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ORIGINAL ARTICLE

Endogenous melatonin and impulsivity in humans.

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Abstract

OBJECTIVES: This study aimed to examine the relationship between salivary melatonin levels and impulsivity in humans, as the literature has not examined this relationship in healthy individuals.
METHODS: We recruited 75 participants aged 18–55 years, measuring their salivary melatonin concentrations using an enzyme immunoassay and their impulsivity using the Barratt Impulsiveness Scale (BIS) scores.
RESULTS: The participants' salivary melatonin levels were positively correlated with impulsivity. With regard to the three main factors of the BIS, melatonin levels were positively correlated with attentional impulsiveness but not with motor impulsiveness or non-planning impulsiveness. Of the six subfactors assessed by the BIS, melatonin levels were positively correlated with attention, motor, and cognitive instability, while negatively correlated with perseverance. They were not correlated with self-control or cognitive complexity.
CONCLUSION: Individuals exhibiting high melatonin levels are more likely to have impulsive attention and cognitive instability, in addition to lacking perseverance.

Abbreviations:

BIS	- the Barratt Impulsiveness Scale
SCN	- Suprachiasmatic nucleus
OFC	- orbitofrontal prefrontal cortex
VMPFC	- ventromedial prefrontal cortex

INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a natural compound primarily synthesized in the pineal gland. Melatonin secretion in the human pineal gland is controlled by the circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, which codes the 24-hour day/night cycle. Therefore, melatonin secretion is inhibited during the day and promoted at night (Amaral & Cipolla-Neto, 2018; Jan *et al.* 1999; Jan *et al.* 2007; Kun *et al.* 2019; Pandi-Perumal *et al.* 2007). Previous studies have explored the effects of melatonin on sleepiness (Cajochen *et al.* 1996; Kun *et al.* 2019; Lieberman *et al.* 1984; Lok *et al.* 2019) and cognitive performance (Graw *et al.* 2001; Kurihara & Ohira, 2022; Lieberman *et al.* 1984; Slotten & Krekling, 1996). However, no study has explored the effects of melatonin on impulsivity.

Impulsivity is a multifaceted concept that includes aspects of disinhibition, inattention, sensation seeking, and deficits in decision-making (Evenden, 1999). Furthermore, these aspects exist in two broad categories of impulsivity: state impulsivity (i.e., impulsivity in the moment) and trait impulsivity (i.e., the inherent characteristics of a person's impulsivity). Impulsivity is a complex trait often studied in patients with mood disorders (Kulacaoglu & Kose, 2018; Peluso *et al.*

2007), ADHD (attention deficit/hyperactivity disorder; Winstanley *et al.* 2006), and substance disorders (Cangemi *et al.* 2010; Patkar *et al.* 2004).

The neuroendocrinological basis of impulsivity in these patients is characterized by melatonin levels. Higher melatonin levels have been found in patients with ADHD with high impulsivity (Avcil *et al.* 2021; Paclt *et al.* 2011). Moreover, children diagnosed with ADHD and having high melatonin levels in their saliva samples were found to have high hyperactivity scores (Paclt *et al.* 2011). Even when blood samples were used, serum melatonin levels were higher in the impulsive ADHD group than in the control group (Avcil *et al.* 2021). Thus, the underlying neuroendocrinological mechanism of impulsivity in ADHD may be based on differences in melatonin secretion.

Prior research has suggested that the relationship between melatonin and impulsivity also exists in animal and healthy human samples. In animals, melatonin receptors are located in the prefrontal cortex and control impulsivity (Kim & Lee, 2011; Uz *et al.* 2005). In humans, high melatonin levels might be related to impulsive traits characterized by slower responses in cognitive performance (Graw *et al.* 2001; Kurihara & Ohira, 2022; Lieberman *et al.* 1984; Slotten & Krekling, 1996), because impulsive people tend to slow down their inhibitions in cognitive tasks (Logan *et al.* 1997). Furthermore, melatonin affects impulsive and reactive aggression (Liu *et al.* 2017). Therefore, melatonin may impact the prefrontal cortex, which in turn could affect impulsivity in humans.

Although previous studies have suggested that melatonin is related to impulsivity in individuals with ADHD (Avcil *et al.* 2021; Paclt *et al.* 2011), it remains unclear whether melatonin is related to impulsivity in healthy people. If melatonin is associated with increased impulsivity in patients with ADHD, then it is possible that the association also exists among healthy individuals. Therefore, in this study, we hypothesized that melatonin levels are correlated with trait impulsivity in healthy individuals.

With human participants, trait impulsivity is most commonly measured using self-report questionnaires, including the Barratt Impulsiveness Scale (BIS; Barratt, 1985); the Urgency, Premeditation, Perseverance, and Sensation Seeking (UPPS) Impulsive Behavior Scale (Whiteside & Lynam, 2001); the Impulsiveness Venturesomeness and Empathy Questionnaire (Eysenck & Eysenck, 1991); and the Lifetime History of Impulsive Behaviors (Schmidt & Catherine, 2000). These questionnaires recognize the multifactorial nature of impulsivity; for example, the BIS-11 is divided into three factors: attentional, motor, and non-planning impulsiveness (Patton *et al.* 1995). Accordingly, we used the BIS-11, a self-reported measurement of trait impulsivity, to measure the personal trait of impulsivity before comparing the BIS-11 scores across salivary melatonin levels.

MATERIAL AND METHODS

Participants

We recruited 75 participants (13 males and 62 females) aged 18–55 years. The participants arrived at a laboratory, lit with natural room lights (<500 lux), between 12 pm and 4 pm. We chose this period of the day and the aforementioned lighting conditions based on prior research that suggests salivary melatonin levels do not fluctuate under these conditions (Mclntyre *et al.* 1989). Upon arrival, the respondents read a consent form and provided written informed consent to participate in the study. This study was conducted in accordance with a protocol approved by the Ethics Committee of the Department of Cognitive and Psychological Sciences of the Graduate School of Informatics at Nagoya University.

Exclusion and Inclusion Criteria

The exclusion criteria were based on a melatonin-related webpage produced by the Electronic Medicines Compendium (eMC), and a previous study (Liu *et al.* 2017). Consequently, the following were excluded from the study: participants with diseases and disorders such as color blindness or weakness, retinal damage, history of seizures, neurological disorders (e.g., Parkinson's disease and epilepsy), chronic diseases (e.g., chronic liver or kidney disease), autoimmune diseases, mental disorders (e.g., depression and anxiety), and sleep disorders (e.g., insomnia and irregular sleep-wake cycles); participants taking the medications mentioned on the eMC webpage; participants currently undergoing hormone replacement therapy, involved in night shift work, who had embarked on trans-meridian travel in the month prior to the experiment, were pregnant or may have become pregnant during the study, or were nursing. Included in the study were participants who usually woke up between 6 am and 9 am and went to sleep between 10 pm and 1 am. Participants were asked to abstain from exercise, caffeine, cigarettes, and alcohol for at least 24 hours before the laboratory study.

Saliva Collection

Before the collection of saliva samples, participants rinsed out their mouths. The saliva samples were collected using passive drool. Samples were stored in a -30° C freezer until study completion. The samples were assayed in a laboratory at Nagoya University. The sampling tubes were centrifuged for 10 min, and hormone concentrations were measured using a salivary melatonin enzyme immunoassay kit (Salimetrics, State College, PA, USA). The intra- and inter-assay coefficients of variation were ≤10%. Melatonin distributions were not skewed and thus did not require transformation. Raw melatonin data were used for the statistical analyses.

Impulsiveness

Impulsiveness was measured using the BIS-11 (Patton *et al.* 1995), which was revised from the BIS-10 (Barratt, 1985). The questionnaire includes 30 items measuring impulsiveness, rated on a scale ranging from 1 (very slightly or not at all) to 5 (extremely). This scale comprises a three-factor (attentional, motor, and non-planning impulsiveness) self-report questionnaire that measures multiple dimensions of impulsivity. The scale comprises six factors that are employed as subscales: attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability.

Statistical Analyses

Pearson's correlation analysis was employed to compare continuous variables of impulsivity depending on salivary melatonin levels. Moreover, p-values of < 0.05 were considered as indicating statistical significance. All statistical analyses were performed using the R software package (Version 4.3.1).

RESULTS

The average melatonin concentration for all participants was 7.3 pg/mL. Pearson's correlation analysis was conducted to examine the relationship between salivary melatonin levels and impulsivity. Salivary melatonin levels and impulsivity scores were used as continuous data. The analysis revealed a significant positive correlation between melatonin levels and impulsivity ($r = 0.054$, $t = 1.630$, 95% confidence interval (CI) [-0.011, 0.119], $p < 0.001$). After classifying the impulsivity score into three sub scores (attention, motor, and non-planning), a positive correlation was observed between melatonin and the attentional score ($r = 0.134$, $t = 4.033$, 95% CI [0.069, 0.198], $p < 0.001$), but not between melatonin and the motor and non-planning scores (Figures 1–3). Table 1 presents the correlations between salivary melatonin levels and the six BIS subscales: attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability.

DISCUSSION

This study examined the relationship between salivary melatonin levels and impulsivity. The results demonstrated that salivary melatonin levels were positively correlated with impulsivity. Regarding the three factors (attentional, motor, and non-planning impulsiveness) of the BIS, melatonin levels were positively correlated with attentional impulsiveness but not with motor impulsiveness nor non-planning impulsiveness. Regarding the subscales of these three factors, melatonin levels were positively correlated with attention, motor, and cognitive instability but were negatively correlated with perseverance. They were not correlated with self-control or cognitive complexity. Taken together, these observations suggest that individuals with high melatonin levels are more likely to have impulsive attention, cognitive instability, and lack perseverance.

In this study, a novel observation was that high impulsivity is manifested in healthy individuals with high melatonin levels and not only in patients diagnosed with ADHD with high melatonin levels as previously thought. Moreover, melatonin was found to be involved in attentional and cognitive impulsiveness rather than motor and non-planning impulsiveness. Furthermore, it was found to be related to a lack of perseverance, or an inability to ignore distracting stimuli or remain focused on a particular task.

Melatonin may be involved in impulsivity in healthy individuals by affecting neurobiological processes. Melatonin receptors are located in the prefrontal cortex, which regulates impulsivity in animals (Kim & Lee, 2011; Uz *et al.* 2005). Moreover, cognitive impulsivity is linked to the orbitofrontal (OFC) and ventromedial areas (VMPFC) of the prefrontal cortex, especially the more anterior sector of this region—the frontal pole (Bechara *et al.* 2000). Therefore, melatonin might be associated with the orbitofrontal and ventromedial areas of the prefrontal cortex. In behavioral tasks, high melatonin levels may be related to impulsive traits characterized by slower responses in cognitive performance (Graw *et al.* 2001; Kurihara & Ohira, 2022; Lieberman *et al.* 1984; Slotten & Krekling, 1996), because impulsive people tend to slow down their inhibitions (Logan *et al.* 1997). Therefore, melatonin may be related to the

Tab. 1. Correlation between salivary melatonin levels and six factors in BIS

Impulsivity (BIS)	r	t	95% CI	p
Attention	0.141	4.293	(0.077, 0.205)	<0.001
Motor	0.105	2.958	(0.033, 0.162)	0.003
Self-control	-0.004	-1.035	(-0.099, 0.030)	0.300
Cognitive complexity	-0.294	1.181	(-0.026, 0.104)	0.237
Perseverance	-0.145	-5.177	(-0.233, -0.106)	<0.001
Cognitive instability	0.074	2.250	(0.009, 0.139)	0.024

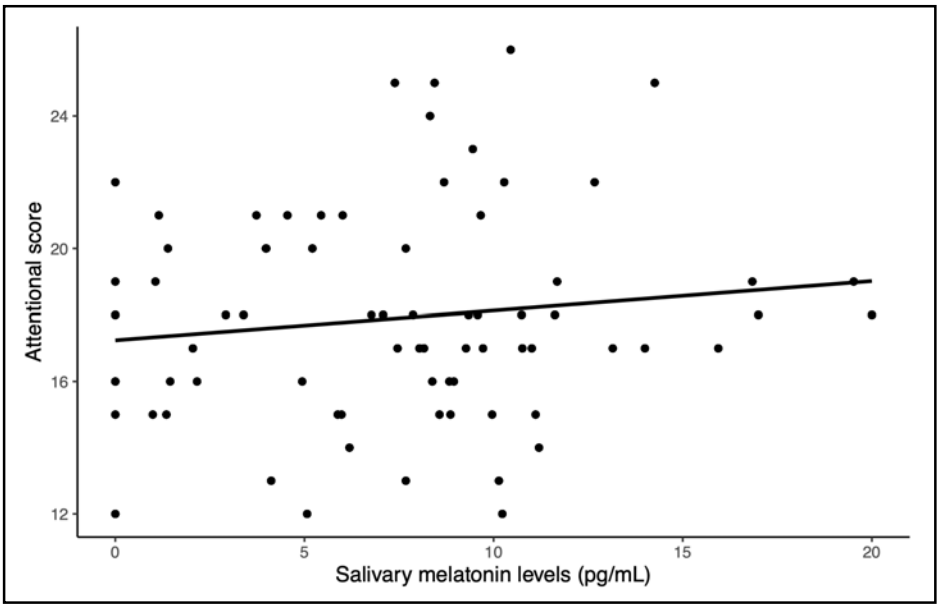

Fig. 1. The correlation between salivary melatonin levels and attentional score. Horizontal axis indicates the levels of melatonin concentrations (pg/mL) and vertical axis indicates the scores of attention in BIS.

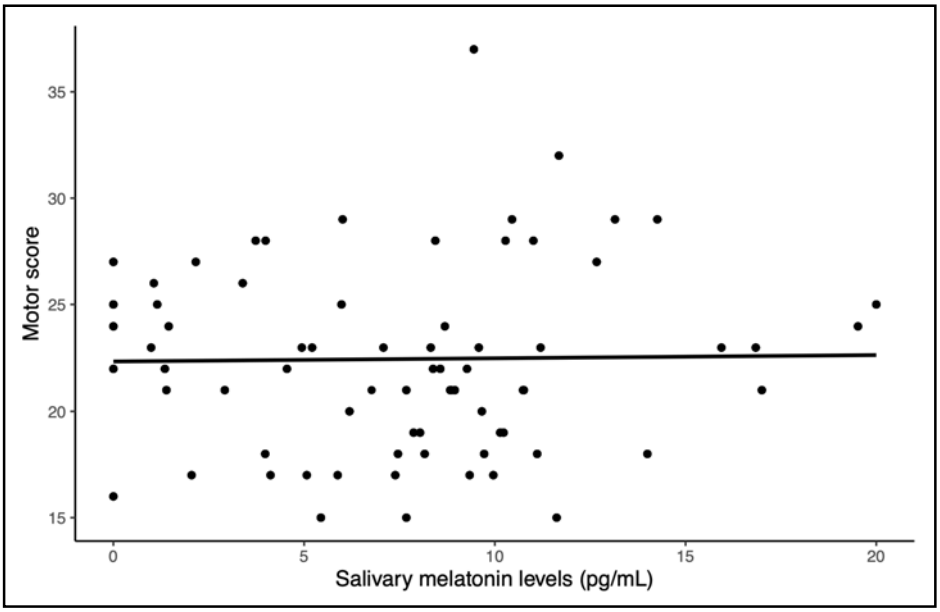

Fig. 2. The correlation between salivary melatonin levels and motor score. Horizontal axis indicates the levels of melatonin concentrations (pg/mL) and vertical axis indicates the scores of motor in BIS.

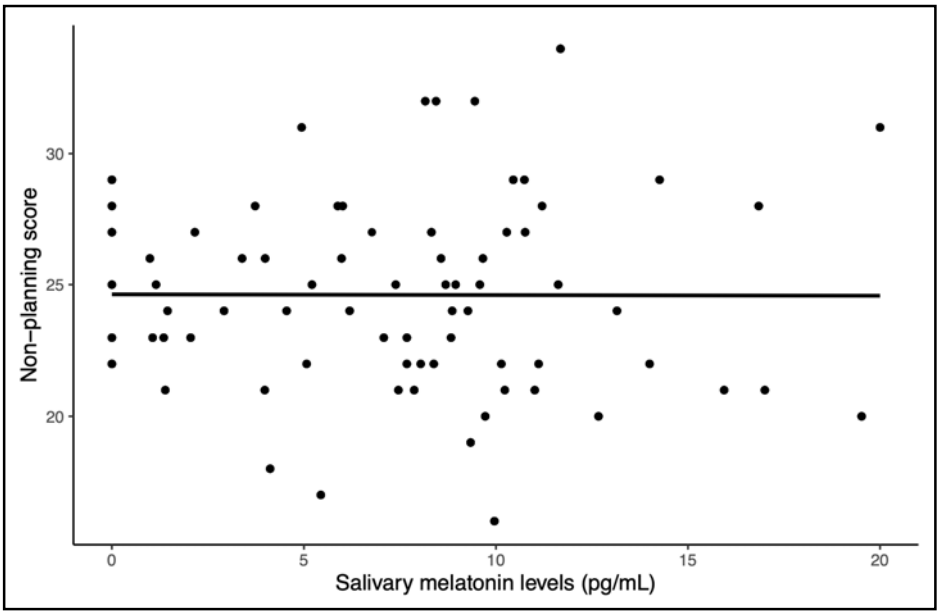

Fig. 3. The correlation between salivary melatonin levels and non-planning score. Horizontal axis indicates the levels of melatonin concentrations (pg/mL) and vertical axis indicates the scores of non-planning in BIS.

prefrontal cortex, specifically the OFC and VPMFC areas, which could have affected impulsivity in this study.

This study has several limitations. First, though we found a positive correlation between salivary melatonin levels and impulsivity, we could not conclude whether elevated melatonin levels precede impulsivity or vice versa as this work was a correlational study. Second, although melatonin is considered to be related to neurobiological regions, such as the prefrontal cortex in animal models (Uz *et al.* 2005), we did not use neuroimaging methods to directly measure these processes. Therefore, further investigations are required to determine whether melatonin affects impulsivity. Third, we used the BIS as an indicator of personal traits of impulsivity; however, state impulsivity can also be measured using behavioral tasks. Behavioral tasks that test impulsivity in humans include temporal discounting (Rachlin *et al.* 1991), Go/No-Go tasks (Stanislaw & Todorov, 1999), information sampling tests (Clark *et al.* 2006; Kagan *et al.* 1964), stop-signal reaction time tasks (Logan, 1994), and risk-taking tests (Bechara *et al.* 1994, Rogers *et al.* 1999). Using these tasks will help to expand the investigation of impulsivity in individuals with high melatonin levels to other kinds of impulsivity, such as impulsivity to rewards. Nevertheless, the present study demonstrated that salivary melatonin levels are related to impulsivity. This may imply that melatonin has a positive relationship with impulsivity such that medical guidelines should advise on the cautions to be taken in the prescription and usage of melatonin. Further research can identify related implications that would help address the link between melatonin and impulsivity.

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CONFLICTS OF INTEREST

We have no financial interests in this manuscript to disclose.

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