European Neuropsychopharmacology (2016) **26**, 1119–1126

www.elsevier.com/locate/euroneuro

Associations of pineal volume, chronotype and symptom severity in adults with attention deficit hyperactivity disorder and healthy controls

Jan Malte Bumb[a,*], Daniela Mier[b], Ingo Noelte[c], Michael Schredl[a], Peter Kirsch[b], Oliver Hennig[a], Luisa Liebrich[e], Sabrina Fenske[b], Barbara Alm[a], Carina Sauer[b], Franz Markus Leweke[a], Esther Sobanski[a,d]

[a]*Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*
[b]*Department of Clinical Psychology, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany*
[c]*Department of Neuroradiology, University Hospital Mannheim, Mannheim, Germany*
[d]*Department of Psychosomatic Medicine, Bad Dürkheim, Germany*
[e]*Department of Internal Medicine, St. Claraspital, Basel, Switzerland*

Received 30 December 2015; received in revised form 18 February 2016; accepted 24 March 2016

KEYWORDS
MPRAGE;
MRI;
Melatonin;
MEQ;
Morningness;
Eveningness

Abstract
The pineal gland, as part of the human epithalamus, is the main production site of peripheral melatonin, which promotes the modulation of sleep patterns, circadian rhythms and circadian preferences (morningness vs. eveningness). The present study analyses the pineal gland volume (PGV) and its association with circadian preferences and symptom severity in adult ADHD patients compared to healthy controls. PGV was determined manually using high-resolution 3 T MRI (T1-magnetization prepared rapid gradient echo) in medication free adult ADHD patients ($N=74$) compared to healthy controls ($N=86$). Moreover, the Morningness-Eveningness Questionnaire (MEQ), the ADHD Diagnostic Checklist and the Wender-Utah Rating Scale were conducted. PGV differed between both groups (patients: $59.9\pm33.8\,mm^3$; healthy controls: $71.4\pm27.2\,mm^3$, $P=0.04$). In ADHD patients, more eveningness types were revealed (patients: 29%; healthy controls: 17%; $P=0.05$) and sum scores of the MEQ were lower (patients: 45.8 ± 11.5; healthy controls 67.2 ± 10.1; $P<0.001$). Multiple regression analyses indicated a positive correlation of PGV and MEQ scores in ADHD ($\beta=0.856$, $P=0.003$) but not in healthy controls ($\beta=0.054$,

*Correspondence to: Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University J5, 68159, Mannheim, Germany. Tel.: +49 621 1703 6161; fax: +49 621 1703 2322.
E-mail address: jan.bumb@zi-mannheim.de (J.M. Bumb).

http://dx.doi.org/10.1016/j.euroneuro.2016.03.016

$P=0.688$). Patients' MEQ scores ($\beta=-0.473$, $P=0.003$) were negatively correlated to ADHD symptoms. The present results suggest a linkage between the PGV and circadian preference in adults with ADHD and an association of the circadian preference to symptom severity. This may facilitate the development of new chronobiological treatment approaches for the add-on treatment in ADHD.

1. Introduction

According to recent meta-analyses, the pooled prevalence of attention deficit hyperactivity disorder (ADHD) is 5.29% (Polanczyk et al., 2014). The disorder may be present in both children and adults, and is characterized by a vast spectrum of attentional deficits and behavioral difficulties, such as hyperactivity and impulsivity. While the burden of this disease is very high, its etiology is still not fully understood. It has been stated that complex and heterogeneous interferences of genetic and environmental factors contribute to its pathophysiology (Banaschewski et al., 2010; Faraone et al., 2005). Among these, altered sleep processes have been repeatedly associated to both, the pathogenesis as well as the course of ADHD (for review see (Yoon et al., 2012)). Studies have reported that 55% of children (Konofal et al., 2010) and 60-80% of adults (Sobanski et al., 2008) with ADHD suffer from altered sleep, such as sleep onset problems, restless and nonrestorative sleep, and increased daytime sleepiness (Schredl et al., 2007; Sobanski et al., 2014, 2008). Polysomnography and actigraphy studies also revealed reduced sleep efficiency, longer sleep onset latencies, increased nocturnal activity and more nocturnal awakenings in adult ADHD patients as compared to healthy controls (Kooij et al., 2001; Philipsen et al., 2005; Sobanski et al., 2008). Recently, it has also been demonstrated that there is a genetic overlap between clock genes and ADHD. In a sophisticated study Baird et al. (2012) stated that the expression of the clock genes *BMAL1* and *PER2* was significantly altered in ADHD. Recent investigations also examined the chronotypes of ADHD patients (Kooij and Bijlenga, 2013; Rybak et al., 2007; Van Veen et al., 2010; Voinescu et al., 2012). The chronotype refers to an attribute of individuals, reflecting at what time of the day they are most alert and active, and/or at what time they preferentially go to bed. There is a wide spectrum of chronotypes ranging from high morningness to high eveningness types (for review see (Imeraj et al., 2012)). The results suggest that ADHD patients might be characterized by a circadian preference toward eveningness (Baird et al., 2012; Rybak et al., 2007). Eveningness has been also associated to subsyndromal psychiatric symptoms in students (Sheaves et al., 2016) and it has been shown that eveningness chronotypes are more vulnerable for a chronic form of jet lag accompanied with sleep disturbances, vulnerability to depression and higher consumption of nicotine and alcohol (Rosenberg et al., 2014). Further, studies showed significant interactions between the chronotype and sleep efficiency (quality and quantity), which was poorer in evening types (Lehnkering and Siegmund, 2007; Vitale et al., 2015).

In general, chronotypes are mediated by the circadian system, which drives sleep/wake cycles in humans. The systems' master clock is in the suprachiasmatic nucleus of the hypothalamus. The suprachiasmatic nucleus receives afferent information via retinal photic input and conducts circadian rhythms via efferent signaling to the pineal gland (Baird et al., 2012). The pineal gland represents the main production site of peripheral melatonin, a versatile hormone participating in the promotion of circadian rhythms and sleep-onset times (Arendt and Skene, 2005). Alterations in the described pathways, e.g. disturbed pineal gland volume (PGV) and melatonin rhythm might thus lead to poor and disturbed sleep (Bumb et al., 2014; Riemann et al., 2002). So far, the only evidence for a link between PGV and chronotype is related to animal studies, demonstrating that nocturnal animals such as owls are characterized by very small and diurnal animals, e.g. horses by bigger pineal glands (for review see (Ralph, 1975)). Otherwise, it has been shown that the melatonin rhythm is related to circadian typology (for review see (Adan et al., 2012)). The acrophase, referring to the time at which the peak of a rhythm occurs, and the offset of human melatonin profiles in blood and saliva samples occur approximately three hours earlier in morningness types if compared to eveningness types (Gibertini et al., 1999; Griefahn et al., 2002; Mongrain et al., 2005, 2004). Moreover, it has been stated that morningness-eveningness questionnaire scores are inversely related to the time of the melatonin peak (Liu et al., 2000).

In addition, it has been suggested that alterations of the human PGV might be associated with psychiatric (schizophrenia and affective disorders) (Bersani et al., 2002; Findikli et al., 2015; Sarrazin et al., 2011) and other diseases, e.g. insomnia (Bumb et al., 2014). Moreover, disturbed sleep is known to induce or exacerbate ADHD symptoms (e.g. sleep deprivation is often accompanied by inattention, impulsivity and restlessness, frequently even in healthy controls) (Yoon et al., 2012), whereas good sleep hygiene and restorative sleep might alleviate attention and concentration in ADHD patients (Yoon et al., 2012). 'Alterations' of circadian rhythms and preferences might cause substantial difficulties and serious problems for e.g. employees or students with ADHD participating in the usual 9-to-5 day. Thus, treatment of disturbed sleep might significantly contribute to daytime functioning in patients with ADHD.

To get first insight into possible alterations of the neuroanatomy of the pineal gland in ADHD, we provide comparative volumetric analyses of the pineal gland in adult patients with ADHD and healthy controls. Moreover, we present the analyses of potential associations of both PGV and chronotype with ADHD symptom severity.