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Review

# Gray matter atrophy in narcolepsy: An activation likelihood estimation meta-analysis

Q1 Hsu-Huei Weng[a,b,c], Chih-Feng Chen[a], Yuan-Hsiung Tsai[a], Chih-Ying Wu[d], Meng Lee[d], Yu-Ching Lin[b,e,g], Cheng-Ta Yang[f,g], Ying-Huang Tsai[f,h,*], Chun-Yuh Yang[i]

[a] Department of Diagnostic Radiology, Chang Gung Memorial Hospital, Chiayi, Chang Gung University College of Medicine, Taiwan
[b] Department of Respiratory Care, Chang Gung University of Science and Technology, Chiayi, Taiwan
[c] Department of Psychology, National Chung Cheng University, Chiayi, Taiwan
[d] Department of Neurology, Chang Gung Memorial Hospital, Chiayi, Chang Gung University College of Medicine, Taiwan
[e] Division of Pulmonary and Critical Care Medicine and Department of Respiratory Care, Chang Gung Memorial Hospital, Chiayi, Taiwan
[f] Division of Pulmonary and Critical Care Medicine of Chang Gung Memorial Hospital, Chiayi, Taiwan
[g] Department of Respiratory Care, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[h] Department of Respiratory Therapy, Chang Gung University, Taoyuan, Taiwan
[i] Faculty of Public Health, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan

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ABSTRACT

The authors reviewed the literature on the use of voxel-based morphometry (VBM) in narcolepsy magnetic resonance imaging (MRI) studies via the use of a meta-analysis of neuroimaging to identify concordant and specific structural deficits in patients with narcolepsy as compared with healthy subjects. We used PubMed to retrieve articles published between January 2000 and March 2014. The authors included all VBM research on narcolepsy and compared the findings of the studies by using gray matter volume (GMV) or gray matter concentration (GMC) to index differences in gray matter. Stereotactic data were extracted from 8 VBM studies of 149 narcoleptic patients and 162 control subjects. We applied activation likelihood estimation (ALE) technique and found significant regional gray matter reduction in the bilateral hypothalamus, thalamus, globus pallidus, extending to nucleus accumbens (NAcc) and anterior cingulate cortex (ACC), left mid orbital and rectal gyri (BAs 10 and 11), right inferior frontal gyrus (BA 47), and the right superior temporal gyrus (BA 41) in patients with narcolepsy. The significant gray matter deficits in narcoleptic patients occurred in the bilateral hypothalamus and frontotemporal regions, which may be related to the emotional processing abnormalities and orexin/hypocretin pathway common among populations of patients with narcolepsy.



**Contents**



Q2 * Corresponding author at: Division of Pulmonary and Critical Care Medicine of Chang Gung Memorial Hospital, Chiayi, 6 West, Chia-Pu Road, Puzih, Chiayi County 61363, Taiwan. Tel.: +886 5 3621000x2620; fax: +886 5 3623002.
*E-mail address:* chestmed@adm.cgmh.org.tw (Y.-H. Tsai).

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## 1. Introduction

Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness (EDS), sudden loss of muscle tone provoked by emotional stimulus (cataplexy), nocturnal sleep fragmentation, and rapid eye movement (REM) sleep phenomena, such as hypnagogic/hypnopompic hallucinations and sleep paralysis (Dauvilliers et al., 2003, 2007; Longstreth et al., 2007). The diagnosis of narcolepsy is made on a combination of elements including description of symptoms, multiple sleep latency test (MSLT) findings by a polysomnography (PSG), sleep-onset rapid eye movement (SOREM) periods, and can be further supported by decreased CSF hypocretin levels (Baumann et al., 2014). Cataplexy is one of the hallmark signs of narcolepsy, although cataplexy can occur independently as well. It is characterized by a sudden bilateral loss of muscle tone that is triggered by strong emotional stimuli (jokes, laughter, etc.) during wakefulness (Overeem et al., 2011). Studies have shown that 60–64% of patients with narcolepsy have cataplexy (Wing et al., 1994; Silber et al., 2002). The prevalence of narcolepsy (with cataplexy) is approximately 26–59 per 100,000 people (Hublin et al., 1994; Mignot, 1998; Ohayon et al., 2002; Wing et al., 2002).

The use of conventional MR imaging has had controversial results in narcolepsy (Plazzi et al., 1996; Bassetti et al., 1997; Frey and Heiserman, 1997; Joo and Hong, 2013). T2-weighted images have not found pontine lesion although some elderly patients had pontine hyperintensities related to vascular processes (Dauvilliers et al., 2007; Longstreth et al., 2007). The alterations of brain morphology and functions are not readily identifiable by plain visible inspection of brain MRI. During the past 3 decades, functional and structural neuroimaging techniques have evolved and have been used to increase our understanding of sleep disorders and structural brain differences. The use of manual volumetry by region-of-interest (ROI) method has found reduced volumes of the amygdala in narcolepsy patients (Brabec et al., 2011) and hippocampus in narcolepsy patients with cataplexy (Joo et al., 2012). Without a priori assumptions about ROIs, voxel-based morphometry (VBM) is an automated whole brain-based analysis that can be used to compare the subtle structural alterations of the gray matter concentration (GMC) or volume (GMV) between groups using Statistical Parametric Mapping (SPM; Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/) (Ashburner and Friston, 2000; Good et al., 2001). VBM has been applied to the study of narcolepsy (Draganski et al., 2002; Brenneis et al., 2005; Buskova et al., 2006; Joo et al., 2009; Kaufmann et al., 2002; Kim et al., 2009; Overeem et al., 2003; Scherfler et al., 2012); however, the results are equivocal (Joo and Hong, 2013). For example, Overeem et al. described no structural change in patients with hypocretin-deficient narcolepsy (Overeem et al., 2003). The 7 other studies reported a variety of atrophic foci of GMC (Draganski et al., 2002; Joo et al., 2009; Scherfler et al., 2012) or GMV (Kaufmann et al., 2002; Brenneis et al., 2005; Buskova et al., 2006; Kim et al., 2009). Diffusion tensor imaging (DTI) (Le Bihan et al., 2001) is an extension of diffusion-weighted imaging (DWI) that can quantify white matter (WM) architecture in vivo. DTI may detect white matter axonal changes in various white matter structures in narcolepsy patients (Menzler et al., 2012; Scherfler et al., 2012). High-resolution cortical thickness measurements by FreeSurfer (Dale et al., 1999; Fischl et al., 1999, 2004; Fischl and Dale, 2000) had demonstrated thickening abnormalities of orbitofrontal gyri, dorsolateral and medial prefrontal cortices, insula, cingulate gyri, middle and inferior temporal gyri, and inferior parietal lobule. These foci may be related to the disturbances in attention, memory, emotion, and sleepiness (Joo et al., 2011; Schaer et al., 2012). Functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI), are sensitive to the changes in the oxidative state of hemoglobin, which reflects oxygen extraction and, hence, regional brain activation (Le Bihan et al., 1995). Two task-based fMRI studies using emotional processing elicited by humorous stimuli demonstrated an abnormal activation of the hypothalamus and an increase in the activation of limbic system particularly in amygdala as well as other cortical regions in narcoleptics with cataplexy (Reiss et al., 2008; Schwartz et al., 2008; Dang-Vu and Schwartz, 2013). The reward processing task fMRI showed abnormal activation of the nucleus accumbens (NAcc) and the ventral midbrain tegmental region in hypocretin-deficient narcoleptic patients with cataplexy (Ponz et al., 2010; Dang-Vu and Schwartz, 2013). Brain proton magnetic resonance spectroscopy (MRS) can be performed using protons to report changes in either the concentration or distribution of chemical substances. The 3 major compounds acquired in proton MRS are N-acetyl aspartate (NAA), creatine (Cr) including creatinine plus phosphocreatinine (Cr + PCr) content and choline (Cho). The ratio of NAA/Cho serves as an indicator of cerebral metabolic impairment, including neuronal loss, axonal injury, and gliosis. The proton MRS of narcolepsy patients can show reduced ratio of NAA/Cr + PCr, reflecting neuronal loss, but could also be due to reduced activity of existing neurons (Rudkin and Arnold, 1999; Joo and Hong, 2013), in the hypothalamus (Lodi et al., 2004) and ventral pons (Ellis et al., 1998; Poryazova et al., 2009). Narcoleptic patients with cataplexy exhibited decreased NAA levels in the hypothalamus (Tonon et al., 2009). Brain metabolites study in narcolepsy patients also revealed increased gamma amino-butyric acid (GABA) level in the medial prefrontal cortex (PFC), might be a compensatory mechanism to reduce nocturnal sleep disturbances in narcolepsy (Kim et al., 2008).



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