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ORIGINAL ARTICLE

Relationship between salivary melatonin and interoceptive awareness.

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Abstract

OBJECTIVES: This study examined the relationship between salivary melatonin levels and interoceptive awareness in humans.
METHODS: We recruited 75 participants aged 18-55 years and measured their salivary melatonin concentrations using an enzyme immunoassay and their interoceptive awareness using the scores of the Multidimensional Assessment of Interoceptive Awareness (MAIA) scale.
RESULTS: Melatonin levels negatively correlated with total interoceptive awareness scores. On the subscales, melatonin levels were negatively correlated with noticing, attention regulation, emotional awareness, self-regulation, body listening, and trust, and were positively correlated with not-distracting; however, there was no correlation with not-worrying.
CONCLUSION: Individuals with high melatonin levels are unlikely to be aware of their bodily sensations and emotional states or to regulate attention and emotions; however, they appear to have a calm mind.

Abbreviations:

MAIA	- Multidimensional Assessment of Interoceptive Awareness
SCN	- Suprachiasmatic nucleus

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 24-hour day/night cycle. 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), body temperature (Cagnacci *et al.* 1992; Dawson *et al.* 1996; Dollins *et al.* 1994; Eo *et al.* 2022; Lok *et al.* 2019; López-Canul *et al.* 2019), autonomic nervous system (Baker & Kimpinski, 2018; Chuang *et al.* 1993; Eo *et al.* 2022) and awareness (Bob & Fedor-Freybergh, 2008; Simek, 2018). However, no studies have explored the effect of melatonin on the awareness of the internal state.

Interoceptive awareness, the ability to detect inner bodily changes, is affected by the neuromodulation of the brain. The release of the neuromodulators such as serotonin, dopamine, and noradrenaline into the hypothalamus activates or inhibits sympathetic nerves (Elam, 1986; Ilhan & Long, 1975; Sakaguchi & Bray, 1989; Svensson, 1987). Then, the body signals such as heart rate are perceived in regions related to interoception, such as the viscerosensory cortex in the mid-insula (Avery *et al.* 2015; Avery *et al.* 2017; Cechetto & Saper, 1987), right anterior insula (Craig, 2009; Critchley *et al.* 2004), and orbitofrontal cortices (Chen *et al.* 2021; Craig, 2002). This neurobiological process supports that serotonin, dopamine, and noradrenaline affect interoception (Angioletti & Balconi, 2021; Livermore *et al.* 2020; Schulz *et al.* 2022).

Melatonin inhibits the sympathetic nervous system and activates the parasympathetic nervous system in the SCN of the hypothalamus (Baker & Kimpinski, 2018; Chuang *et al.* 1993; Eo *et al.* 2022), which may modulate the interoceptive signals from the body and awareness which are associated with the activations of the anterior insula (Craig, 2009; Critchley *et al.* 2004). Although previous research suggests that melatonin is related to impairments in the awareness of the external state in humans (Bob & Fedor-Freybergh, 2008; Simek, 2018), it is unclear whether melatonin is related to the awareness of the internal state in humans. If melatonin is associated with impaired awareness, then it should also be associated with a decrease in awareness of body signals. Therefore, in this study, we hypothesized that melatonin levels correlate with a decline in interoceptive awareness in humans.

MATERIAL AND METHODS

Participants

We recruited 75 participants (13 males and 62 females) aged 18-55 years. The participants arrived at a laboratory with natural room lights (<500 lux) between 12 pm and 4 pm. We chose these daytime and lighting conditions because salivary melatonin levels do not fluctuate under lighting conditions or during this period (Mclntyre *et al.* 1989). Upon arrival, participants read the consent form and provided written consent to participate in the study.

This study was conducted according to 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 the webpage on melatonin, the Electronic Medicines Compendium (eMC) and a previous study (Liu *et al.* 2017). 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 cycle) were excluded from the study. Participants taking medications mentioned on the eMC webpage were excluded. Participants who were currently on hormone replacement therapy, involved in night shift work, performed trans-meridian travel in the month prior to the experiment, were pregnant or may have become pregnant during the study, or were nursing were also excluded. Participants who usually woke up between 6 am and 9 am and went to sleep between 10 pm and 1 am were included in the study. Participants were asked to abstain from exercise, caffeine, cigarettes, and alcohol for at least 24 h before the laboratory study.

Saliva Collection

Before collecting saliva samples, participants rinsed their mouths. The saliva sample was collected using a passive drool. Samples were stored in a -30°C freezer until study completion. The samples were assayed in a laboratory at the Nagoya University. The sampling tubes were centrifuged for 10 min and hormone

Tab. 1. Descriptive statistics for interoceptive awareness depending on salivary melatonin levels

	High melatonin levels		Low melatonin levels	
Interoceptive awareness (MAIA)	M	SD	M	SD
Noticing	3.38	0.938	3.66	1.07
Not-distracting	3.96	1.24	3.6	1.12
Not-worrying	3.22	0.814	2.98	0.852
Attention regulation	3.07	0.826	3.74	0.865
Emotional awareness	3.06	0.997	3.46	1.13
Self-regulation	3.19	0.924	3.7	0.889
Body-listening	2.32	0.841	2.78	1.17
Trusting	3.34	0.989	3.75	1.12
Total MAIA scores	25.6	4.08	27.7	4.9

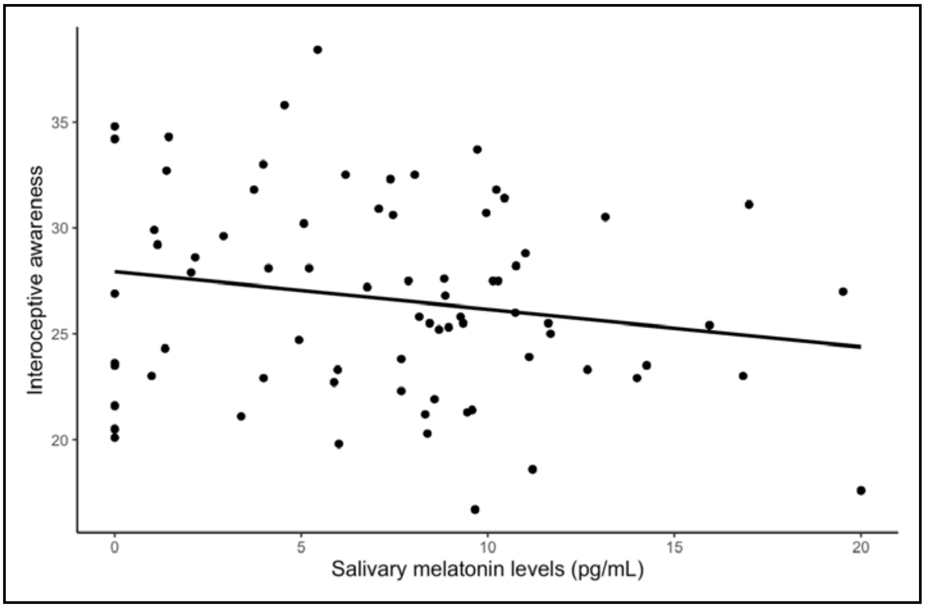

Fig. 1. The correlation between salivary melatonin levels and interoceptive awareness. Horizontal axis indicates the levels of melatonin concentrations (pg/ml) and vertical axis indicates the scores of interoceptive awareness in MAIA.

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 statistical analyses.

Interoceptive Awareness

Interoceptive awareness was measured by using a Multidimensional Assessment of Interoceptive Awareness scale (Mehling *et al.* 2012). This is an 8-scale (noticing, not distracting, not worrying, attention regulation, emotional awareness, self-regulation, body listening, and trust) state-trait questionnaire with 32 items that measure multiple dimensions of interoception.

Statistical Analyses

Pearson's correlation analysis was used for the comparison of continuous variables of interoception depending on salivary melatonin levels. *P* values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the R software package (Version 4.3.1).

RESULTS

The average melatonin concentrations were 7.3 pg/mL for all participants. Splitting the continuous salivary melatonin data into categorical data by a median split, the average melatonin concentration for the low melatonin condition was 3.5 pg/mL, and that for high melatonin condition was 11.2 pg/mL. Descriptive statistics for interoceptive awareness are presented in Table 1, where M is the mean value and SD is the standard deviation.

To examine the relationship between salivary melatonin levels and interoceptive awareness, Pearson's correlation analysis was conducted. Salivary melatonin levels and interoceptive awareness scores were used as continuous data. The analysis revealed a significant negative correlation between melatonin levels and interoceptive awareness (r = -0.185, t = -5.648, 95% confidence interval (CI) [-0.247, -0.121], $p < 0.001$) (Figure 1) The salivary melatonin levels and subscales of interoceptive awareness are presented in Table 2.

DISCUSSION

This study demonstrated that salivary melatonin levels negatively correlated with interoceptive awareness scores. On the subscales, melatonin levels were negatively correlated with noticing, attention regulation, emotional awareness, self-regulation, body listening, and trust; and were positively correlated with not-distracting. They were not correlated with not-worrying.

Taken together, these observations suggest that individuals with high melatonin levels are unlikely to be aware of bodily sensations and emotional states and are unlikely to regulate attention and emotions; however, they have a calm mind.

Melatonin affects sympathetic inhibition or parasympathetic stimulation (Baker & Kimpinski, 2018; Chuang *et al.* 1993; Eo *et al.* 2022), leading to a resting condition with decreased heart rate and blood pressure (Harris *et al.* 2001; Pechanova *et al.* 2014; Simko *et al.* 2016). Because the physiological signals become calm, the participants may be unaware of their body signals. Furthermore, our results are consistent with the role of melatonin in awareness (Bob & Fedor-Freybergh, 2008; Simek, 2018). Consciousness and awareness are closely related to interoceptive awareness (Craig, 2009;

Tab. 2. Correlation between salivary melatonin levels and subscores in MAIA

Interoceptive awareness (MAIA)	r	t	95% CI	p
Noticing	-0.086	-2.602	(-0.150, -0.021)	0.009
Not-distracting	0.105	3.192	(0.040, 0.170)	0.001
Not-worrying	-0.004	-0.129	(-0.069, 0.061)	0.894
Attention regulation	-0.294	-9.221	(-0.352, -0.233)	<0.001
Emotional awareness	-0.145	-4.408	(-0.208, -0.080)	<0.001
Self-regulation	-0.184	-5.622	(-0.246, -0.120)	<0.001
Body-listening	-0.138	-4.201	(-0.202, -0.074)	<0.001
Trusting	-0.142	-4.302	(-0.205, -0.077)	<0.001
Total MAIA scores	-0.185	-5.648	(-0.247, -0.121)	<0.001

Damasio, 2003; Park & Tallon-Baudry, 2014; Suzuki *et al.* 2013; Tsakiris *et al.* 2011), and both awareness and interoceptive awareness are similarly associated with activation of the anterior insula (Craig, 2009; Critchley *et al.* 2004). Therefore, salivary melatonin secretions might inhibit the sympathetic nervous system and activate the parasympathetic nervous system in the hypothalamus (Baker & Kimpinski, 2018; Chuang *et al.* 1993; Eo *et al.* 2022). This may result in modifications of activities in various brain areas (e.g., the anterior insula) related to awareness—including interoception (Critchley *et al.* 2004).

This study had several limitations. First, though we found a negative correlation between salivary melatonin levels and interoceptive awareness, this study being a correlational study, we could not conclude whether melatonin affected interoceptive awareness or vice versa. Second, although melatonin is considered to be related to neurobiological and psychophysiological changes (Baker & Kimpinski, 2018; Chuang *et al.* 1993; Eo *et al.* 2022; Liu *et al.* 2017), we did not use neuroimaging or psychophysiological methods to measure these direct processes. Further such investigations are needed to determine whether melatonin affects interoception. Third, we used the MAIA as an indicator of the personal traits of interoceptive awareness; however, interoception can also be measured using behavioral tasks, such as the heartbeat counting task (Dale & Anderson, 1978; Schandry, 1981) and heartbeat detection tasks (Katkin *et al.* 1983; Whitehead *et al.* 1977). Using these tasks will help investigate further dimensions of interoception, such as interoceptive accuracy and interoceptive sensitivity (Garfinkel *et al.* 2015; Kleckner *et al.* 2015). Future studies should explore interoception changes in individuals with higher melatonin levels using these behavioral tasks. Nevertheless, the present study demonstrated that the level of salivary melatonin is related to interoceptive awareness. Further research may identify further related implications that would help address the links between melatonin and interoceptive awareness.

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CONFLICTS OF INTEREST

We have no financial interests in this manuscript to disclose.

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