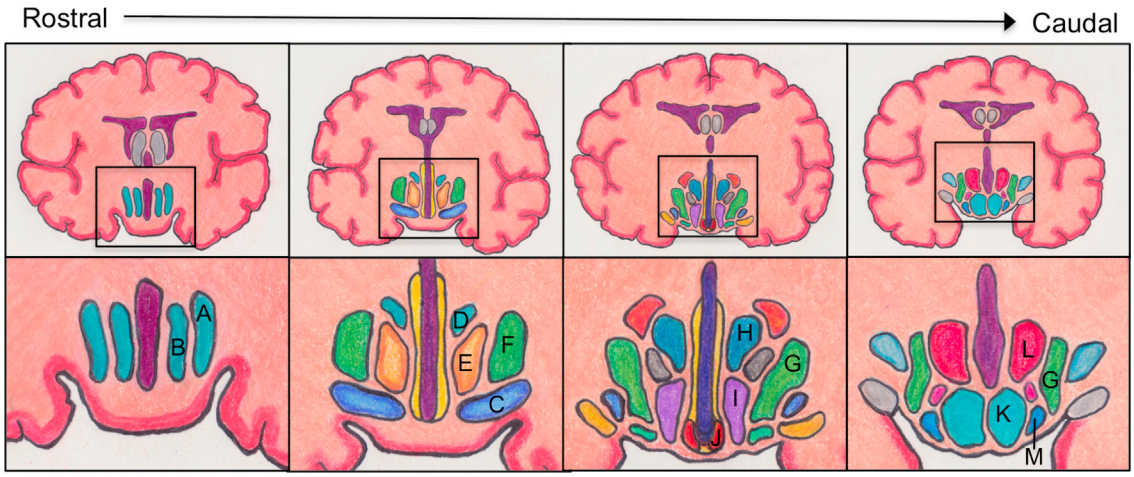
Since cognitive deficits are the most prominent feature of the disease, AD research has placed emphasis on brain regions associated with cognition and memory, such as the hippocampus and entorhinal cortex (Musiek and Holtzman, 2015). However, AD patients exhibit significant non-cognitive deficits such as weight loss, sleep-wake disorders, and neuroendocrine alterations attributable to hypothalamic dysfunction (Csernansky et al., 2006; Prinz et al., 1982; White et al., 1996). These alterations can occur prior to the initial mental decline and progressively worsen as the disease advances (Johnson et al., 2006; Ju et al., 2013; White et al., 1996), suggesting that they are an intrinsic feature of AD pathophysiology. Although recent reviews have addressed selected features of AD attributable to hypothalamic dysfunction, such as systemic metabolic deficits or the sleep abnormalities (Kiliaan et al., 2014; Musiek et al., 2015), an appraisal of how AD affects the hypothalamus in light of recent advances in both hypothalamic physiology and AD pathobiology is conspicuously missing from the recent literature. Therefore, in this article we sought to provide an integrated view of the bidirectional relationships between hypothalamic dysfunction and AD, building a case for the hypothalamus as a contributor and a target of AD pathology and emphasizing its implications for the early diagnosis and treatment of the disease.

## Alterations in the Structure of the Hypothalamus in AD

Despite occupying only 4 $cm^3$ of the brain, about the size of an almond, the hypothalamus is the master coordinator of a myriad of homeostatic functions essential for life such as growth, reproduction, sleep, metabolism, and autonomic homeostasis (Swaab, 1997). The hypothalamus is divided into different regions, each having specific nuclei or clustering of neurons with distinct behavioral and/or physiological roles (Figure 1) (Swaab, 1997). In the following sections, we will describe the evidence for alterations in the hypothalamus in AD from classical neuropathological to more recent neuroimaging studies.

### *Neuropathology*

Several autopsy studies have reported amyloid plaques and neurofibrillary tangles in the hypothalamus of AD subjects (Table 1). One of the earliest studies (Stief, 1927) described a 70-year-old woman with dementia and a striking loss in body weight (from 34.5 kg on presentation to 28 kg at time of death). At autopsy, the body was noted to be completely devoid of fat tissue, and in the brain, plaques and tangles were found not only in the cortex but also in the paraventricular nucleus of the hypothalamus and mammillary bodies (Stief, 1927). Since then, several other studies have reported plaques and tangles throughout the hypothalamus in patients with AD, including the landmark paper of Braak and Braak (1991) on staging of AD




| Nuclei (Figure Label) | Region | Function | Select Neuropeptides Neurotransmitters |
|---|---|---|---|
| Preoptic, lateral (A) and medial (B) | • Anterior<br>• Preoptic<br>• Medial | • Reproduction<br>• Thermoregulation<br>• Sexual behavior | • GnRH |
| Supraoptic (C) | • Anterior<br>• Medial | • Neurosecretory | • Vasopressin<br>• Oxytocin |
| Paraventricular (D) | • Anterior<br>• Medial | • Hormonal regulation<br>• Fluid balance<br>• Gastrointestinal<br>• Cardiovascular | • TRH<br>• CRH<br>• Oxytocin<br>• Somatostatin |
| Anterior (E) | • Anterior<br>• Medial | • Thermoregulation<br>• Sweating | • ? |
| Suprachiasmatic (F) | • Anterior<br>• Medial | • Circadian rhythm | • Vasopressin<br>• VIP<br>• Neurotensin |
| Lateral (G) | • Anterior<br>• Tuberal<br>• Lateral | • Thirst<br>• Hunger<br>• Arousal | • Orexin<br>• MCH |
| Dorsomedial (H) | • Tuberal<br>• Medial | • Cardiovascular<br>• Gastrointestinal<br>• Systemic metabolism | • NPY |
| Ventromedial (I) | • Tuberal<br>• Medial | • Satiety<br>• Sexual behavior | • BDNF |
| Arcuate (J) | • Tuberal<br>• Medial | • Appetite control | • NPY<br>• AgRP<br>• POMC<br>• CART |
| Mammillary (K) | • Posterior<br>• Medial | • Memory | • Glutamate<br>• Enkephalin<br>• CCK |
| Posterior (L) | • Posterior<br>• Medial | • Cardiovascular | • Dynorphin |
| Tuberomamillary (M) | • Posterior<br>• Lateral | • Arousal<br>• Systemic metabolism | • Histamine |

**Figure 1. Hypothalamic Nuclei: Structure and Function**

Coronal brain images illustrate the hypothalamus and the location of its nuclei (lettered) in order from most rostral (left) to caudal (right) with a description of key functions and neurotransmitters/neuropeptides associated with each hypothalamic nuclei. Abbreviations: AgRP, agouti related peptide; BDNF, brain-derived neurotrophic factor; CART, cocaine and amphetamine related transcript; CRH, corticotropin releasing hormone; GnRH, gonadotropin releasing hormone; MCH, melanin concentrating hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; TRH, thyrotropin releasing hormone; VIP, vasoactive intestinal peptide.

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