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Pineal gland abnormality in major depressive disorder

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ABSTRACT

Patients with major depressive disorder (MDD) often have circadian rhythm alteration and sleep disturbance. The pineal gland regulates the circadian rhythm and sleep by the secretion of melatonin neurohormone. However, the relationship between pineal abnormality and MDD remains elusive. 50 patients with MDD and 35 gender- and age-matched healthy controls underwent high-resolution structural MRI. Pineal parenchymal volume (PPV) was measured manually. Inter-group differences in prevalence of pineal cyst and PPV were examined. In addition, we investigated the correlations between PPV and symptom severity as well as sleep variables in the patient group. Compared to healthy controls, patients with MDD had a higher prevalence of pineal cyst. Moreover, patients had significantly decreased PPV relative to controls. However, no significant correlations were observed between PPV and symptom severity as well as sleep variables. Our findings suggest that pineal abnormality may play a critical role in depression.

1. Introduction

Major depressive disorder (MDD) is a potentially debilitating psychiatric disorder affecting more than 300 million people worldwide. It is characterized by periods of time when individuals experience guilt, sadness, a loss of interest or pleasure in their daily lives. Moreover, these depressive symptoms last for the majority of a two week period and are not caused by drug or other inducements (Melhuish Beaupre et al., 2018). MDD is heterogeneous and caused by genetic and environmental factors as well as their interactions (Cohen-Woods et al., 2013). However, the exact etiology of depression is still not entirely clear.

The human pineal gland is a small neuroendocrine organ which is a part of the diencephalon, and it regulates the circadian rhythm and sleep by the secretion of melatonin neurohormone (Acer et al., 2011). Melatonin secretion in the pineal gland is controlled by an endogenous circadian timing system located in the suprachiasmatic nucleus of the hypothalamus and is suppressed by light, resulting in a high blood melatonin level at night and a low level during the day (Brown, 1994; Macchi and Bruce, 2004). There is evidence that depression is linked to the alterations of melatonin secretion and associated changes in biological rhythms. For instance, patients with MDD often have circadian rhythm alteration and sleep disturbance (Dmitrzak-Weglarz and Reszka, 2017; Germain and Kupfer, 2008; Karatsoreos, 2014), which may be attributed to abnormal melatonin secretion (Dmitrzak-Weglarz and Reszka, 2017; Lanfumey et al., 2013). It has also been shown that the melatonin secretion decreases during the depression onset and increases after remission (Dmitrzak-Weglarz and Reszka, 2017), suggesting that the melatonin level may serve as an effective indicator for the diagnosis of depression (Srinivasan et al., 2006). Moreover, melatonin has been used to treat depression despite inconsistent therapeutic effects (Dmitrzak-Weglarz and Reszka, 2017).

MDD is present with circadian disruption in both physiology and behavior (Karatsoreos, 2014). The disruption of the circadian clock manifests as changes in sleep-wake cycles (Turek, 2007), such as insomnia or hypersomnia (Dmitrzak-Weglarz and Reszka, 2017), and diurnal variation in mood (Gordijn et al., 1994). These abnormalities in turn affect other physiological and endocrine systems, with disturbances in the diurnal rhythms of hormonal secretion, levels of activity, core body temperature and food intake (Bunney and Bunney, 2013; Lam and Levitan, 2000). The links between depression and circadian function might occur at many levels (Wirz-Justice, 2009). An interesting example of this multi-level interaction is evident in the development and use of agomelatine, a melatonin agonist that also has

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serotonergic activity (Karatsoreos, 2014). The agomelatine is actively being used for its antidepressant actions (de Bodinat et al., 2010) and has been shown to increase the relative magnitude of circadian rhythms in the rest-activity cycle, which may lead to an improvement in sleep and a parallel improvement in depressive symptoms (Kasper et al., 2010).

In healthy individuals, smaller pineal volume is correlated with greater sleep-rhythm disturbance (Liebrich et al., 2014), and the secretion of melatonin is related to pineal volume, especially pineal parenchymal volume (PPV) (Liebrich et al., 2014; Nölte et al., 2009). Prior studies have demonstrated that pineal volume alterations might be associated with a variety of clinical conditions including primary insomnia (Bumb et al., 2014), psychiatric disorders (e.g., schizophrenia, attention deficit hyperactivity disorder) (Bersani et al., 2002; Bumb et al., 2016; Findikli et al., 2015), and neurological diseases (e.g., Alzheimer disease) (Matsuoka et al., 2018). Moreover, there is evidence that school-age children in pineal cysts have significantly increased levels of sleepiness and difficulty in sleep initiation and maintenance (DelRosso et al., 2018). Evans et al. have suggested that pineal cysts may be related to migraine (Evans and Peres, 2010). Given these findings, one may speculate that circadian rhythm alteration and sleep disturbance in patients with MDD might be associated with pineal abnormality and its related melatonin secretion change. A better clarification of this issue may provide insights into the underlying neuropathological mechanism of depression.

In this study, we aimed to investigate MDD-related pineal abnormality by comparing pineal cyst prevalence and PPV between patients suffering from MDD and gender- and age-matched healthy controls. We hypothesized that patients with MDD would have higher pineal cyst prevalence and reduced pineal volume relative to healthy controls.

2. Materials and methods

2.1. Participants

Patients were recruited consecutively from the inpatient and outpatient departments of Hefei Fourth People's Hospital. Healthy controls were enrolled from the local community via poster advertisements. This study comprised a total of 85 right-handed subjects, including 50 patients with MDD and 35 matched healthy controls. The diagnoses of depression were confirmed by two well-trained clinical psychiatrists in accordance with the International Classification of Diseases (ICD-10) criteria. Healthy controls were carefully screened to confirm an absence of any psychiatric illness using MINI-International Neuropsychiatric Interview. Exclusion criteria for all participants included: 1) the presence of other psychiatric disorders such as schizophrenia, bipolar disorder, substance-induced mood disorder, anxiety disorders, substance abuse or dependence; 2) a history of significant neurological or physical diseases; 3) a history of head injury with loss of consciousness; 4) pregnancy or any contraindications for MRI; 5) neoplastic lesion of the pineal gland. Additional exclusion criterion for the healthy control subjects was a family history of major psychiatric or neurological illness among their first-degree relatives. 24-item Hamilton Rating Scale for Depression (HAMD) (Williams, 1988) and 14-item Hamilton Rating Scale for Anxiety (HAMA) (Thompson, 2015) were applied to capture the severity of depression and anxiety symptoms. Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality. All patients were receiving their regular antidepressant medications (Table S1 in the Supplementary Materials), either with selective serotonin reuptake inhibitors or with selective serotonin norepinephrine reuptake inhibitors. This more natural setting allows us to perform a more conservative analysis to identify aberrations in MDD, and thus should better reflect the overall population of MDD patients. This study was approved by the ethics committee of The First Affiliated Hospital of Anhui Medical University. Written informed consent was obtained from all participants after they had been given a complete description of the study.

2.2. Image acquisition

MRI scans were obtained using a 3.0-Tesla MR system (Discovery MR750w, General Electric, Milwaukee, WI, USA) with a 24-channel head coil. Earplugs were used to reduce scanner noise, and tight but comfortable foam padding was used to minimize head motion. During the scans, all participants were instructed to keep their eyes closed, relax but not fall asleep, think of nothing in particular, and move as little as possible. High-resolution 3D T1-weighted structural images were acquired by employing a brain volume (BRAVO) sequence with the following parameters: repetition time (TR) = 8.5 ms; echo time (TE) = 3.2 ms; inversion time (TI) = 450 ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix size = 256 × 256; slice thickness = 1 mm, no gap; voxel size = 1 mm × 1 mm × 1 mm; 188 sagittal slices; and acquisition time = 296 s.

2.3. Image processing

All images were checked to ensure only images without visible artifacts were included in subsequent analyses. The pineal gland was identified in the 3D T1-weighted structural images from multiple planes. Benefiting from the surrounding cerebrospinal fluid, the pineal borders were determined easily according to the adjacent structures including the corpora quadrigemina, medial boundary of the thalamus, posterior commissure and habenulae (Fig. 1A and B). The pineal parenchyma without and with pineal cyst were manually delineated and the pineal parenchymal volume was measured by using the MRIcron software (Fig. 1C and D). Since pineal cysts do not contain pinealocytes, the pineal parenchymal volume was computed by subtracting the pineal cyst volume from the total pineal volume, i.e., pineal parenchymal volume (PPV) = total pineal volume (cyst included) - pineal cyst volume. Two raters who were blinded to the clinical data measured the PPV of all participants separately. The intra-class correlation coefficient (ICC) was calculated to test the inter-rater variability. Finally, the mean PPV values of the two raters' measurement were used for further statistical analyses. In addition, total intracranial volume (TIV) was assessed by using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat) implemented in the Statistical Parametric Mapping software (SPM12,

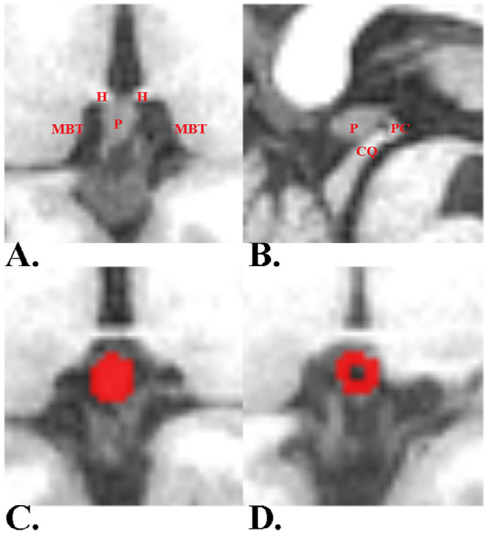

Fig. 1. The pineal gland and its surrounding structures in axial (A) and sagittal (B) positions, and delineation of the pineal parenchyma without (C) and with (D) pineal cyst. Abbreviations: P, pineal; H, habenulae; MBT, medial boundary of the thalamus; CQ, corpora quadrigemina; PC, posterior commissure.

http://www.fil.ion.ucl.ac.uk/spm).

2.4. Polysomnography

Full overnight polysomnography (PSG) monitoring was performed on the patients using the Embla N7000 instrument (New York, USA). Standard elctroencephalogram (EEG), electrocardiogram (ECG), chin electromyogram (EMG), electrooculogram (EOG), oral and thoracic, nasal airflow and abdominal movements, body position, oximetry, and snoring were recorded. We acquired some relevant PSG parameters including apnea hypopnea index (AHI, the AHI was calculated as the average of the total number of apnea and hypopnea events experienced per hour of sleep), saturation of oxygen (SaO_2), time in bed (TIB), total sleep time (TST), sleep period time (SPT), rapid eye movement (REM), non-rapid eye movement (NREM), REM sleep latency, NREM sleep phase 1 (N1), NREM sleep phase 2 (N2), NREM sleep phase 3 (N3), N1 latency, N2 latency, N3 latency. Excessive daytime sleepiness was evaluated by using the Epworth Sleepiness Scale (ESS) (Johns, 1991).

2.5. Statistical analysis

The statistical analyses were performed by using the SPSS 23.0 software package (SPSS, Chicago, Ill). Age, educational years, TIV and clinical variables (HAMD and HAMA) were compared between MDD patients and healthy controls by using two-sample *t*-tests. Group differences in gender and the prevalence of pineal cyst were tested by using Pearson Chi-square test. A general linear model was used to test differences in PPV between patients with MDD and healthy controls, adjusting for age, gender, educational years and TIV. In addition, we compared PPV depending on the presence or absence of pineal cysts in MDD patients and healthy controls, separately. Pearson's correlation analyses were performed to examine the associations between PPV and clinical variables (HAMD, HAMA, PSQI and multiple PSG parameters) in the patient group. For these analyses, $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Participant characteristics

The characteristics of participants are shown in Table 1. The patient and control groups did not differ in gender (chi-square test, $\chi^2 = 1.510$, $P = 0.219$), age (two-sample *t*-test, $t = -0.282$, $P = 0.778$), and educational years (two-sample *t*-test, $t = -1.808$, $P = 0.074$). Compared with healthy controls, MDD patients exhibited reduced TIV (two-sample *t*-test, $t = -2.055$, $P = 0.043$), and increased HAMD (two-sample *t*-test, $t = 13.527$, $P < 0.001$) and HAMA (two-sample *t*-test, $t = 11.921$, $P < 0.001$).

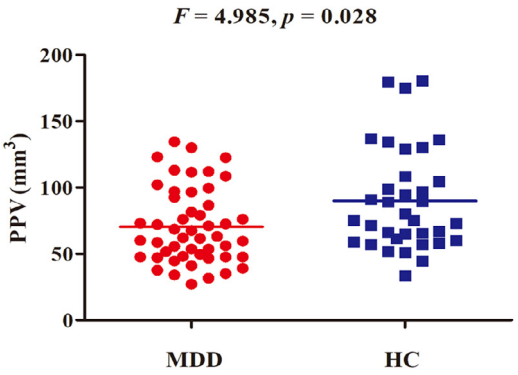

Fig. 2. Pineal parenchymal volume reduction in patients with MDD. Abbreviations: PPV, pineal parenchymal volume; MDD, major depression disorder; HC, healthy controls.

3.2. Pineal abnormality in patients with MDD

Patients with MDD had a higher prevalence of pineal cyst (62% vs. 40%, chi-square test, $\chi^2 = 4.000$, $P = 0.046$) compared to healthy controls. The ICC of inter-rater PPV measurement was 0.991, implying an excellent inter-rater reliability. Mean PPV in patients with MDD was 70.47 ± 28.30 mm^3 (95% confidence interval [CI]: 62.43, 78.51 mm^3), and that in healthy controls was 89.87 ± 38.81 mm^3 (95% CI: 76.54, 103.20 mm^3). Patients had significantly decreased PPV ($F = 4.985$, $P = 0.028$) relative to controls when controlling for age, gender, educational years and TIV (Fig. 2). As shown in Table S2 in the Supplementary Materials, there were no significant differences between individuals with and without pineal cysts for both patient and control groups ($P > 0.05$). In patients with MDD, we did not find any significant correlations between PPV and clinical variables (HAMD, HAMA and PSQI) ($P > 0.05$). In addition, there were no significant correlations between PPV and PSG parameters ($P > 0.05$) in the patient group (Table S3 in the Supplementary Materials).

4. Discussion

In the present study, we found higher cyst prevalence and decreased volume of the pineal gland in patients with MDD, which is inconsistent with prior finding that there is no difference in the pineal volume between depressed patients and controls (Findikli et al., 2015). In addition, Sarrazin et al. found that there was no difference in total pineal volume between patients with bipolar disorder and healthy subjects (Sarrazin et al., 2011). Differences in sample sizes, pineal delineation strategies, MRI scanners may lead to these discrepancies. Carpenter et al. have reported that although melatonin levels are related to both sleep-wake cycles and functioning in young people with affective

Table 1
Summary of Demographic and Clinical Characteristics.

Characteristic	MDD ($n = 50$)*	HC ($n = 35$)*	Statistics	*p* value
Gender (female/male)	31/19	17/18	$\chi^2 = 1.510$	0.219[a]
Age (years)	42.10 ± 10.52 (18–60)	42.74 ± 10.04 (23–56)	$t = -0.282$	0.778[b]
Education (years)	9.30 ± 3.80 (5–16)	10.89 ± 4.23 (5–18)	$t = -1.808$	0.074[b]
HAMD	29.42 ± 11.59 (3–52)	2.49 ± 2.37 (0–12)	$t = 13.53$	< 0.001[b]
HAMA	19.06 ± 7.41 (7–35)	2.86 ± 3.72 (0–21)	$t = 11.92$	< 0.001[b]
PSQI[c]	11.96 ± 5.43 (1–23)	–	–	–
TIV (cm^3)	1458.00 ± 157.90	1523.50 ± 123.10	$t = -2.055$	0.043[b]

* Except for gender designation, data are means ± standard deviations. Numbers in parentheses are the range. Abbreviations: MDD, major depressive disorder; HC, healthy control; TIV, total intracranial volume; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; PSQI, Pittsburgh Sleep Quality Index.

[a] The *P* value was obtained by chi-square test.

[b] The *P* values were obtained by two-sample *t*-tests.

[c] The data are available for 48 of 50 patients.

disorders, pineal size and presence of cyst are not directly related to sleep disturbances or depressive symptoms, indicating abnormalities in pineal function rather than structure (Carpenter et al., 2017). However, this study did not enroll healthy controls, and the lack of inter-group comparison analysis may prevent researchers from drawing a clear conclusion on the relationship between pineal structural abnormality and affective disorders.

In humans, the pineal gland arises out of the third ventricle, and reaches its final size in early childhood (Golan et al., 2002; Schmidt et al., 1995; Sumida et al., 1996). It regulates the circadian rhythm and sleep by the secretion of melatonin neurohormone (Acer et al., 2011; Brown, 1994; Macchi and Bruce, 2004). Pineal volume alterations have been observed in many mental illnesses, such as primary insomnia (Bumb et al., 2014), psychiatric disorders (e.g., schizophrenia, attention deficit hyperactivity disorder) (Bersani et al., 2002; Bumb et al., 2016; Findikli et al., 2015), and neurological diseases (e.g., Alzheimer disease) (Matsuoka et al., 2018). In this study, the prevalence of pineal cyst in healthy subjects is 40%, which is in line with previous reports (Hasegawa et al., 1987; Pu et al., 2007; Tapp, 1979; Tapp and Huxley, 1972). The higher pineal cyst prevalence (62%) may be another MDD-related pathological feature of the pineal gland.

In this study, we found decreased TIV in the MDD patients, which is consistent with previous findings of reduced volumes in widespread brain regions, such as the orbitofrontal cortex, prefrontal cortex, insula, supplementary motor area, middle temporal gyrus, anterior cingulate cortex, hippocampus, putamen, caudate, pallidum, thalamus, parahippocampal gyrus and fusiform gyrus (Amico et al., 2011; Baumann et al., 1999; Bielau et al., 2005; Kim et al., 2008; Koolschijn et al., 2009; Lorenzetti et al., 2009; Matsuo et al., 2008; Nugent et al., 2013; Parashos et al., 1998; Soriano-Mas et al., 2011; Vasic et al., 2008; Wagner et al., 2011; Zhang et al., 2018, 2016).

It is well-established that patients with MDD have circadian rhythm alterations resulting in disturbed sleep (Dmitrzak-Weglarz and Reszka, 2017; Germain and Kupfer, 2008; Karatsoreos, 2014). For example, some patients with MDD suffer from hypersomnia or insomnia (Dmitrzak-Weglarz and Reszka, 2017). Subjective sleep complaints are common in patients with MDD, and up to 90% of patients have trouble in falling asleep and staying asleep, and have symptoms of early morning awakenings (Almeida and Pfaff, 2005; Tsuno et al., 2005). Once the circadian rhythm is disrupted, hormonal and metabolic changes occur accordingly, which in turn leads to the development or exacerbation of depressive symptoms in MDD. For example, Emens et al. have found that severity of depressive symptoms is correlated with circadian misalignment in MDD (Emens et al., 2009). However, we cannot rule out the possibility that depressed mood may render patients particular susceptible to sleep disturbance. Combined, depression and sleep disturbance are often comorbidity and have interaction. Previous studies have found that melatonin plays an important role in the initiation and maintenance of sleep (Brzezinski et al., 2005; Buscemi et al., 2005; Cajochen et al., 2003; Kim et al., 2013). The disturbance of endogenous melatonin secretion rhythm will result in the disturbance of sleep-wake cycle (Micic et al., 2015; Saxvig et al., 2013) and intake of exogenous melatonin can effectively reduce the latency of sleep initiation, increase sleep time, improve sleep efficiency and correct the circadian rhythm abnormality (Brzezinski et al., 2005; Buscemi et al., 2005; Cajochen et al., 2003; Kim et al., 2013). Smaller pineal volume has been shown to correlate with melatonin deficit (Kunz et al., 1999; Liebrich et al., 2014; Mahlberg et al., 2009; Matsuoka et al., 2018; Nölte et al., 2009) and greater sleep-rhythm disturbance (Liebrich et al., 2014). All of these findings converge to support the notion that pineal gland abnormality may serve as a potential mediator of the interaction between disturbed sleep and depression.

Several limitations must be taken into account when interpreting the findings. First, serum levels of melatonin were not measured, which precludes us from exploring the relationship between melatonin level and pineal abnormality in patients with MDD. Moreover, we did not control for the effect of antidepressant medication, which may influence the melatonin secretion. Second, pineal calcification is not taken into account because MRI has limitations in detecting calcification. The degree of pineal calcification may vary across the participants, which may have affected our results and interpretation. Third, the evaluation of pineal cysts using T1 weighted images is difficult. Future investigations into pineal cyst morphometry would be improved by including a TrueFISP/FIESTA sequence to enhance cyst identification (Bumb et al., 2012; Nölte et al., 2009). Finally, the sample size was relatively small, which may lead to non-significant correlations between pineal abnormality and psychometric data in patients with MDD due to a limited statistical power. In future study, larger sample is needed to validate the current findings.

In conclusion, in this study we present evidence that patients with MDD had higher prevalence of pineal cyst and reduced parenchymal volume relative to healthy controls, suggesting a critical role of pineal abnormality in the interaction between sleep disturbance and depression.

Contributions

Wenming Zhao, Dao-min Zhu, Jiajia Zhu and Yongqiang Yu conceptualized and designed the study. Wenming Zhao was responsible for conducting the analyses, preparing the first draft of the manuscript, and preparing the manuscript for submission. Jiajia Zhu was responsible for obtaining funding for the study, supervising the analyses, and editing drafts of the manuscript. Wenming Zhao, Yu Zhang, Cun Zhang, Yajun Wang, Ya Bai and Ying Yang were responsible for data collection and initial data preprocessing. All authors contributed to and approved the final manuscript.

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Conflict of interest

All the authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.05.004.

References

Acer N., T.M., Yalçın, S.S., Duvernoy, H.M., 2011. Anatomy of the human pineal gland. In: Turgut, M., Kumar, R. (Eds.), Pineal Gland and Melatonin: Recent Advances in Development, Imaging, Disease and Treatment. Nova Science.

Almeida, O.P., Pfaff, J.J., 2005. Sleep complaints among older general practice patients: association with depression. Br. J. Gen. Pract. 55, 864–866.

Amico, F., Meisenzahl, E., Koutsouleris, N., Reiser, M., Moller, H.J., Frodl, T., 2011. Structural MRI correlates for vulnerability and resilience to major depressive disorder. J. Psychiatry Neurosci. 36, 15–22.

Baumann, B., Danos, P., Krell, D., Diekmann, S., Leschinger, A., Stauch, R., Wurthmann, C., Bernstein, H.G., Bogerts, B., 1999. Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a postmortem study. J. Neuropsychiatry. Clin. Neurosci. 11, 71–78.

Bersani, G., Garavini, A., Iannitelli, A., Quartini, A., Nordio, M., Di Biasi, C., Pancheri, P., 2002. Reduced pineal volume in male patients with schizophrenia: no relationship to clinical features of the illness. Neurosci. Lett. 329, 246–248.

Bielau, H., Trubner, K., Krell, D., Agelink, M.W., Bernstein, H.G., Stauch, R., Mawrin, C.,

Danos, P., Gerhard, L., Bogerts, B., Baumann, B., 2005. Volume deficits of subcortical nuclei in mood disorders a postmortem study. Eur. Arch. Psychiatry Clin. Neurosci. 255, 401–412.
Brown, G.M., 1994. Light, melatonin and the sleep-wake cycle. J. Psychiatry Neurosci. 19, 345–353.
Brzezinski, A., Vangel, M.G., Wurtman, R.J., Norrie, G., Zhdanova, I., Ben-Shushan, A., Ford, I., 2005. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep. Med. Rev. 9, 41–50.
Bumb, J.M., Brockmann, M.A., Groden, C., Al-Zghloul, M., Nolte, I., 2012. TrueFISP of the pediatric pineal gland: volumetric and microstructural analysis. Clin. Neuroradiol. 22, 69–77.
Bumb, J.M., Mier, D., Noelte, I., Schredl, M., Kirsch, P., Hennig, O., Liebrich, L., Fenske, S., Alm, B., Sauer, C., Leweke, F.M., Sobanski, E., 2016. Associations of pineal volume, chronotype and symptom severity in adults with attention deficit hyperactivity disorder and healthy controls. Eur. Neuropsychopharmacol. 26, 1119–1126.
Bumb, J.M., Schilling, C., Enning, F., Haddad, L., Paul, F., Lederbogen, F., Deuschle, M., Schredl, M., Nolte, I., 2014. Pineal gland volume in primary insomnia and healthy controls: a magnetic resonance imaging study. J. Sleep. Res. 23, 276–282.
Bunney, B.G., Bunney, W.E., 2013. Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms. Biol. Psychiatry 73, 1164–1171.
Buscemi, N., Vandermeer, B., Hooton, N., Pandya, R., Tjosvold, L., Hartling, L., Baker, G., Klassen, T.P., Vohra, S., 2005. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J. Gen. Intern. Med. 20, 1151–1158.
Cajochen, C., Krauchi, K., Wirz-Justice, A., 2003. Role of melatonin in the regulation of human circadian rhythms and sleep. J. Neuroendocrinol. 15, 432–437.
Carpenter, J.S., Abelmann, A.C., Hatton, S.N., Robillard, R., Hermens, D.F., Bennett, M.R., Lagopoulos, J., Hickie, I.B., 2017. Pineal volume and evening melatonin in young people with affective disorders. Brain. Imaging. Behav. 11, 1741–1750.
Cohen-Woods, S., Craig, I.W., McGuffin, P., 2013. The current state of play on the molecular genetics of depression. Psychol. Med. 43, 673–687.
de Bodinat, C., Guardiola-Lemaitre, B., Mocaer, E., Renard, P., Munoz, C., Millan, M.J., 2010. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat. Rev. Drug. Discov. 9, 628–642.
DelRosso, L.M., Martin, K., Bruni, O., Ferri, R., 2018. Sleep disorders in children with incidental pineal cyst on MRI: a pilot study. Sleep. Med. 48, 127–130.
Dmitrzak-Weglarz, M., Reszka, E., 2017. Pathophysiology of Depression: molecular Regulation of Melatonin Homeostasis - Current Status. Neuropsychobiology 76, 117–129.
Emens, J., Lewy, A., Kinzie, J.M., Arntz, D., Rough, J., 2009. Circadian misalignment in major depressive disorder. Psychiatry Res. 168, 259–261.
Evans, R.W., Peres, M.F., 2010. Headaches and pineal cysts. Headache 50, 666–668.
Findikli, E., Inci, M.F., Gokce, M., Findikli, H.A., Altun, H., Karaaslan, M.F., 2015. Pineal gland volume in schizophrenia and mood disorders. Psychiatr. Danub. 27, 153–158.
Germain, A., Kupfer, D.J., 2008. Circadian rhythm disturbances in depression. Hum. Psychopharmacol. 23, 571–585.
Golan, J., Torres, K., Staskiewicz, G.J., Opielak, G., Maciejewski, R., 2002. Morphometric parameters of the human pineal gland in relation to age, body weight and height. Folia. Morphol. (Warsz). 61, 111–113.
Gordijn MC, B.D., Bouhuys, A.L., Reinink, E., Van den Hoofdakker, R.H., 1994. A longitudinal study of diurnal mood variation in depression; characteristics and significance. J. Affect. Disord. 31, 261–273.
Hasegawa, A., Ohtsubo, K., Mori, W., 1987. Pineal gland in old age; quantitative and qualitative morphological study of 168 human autopsy cases. Brain. Res. 409, 343–349.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540–545.
Karatsoreos, I.N., 2014. Links between Circadian Rhythms and Psychiatric Disease. Front. Behav. Neurosci. 8, 162.
Kasper, S., Hajak, G., Wulff, K., Hoogendijk, W.J., Montejo, A.L., Smeraldi, E., Rybakowski, J.K., Quera-Salva, M.A., Wirz-Justice, A.M., Picarel-Blanchot, F., Bayle, F.J., 2010. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. J. Clin. Psychiatry 71, 109–120.
Kim, M.J., Hamilton, J.P., Gotlib, I.H., 2008. Reduced caudate gray matter volume in women with major depressive disorder. Psychiatry Res. 164, 114–122.
Kim, M.J., Lee, J.H., Duffy, J.F., 2013. Circadian Rhythm Sleep Disorders. J. Clin. Outcomes. Manag. 20, 513–528.
Koolschijn, P.C.M.P., van Haren, N.E.M., Lensvelt-Mulders, G.J.L.M., Hulshoff Pol, H.E., Kahn, R.S., 2009. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum. Brain. Mapp. 30, 3719–3735.
Kunz, D., Schmitz, S., Mahlberg, R., Mohr, A., Stoter, C., Wolf, K.J., Herrmann, W.M., 1999. A new concept for melatonin deficit: on pineal calcification and melatonin excretion. Neuropsychopharmacology 21, 765–772.
Lam, R.W., Levitan, R.D., 2000. Pathophysiology of seasonal affective disorder: a review. J. Psychiatry Neurosci. 25, 469–480.
Lanfumey, L., Mongeau, R., Hamon, M., 2013. Biological rhythms and melatonin in mood disorders and their treatments. Pharmacol. Ther. 138, 176–184.
Liebrich, L.-S., Schredl, M., Findeisen, P., Groden, C., Bumb, J.M., Nölte, I.S., 2014. Morphology and function: MR pineal volume and melatonin level in human saliva are correlated. J. Magn. Reson. Imaging 40, 966–971.
Lorenzetti, V., Allen, N.B., Fornito, A., Yucel, M., 2009. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J. Affect. Disord. 117, 1–17.
Macchi, M.M., Bruce, J.N., 2004. Human pineal physiology and functional significance of melatonin. Front. Neuroendocrinol. 25, 177–195.
Mahlberg, R., Kienast, T., Hadel, S., Heidenreich, J.O., Schmitz, S., Kunz, D., 2009. Degree of pineal calcification (DOC) is associated with polysomnographic sleep measures in primary insomnia patients. Sleep. Med. 10, 439–445.
Matsuo, K., Rosenberg, D.R., Easter, P.C., MacMaster, F.P., Chen, H.H., Nicoletti, M., Caetano, S.C., Hatch, J.P., Soares, J.C., 2008. Striatal volume abnormalities in treatment-naive patients diagnosed with pediatric major depressive disorder. J. Child. Adolesc. Psychopharmacol. 18, 121–131.
Matsuoka, T., Imai, A., Fujimoto, H., Kato, Y., Shibata, K., Nakamura, K., Yokota, H., Yamada, K., Narumoto, J., 2018. Reduced pineal volume in alzheimer disease: a retrospective cross-sectional MR imaging study. Radiology 286, 239–248.
Melhuish Beaupre, L., Brown, G.M., Kennedy, J.L., 2018. Circadian genes in major depressive disorder. World. J. Biol. Psychiatry 1–11.
Micic, G., Lovato, N., Gradisar, M., Burgess, H.J., Ferguson, S.A., Kennaway, D.J., Lack, L., 2015. Nocturnal melatonin profiles in patients with delayed sleep-wake phase disorder and control sleepers. J. Biol. Rhythms. 30, 437–448.
Nölte, I., Lütkhoff, A.-T., Stuck, B.A., Lemmer, B., Schredl, M., Findeisen, P., Groden, C., 2009. Pineal volume and circadian melatonin profile in healthy volunteers: an interdisciplinary approach. J. Magn. Reson. Imaging 30, 499–505.
Nugent, A.C., Davis, R.M., Zarate Jr., C.A., Drevets, W.C., 2013. Reduced thalamic volumes in major depressive disorder. Psychiatry Res. 213, 179–185.
Parashos, I.A., Tupler, L.A., Blitchington, T., Krishnan, K.R., 1998. Magnetic-resonance morphometry in patients with major depression. Psychiatry Res. 84, 7–15.
Pu, Y., Mahankali, S., Hou, J., Li, J., Lancaster, J.L., Gao, J.H., Appelbaum, D.E., Fox, P.T., 2007. High prevalence of pineal cysts in healthy adults demonstrated by high-resolution, noncontrast brain MR imaging. AJNR. Am. J. Neuroradiol. 28, 1706–1709.
Sarrazin, S., Etain, B., Vederine, F.E., d'Albis, M.A., Hamdani, N., Daban, C., Delavest, M., Lepine, J.P., Leboyer, M., Mangin, J.F., Poupon, C., Houenou, J., 2011. MRI exploration of pineal volume in bipolar disorder. J. Affect. Disord. 135, 377–379.
Saxvig, I.W., Wilhelmsen-Langeland, A., Pallesen, S., Vedaa, O., Nordhus, I.H., Sorensen, E., Bjorvatn, B., 2013. Objective measures of sleep and dim light melatonin onset in adolescents and young adults with delayed sleep phase disorder compared to healthy controls. J. Sleep. Res. 22, 365–372.
Schmidt, F., Penka, B., Trauner, M., Reinsperger, L., Ranner, G., Ebner, F., Waldhauser, F., 1995. Lack of pineal growth during childhood. J. Clin. Endocrinol. Metab. 80, 1221–1225.
Soriano-Mas, C., Hernandez-Ribas, R., Pujol, J., Urretavizcaya, M., Deus, J., Harrison, B.J., Ortiz, H., Lopez-Sola, M., Menchon, J.M., Cardoner, N., 2011. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. Biol. Psychiatry 69, 318–325.
Srinivasan, V., Smits, M., Spence, W., Lowe, A.D., Kayumov, L., Pandi-Perumal, S.R., Parry, B., Cardinali, D.P., 2006. Melatonin in mood disorders. World. J. Biol. Psychiatry 7, 138–151.
Sumida, M., Barkovich, A.J., Newton, T.H., 1996. Development of the pineal gland: measurement with MR. AJNR. Am. J. Neuroradiol. 17, 233–236.
Tapp, E., 1979. The histology and pathology of the human pineal gland. Prog. Brain Res. 52, 481–500.
Tapp, E., Huxley, M., 1972. The histological appearance of the human pineal gland from puberty to old age. J. Pathol. 108, 137–144.
Thompson, E., 2015. Hamilton rating scale for anxiety (HAM-A). Occup. Med. (Lond.). 65, 601.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66, 1254–1269.
Turek, F.W., 2007. From circadian rhythms to clock genes in depression. Int. Clin. Psychopharmacol 22 (Suppl 2), S1–S8.
Vasic, N., Walter, H., Hose, A., Wolf, R.C., 2008. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. J. Affect. Disord. 109, 107–116.
Wagner, G., Koch, K., Schachtzabel, C., Schultz, C.C., Sauer, H., Schlosser, R.G., 2011. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? Neuroimage 54, 1607–1614.
Williams, J.B., 1988. A structured interview guide for the Hamilton depression rating scale. Arch. Gen. Psychiatry 45, 742–747.
Wirz-Justice, A., 2009. From the basic neuroscience of circadian clock function to light therapy for depression: on the emergence of chronotherapeutics. J. Affect. Disord. 116, 159–160.
Zhang, F.F., Peng, W., Sweeney, J.A., Jia, Z.Y., Gong, Q.Y., 2018. Brain structure alterations in depression: psychoradiological evidence. CNS. Neurosci. Ther. 24, 994–1003.
Zhang, H., Li, L., Wu, M., Chen, Z., Hu, X., Chen, Y., Zhu, H., Jia, Z., Gong, Q., 2016. Brain gray matter alterations in first episodes of depression: a meta-analysis of whole-brain studies. Neurosci. Biobehav. Rev. 60, 43–50.