Research Article

Effects of hypnotics on prefrontal cortex activity during a verbal fluency task in healthy male subjects: a near-infrared spectroscopy study

Yoshiyuki Tsuruta[1], Kunihiro Iwamoto[1#]*, Masahiro Banno[1], Naoko Kawano[1,2], Kunihiro Kohmura[1], Seiko Miyata[1], Hiroshige Fujishiro[1], Yukihiro Noda[1,3], Akiko Noda[4], Shuji Iritani[1], Norio Ozaki[1]

Running head: Effects of two different hypnotics on NIRS

Key words: hypnotics; ramelteon; triazolam; near-infrared spectroscopy (NIRS); brain activity; sleepiness

[1] Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

[2] Institutes of Innovation for Future Society, Nagoya University, Nagoya, Aichi, Japan

[3] Division of Clinical Science and Neuropsychopharmacology, Meijo University, Graduate School of Pharmacy, Nagoya, Aichi, Japan

[4] Department of Biomedical Sciences, College of Life and Health Sciences, Chubu University. Kasugai, Aichi. Japan

#equal first author contribution

*****Correspondence to: Kunihiro Iwamoto, MD, PhD, Department of Psychiatry, Nagoya University, Graduate School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8550, Japan

Tel: +81 52 744 2282. Fax: +81 52 744 2293.

E-mail: iwamoto@med.nagoya-u.ac.jp

This work was supported in part by research grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan; the Ministry of Health, Labour and Welfare of Japan; the Academic Frontier Project for Private Universities, Comparative Cognitive Science Institutes, Meijo University; Grant-in-Aid for “Center of Innovation for Personalized and Diverse Society” carried out under the Center of Innovation Program from the Japan Science and Technology Agency, JST; Grant-in-Aid for Scientific Research on Innovative Areas (JP15H05935); the Research on Regulatory Science of Pharmaceuticals and Medical Devices from Japan Agency for Medical Research and Development, AMED (JP18mk0101055), the NEXCO Group Companies’ Support Fund to Disaster Prevention Measures on Expressways; the General Insurance Association of Japan; the Daiwa Syoken Health Foundation; the Mitsui-Sumitomo Wellness Foundation; and the Japan Foundation for Neuroscience and Mental Health.

ABSTRACT

***Objective*:** To assess the effects of hypnotics on prefrontal cortex activity in healthy subjects using near-infrared spectroscopy (NIRS) in a double-blind, placebo-controlled crossover trial.

***Methods*:** Eighteen healthy males received acute doses of ramelteon (8 mg), triazolam (0.125 mg), or placebo in a predetermined randomization schedule, with a washout period of more than 1 week. All subjects performed a verbal fluency task during NIRS assessments at baseline and at 1 and 4 h post-dosing. The number of words correctly generated during the task (behavioral performance) and scores on the Stanford Sleepiness Scale (SSS) were also recorded at each test time.

***Results*:** Compared with the placebo, triazolam (0.125 mg) significantly decreased oxyhemoglobin (oxy-Hb) concentration change in NIRS during the post-task period and significantly increased behavioral performance, while triazolam (0.125 mg) and ramelteon (8 mg) significantly increased SSS scores.

***Conclusions*:** The differential effects of two types of hypnotics on oxy-Hb change measured by NIRS were observed in acute dosing, suggesting that when assessing the brain activity of patients with psychiatric disorders, researchers should consider how certain types of hypnotics can influence brain function. This would also provide useful information to clinicians when prescribing hypnotics suitable for their patients' conditions.

INTRODUCTION

Near-infrared spectroscopy (NIRS), a noninvasive functional brain imaging technique that can determine changes in blood volume in an anatomical region of interest by measuring the absorbance by hemoglobin (Hb) of light in the near-infrared spectrum, has recently been receiving increasing attention in neuroscientific and psychiatric research because it allows brain activity to be assessed under natural conditions and is considered suitable for psychiatric patients. NIRS scans have shown decreased frontal lobe activity in patients with a variety of psychiatric disorders, including major depressive disorder, bipolar, panic, eating, and attention deficit hyperactivity disorders, schizophrenia, Alzheimer's dementia, and alcoholism) (Kameyama et al., 2006; Katayama et al., 2014; Schecklmann et al., 2007; Suda et al., 2010; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004), thereby showing promise as a useful differential diagnostic tool in psychiatric clinical practice (Takizawa et al., 2014).

In addition to the influences attributable to specific diseases, several factors, including age, sex, and sleepiness, can influence changes in Hb concentration in NIRS (Kameyama, Fukuda, Uehara, & Mikuni, 2004; Suda et al., 2008). For example, sleep disturbance is typically associated with psychiatric patients (Wulff, Gatti, Wettstein, & Foster, 2010), and sleep complaints have been shown to reduce prefrontal activation as measured by NIRS in patients with major depression (Nishida et al., 2017). We have previously described that acute and subchronic deficient sleep may reduce peak oxyhemoglobin (oxy-Hb) concentration in the lateral frontal lobes (S. Miyata et al., 2015; Miyata et al., 2010), and that NIRS measurements are differentially affected by mirtazapine and trazodone **(Kohmura et al., 2013)**, which are sedative antidepressants commonly used to treat chronic insomnia in the US. In addition, antidepressants have

recently been shown to have a dose-dependent effect on NIRS signals (Takamiya et al., 2017). Although the effects of hypnotics on brain function have been investigated in terms of functional brain imaging techniques such as positron emission tomography (PET) (Mintzer et al., 2006) and functional magnetic resonance imaging (fMRI) (Licata, Lowen, Trksak, Maclean, & Lukas, 2011), to our knowledge, no studies have clarified the effects of hypnotics in terms of NIRS measurements.

In many European countries, benzodiazepine receptor agonists are commonly prescribed to treat insomnia (Clay, Falissard, Moore, & Toumi, 2013). **These drugs are most prescribed for patients with insomnia in Japan (*Report of the International Narcotics Control Board for 2015,* 2015)**. However, these hypnotics frequently lead to residual morning sedation and cognitive impairments, including impaired driving performance (Barker, Greenwood, Jackson, & Crowe, 2004; Takahashi et al., 2010; Vermeeren, 2004). Ramelteon, a selective melatonin receptor (MT1/MT2) agonist, promotes sleep without significantly interacting with GABA-benzodiazepine and muscarinic receptors, has been reported to have minimal effects on sedation and cognitive function (Johnson, Suess, & Griffiths, 2006); however, similar to benzodiazepine receptor agonists, ramelteon has also been shown to impair driving performance (Mets et al., 2011; A. Miyata et al., 2015). Although the differential effects of these hypnotics on brain function can be estimated according to their pharmacological profiles, to our knowledge, they have not been demonstrated simultaneously.

Therefore, the objective of the present study was to examine the effects of triazolam and ramelteon on brain activity in healthy volunteers using multichannel NIRS. We chose triazolam for short elimination half-life like ramelteon. Furthermore,

triazolam is still frequently prescribed for insomnia patients in the Western country and Japan (McKean & Vella-Brincat, 2011; Ohayon, Lemoine, Arnaud-Briant, & Dreyfus, 2002; Suzuki et al., 2018).

METHODS

Participants

The study participants were 18 healthy, male, right-handed Japanese volunteers (mean age: 34.0 years; standard deviation [SD]: 9.9 years; age range: 22–44 years). The study protocol was approved by the Nagoya University Graduate School of Medicine and Nagoya University Hospital ethics review committees (No. 2010-0970-2), and written informed consent was obtained from all participants prior to enrolment. In addition, all participants took part in interviews conducted by one of the experimenters using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders to confirm the absence of any psychiatric disorders. None of the participants were in poor health, receiving any concomitant medications likely to affect brain function, or had any significant clinical history of physical or mental illness. They have never taken hypnotics in the past.

Drug administration and study design

A double-blind, placebo-controlled crossover design was used in which each participant was assigned to receive three different treatments (8 mg ramelteon, 0.125 mg triazolam, and placebo in identical capsules) across three different treatment sessions according to a randomization schedule. Participants were randomized to pre-determined and counterbalanced regimen in order of enrollment. The doses selected were based on

generally recommended clinical starting dose. Each treatment session was separated by a washout period of at least 7 days. Each participant was administered one of the three test drugs after baseline NIRS assessment at 09:00. The NIRS assessments were repeated at 1 h and 4 h post-dosing. All participants then completed a verbal fluency task while their prefrontal cortical activity was measured using an NIRS recorder (FOIRE-3000; Shimadzu, Kyoto, Japan). In addition, the Stanford Sleepiness Scale (SSS) was used to assess subjective sleepiness at the time of the examination. The SSS (one item) is a seven-point, self-reporting measure of alertness with proven sensitivity (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973). Higher value means increased sleepiness.

Activation task

Changes in Hb concentration were measured while participants completed a letter-version verbal fluency task that has been administered in many previous studies (Kameyama et al., 2004; Kameyama et al., 2006; Katayama et al., 2014; Kohmura et al., 2013; Suda et al., 2008; Suda et al., 2010; Suto et al., 2004). Throughout the measurements, the participants remained seated on a comfortable chair with their eyes open in a sunlit room. Regarding the task, the participants were given oral instructions to generate as many common nouns (excluding proper nouns and repetitions) as possible beginning with the Japanese syllables ‘a’, ‘ki’, ‘ha’, ‘to’, ‘se’, ‘o’, ‘i’, ‘no’, or ‘ta’. Stimulus syllables were counterbalanced for each treatment condition. In total, all participants performed a 30-s pre-task, a 60-s verbal fluency task, and 60-s post-task. Performance was judged based on the number of words generated during the verbal fluency task. The participants were instructed to repeat the vowels ‘a’, ‘i’, ‘u’, ‘e’, and

‘o’ during both the pre- and post-task periods as the Japanese counterparts of A, B, and C in English (Kameyama et al., 2004). Practice sessions were conducted before the main examinations when the NIRS responses were actually recorded until the experimenter judged that the participants fully understood the procedure.

NIRS measurements

Relative changes in oxy-Hb and deoxygenated hemoglobin (deoxy-Hb) were measured using a functional NIRS system (FOIRE-3000; Shimadzu, Kyoto, Japan) at three different wavelengths (780, 805, and 830 nm). An NIRS shell with 3×5 arrays of light emitters and detectors (distance between probes: 3 cm), which can measure the relative concentrations of oxy-Hb and deoxy-Hb at 22 different measurement points in a 9×15 cm area, was used (Figure 1). According to the International 10-20 system used in electroencephalography, the NIRS shell was placed over the frontal region, with the lowest probes positioned along the Fp1-2 line (Okamoto et al., 2004). The NIRS channels 1-4, 6-8, 10-13, 15-17, and 19-22 were roughly localized on superior frontal gyrus and channels 5, 9, 14, and 18 were roughly localized on middle frontal gyrus. Positions of NIRS channels were shown on International 10-20 system (Kato et al., 2018) (Figure 2).

Data analysis and statistics

Next, oxy-Hb values in the 22 channels located above the prefrontal cortex were analyzed. We focused on changes in oxy-Hb concentration as they are thought to reflect cognitive activation more directly than changes in deoxy-Hb, based on a stronger correlation with blood-oxygenation level-dependent signals as measured by fMRI

(Strangman, Culver, Thompson, & Boas, 2002). Near-infrared light absorption was measured using a temporal resolution of 0.1 s. Waveforms of oxy-Hb changes were acquired across participants during the task for all 22 channels. NIRS data containing motion artifacts as determined by close observation were excluded from further statistical analysis (data were excluded from two participants in total). A low-pass filter with a high cutoff of 0.1 Hz was used to exclude short-term motion artifacts, and oxy-Hb data showing low signal-to-noise ratios in channels 1–5, 7, 9, 14, 16, and 18–22 were excluded from further analysis. Next, oxy-Hb concentrations during the task and post-task periods were averaged. The pre-task baseline value was computed by calculating the mean across the last 10 s of the 30-s pre-task period. Changes in oxy-Hb concentration during the verbal fluency task and post-task at baseline and at 1 h and 4 h post-dosing were analyzed statistically after subtracting the changes between the task period and pre-task baseline and between the post-task period and pre-task baseline. Data were analyzed using a linear mixed model with restricted maximum likelihood estimation in which the participants were random effects and the study drug (ramelteon, triazolam, or placebo) and time (baseline, 1 h, and 4 h post-dosing) were fixed effects. The linear mixed model uses all available data (and can handle missing data more appropriately), can account for correlations between repeated measurements in the same participant, and has greater flexibility in terms of modeling time effects. Akaike's information criterion and Schwarz's Bayesian criterion were used to select the best-fitting covariance structure. Post hoc multiple comparison testing (Fisher's protected least significant difference) was used to compare the effects between each drug condition at each post-dosing point when a significant interaction between factors or a significant main effect of the drug was observed. The numbers of words and SSS

scores were also analyzed using the linear mixed model. Exploratory correlational analyses between changes in oxy-Hb concentration and numbers of words and SSS scores were performed for each channel using Spearman's ρ. All statistical tests were two-tailed with alpha set at 0.05.

RESULTS

Behavioral performance

The numbers of words correctly generated during the 60-s verbal fluency task period for each test time are summarized in Table 1. A significant drug × time interaction ($F(4, 102) = 3.92$, $p = 0.005$) and post hoc test showed that the numbers of words under the triazolam condition were significantly greater compared with the ramelteon condition at 1 h and 4 h post-dosing (both $p = 0.003$) and with the placebo condition at 1 h and 4 h post-dosing ($p = 0.03$ and $p = 0.01$, respectively). No correlations were observed between the numbers of words correctly generated and changes in oxy-Hb concentration.

SSS scores

The SSS scores are summarized in Table 1. A significant drug effect was observed ($F(2, 77) = 9.53$, $p < 0.001$). The post hoc test showed that SSS scores under the ramelteon and triazolam conditions were significantly greater compared with the placebo condition (both $p = 0.03$) at 1 h post-dosing. No correlations were observed between SSS scores and changes in oxy-Hb concentration except for channel 11 ($\rho = -0.18$, $p = 0.028$).

NIRS response

No significant drug × time interaction or drug effect was found during the task period. Regarding the post-task period, significant drug effects were observed in channels 8 ($F(2, 120) = 3.55$, $p = 0.03$), 11 ($F(2, 120) = 2.46$, $p = 0.09$), 12 ($F(2, 120) = 5.65$, $p = 0.005$), 13 ($F(2, 120) = 2.86$, $p = 0.06$), 15 ($F(2, 120) = 3.36$, $p = 0.04$), and 17 ($F(2, 120) = 2.49$, $p = 0.09$). The post hoc test showed that the oxy-Hb decreases during the post-task period with triazolam were larger than those with placebo in channels 11 ($p = 0.08$), 12 ($p = 0.046$), and 15 ($p = 0.03$) at 1 h post-dosing and in channels 8 ($p = 0.06$), 12 ($p = 0.08$), and 15 ($p = 0.05$) at 4 h post-dosing. Typical examples of changes in oxy-Hb concentration during the pre-task, task, and post-task periods in channels 12 (left superior frontal gyrus) and 15 (right superior frontal gyrus) at 1 h post-dosing are shown in Figure 3.

DISCUSSION

In the present study, we measured changes in oxy-Hb concentration using NIRS to examine the effects of two different hypnotics on cortical activity during the performance of a verbal fluency task. Although both ramelteon and triazolam yielded greater subjective sleepiness, triazolam resulted in decreased brain activity compared with placebo in some channels during the post-task period. The differential effects of ramelteon and triazolam, as well as antidepressants, on brain activity should be considered (Kohmura et al., 2013; Takamiya et al., 2017) when performing NIRS.

In the present study, we assumed that the superior frontal gyrus would be activated in relation to changes in oxy-Hb concentration (Tsuzuki et al., 2007). Although no difference in activation was observed during the task period among the

three drug conditions, triazolam significantly reduced brain activity, mainly in the central area of the prefrontal cortex during the post-task period. Triazolam reduced activation in the prefrontal cortex during a verbal learning task in a previous PET study (Mintzer et al., 2006) and zolpidem, a benzodiazepine receptor agonist similar to triazolam, reduced activation in the occipital cortex during a checkerboard task in a previous fMRI study (Licata et al., 2011). However, no studies have examined the effects of hypnotics on brain blood flow as measured by NIRS during a verbal fluency task. Most hypnotics are benzodiazepine receptor agonists and have been known to impair various aspects of cognition (Barker et al., 2004; Vermeeren, 2004). Benzodiazepine receptors are widely distributed throughout the brain (McCabe & Wamsley, 1986; Zezula, Cortes, Probst, & Palacios, 1988), and previous fMRI and PET studies have demonstrated that benzodiazepine receptor agonists inhibit neuronal activities involved in separate cognitive tasks (Licata et al., 2011; Mintzer et al., 2006). The results of an electroencephalogram study demonstrated that low doses of triazolam, similar to those used in the present study, can cause cortical dysfunction (Urata et al., 1996). These past findings regarding the decreased prefrontal cortex activity associated with triazolam are consistent with those of the present study.

On the other hand, the effect of ramelteon on brain activity has not been examined. To the best of our knowledge, this is the first study to elucidate the effects of ramelteon on brain activity during a cognitive task. Ramelteon had little effect on prefrontal activity during both the task and post-task periods, similar to that of the placebo. Previous studies using NIRS demonstrated that subjective sleepiness decreased prefrontal activity during a verbal fluency task (S. Miyata et al., 2015; Suda et al., 2008). In the present study, both triazolam and ramelteon increased subjective sleepiness;

however, the extent of sleepiness was small compared with previous studies, meaning that it may contribute little to brain activity. In addition, ramelteon, a selective MT1/MT2 agonist, shows higher affinities for these receptors on the suprachiasmatic nucleus and no relevant affinity for the GABA receptor complex throughout the brain (Pandi-Perumal, Srinivasan, Poeggeler, Hardeland, & Cardinali, 2007). This mechanism of action may also be attributed to the different results of the two drugs. The dosage and duration of medication can affect consequences. Therefore, further investigation of the effects of different factors that may impact brain function using other neuroimaging procedures such as fMRI is warranted.

Different brain activities under the triazolam and ramelteon conditions offer some clinical suggestions. Decreased cortical activation during cognitive tasks has been reported in healthy older subjects compared with young adults (Herrmann, Walter, Ehlis, & Fallgatter, 2006) and in patients with Alzheimer's dementia compared with healthy older subjects (Herrmann, Langer, Jacob, Ehlis, & Fallgatter, 2008). In addition, triazolam may affect brain activity in the elder, resulting in cognitive impairment and an increased risk of falls. By contrast, ramelteon may be safer in terms of effects on brain activity, and may therefore be more suitable for older people and patients with cognitive vulnerabilities. Further investigations involving insomniacs are needed to elucidate the potential confounding effects of these drugs and insomnia.

The results in regard to SSS scores indicated that sleepiness was equally increased with ramelteon and triazolam compared with placebo; however, a significant difference was observed between triazolam and ramelteon for the number of words correctly expressed during the verbal fluency task. In the present study, triazolam improved behavioral performance, which was similar to the finding in a previous study

that benzodiazepines improved verbal fluency in patients with obsessive compulsive disorder (Mataix-Cols, Alonso, Pifarre, Menchon, & Vallejo, 2002). Since better performance in a verbal fluency task has been shown to be associated with decreased oxy-Hb concentration in patients with bipolar disorder (Kameyama et al., 2006), improved behavioral performance may have affected oxy-Hb concentration under the triazolam condition during the post-task period in the present study. Although no correlation was found between changes in oxy-Hb concentration and number of words generated, we cannot deny the possibility that the slight increase in word production decreased brain activity in the post-task period.

Several limitations must be considered when interpreting the results of the present study. First, unlike fMRI, NIRS measurements are limited to the brain surface. In addition, we did not measure a considerable area outside of the NIRS shell. Second, the repeated-measure design may have affected the present results because multiple measurements tend to reduce oxy-Hb concentrations below a significant level (Kono et al., 2007). Third, to examine carefully the effects of drug and adverse reaction on brain function, the initial low doses of both triazolam and ramelteon were acutely administered to the participants. Nevertheless, we have to recognize that these doses pose a methodological problem because the initial low doses may be insufficient to affect brain activity. Finally, all participants in the present research were healthy men who were not currently taking any drugs. On the whole, most patients with psychiatric disorders are using alternative pharmacotherapies, so extracting particular responses to a single specific administered drug would be difficult. In addition, hormonal changes related to the menstrual cycle can affect cognitive function (Hampson, 1990; Maki, Rich, & Rosenbaum, 2002; Phillips & Sherwin, 1992), thereby influencing performance in

cognitive tasks. Changes in brain function in patients with psychiatric disorders could vary from those in healthy participants, and sensitivity and response to a drug might differ in women and the elderly. Therefore, the results of this study, which comprised only healthy participants, might not be just as valid for patients with psychiatric disorders.

CONCLUSION

We found that two types of hypnotics with different mechanisms of action differentially affected brain function as measured by NIRS with acute dosing. The benzodiazepine receptor agonist, triazolam, may reduce cortical activity with acute dosing, while the melatonin receptor agonist, ramelteon, may not. In conjunction with age, sex, and sleepiness, all of which should be considered when assessing cortical activity, the medication and type of hypnotic taken by patients with a psychiatric disorder appear to represent factors affecting changes in Hb concentration as measured by NIRS. The differential effects of these drugs on brain activity may provide useful information for clinicians when prescribing hypnotics suitable for a patient’s specific conditions.

CONFLICT OF INTEREST

Dr. Iwamoto has received speakers' honoraria from, or has served as a consultant to, Dainippon Sumitomo, Janssen, Meiji Seika Pharma, Mochida, Otsuka, Taisho, Takeda, Tanabe Mitsubishi, and Pfizer. Dr. Banno has received speaker honoraria from Dainippon Sumitomo, Eli Lilly, and Otsuka, honoraria for a manuscript from Seiwa Shoten Co., Ltd., SENTAN IGAKU-SHA Ltd., and Kagakuhyoronsha Co., Ltd., and travel fees from Yoshitomi Pharmaceutical Industries, Ltd. Dr. Kohmura has received speakers' honoraria from Dainippon Sumitomo and Meiji Seika Pharma. Dr. Fujishiro has received speakers' honoraria from Dainippon Sumitomo, Eisai, Fujifilm Pharma, Mochida, MSD, Otsuka, and Takeda. Dr. Y. Noda has received research support or speakers' honoraria from Dainippon Sumitomo, Janssen, and Meiji Seika Pharma. Dr. Iritani has received speakers' honoraria from Dainippon Sumitomo, Eisai, Janssen, Mochida, Novartis Pharma, Ono, and Pfizer. Dr. Ozaki has received research support or speakers' honoraria from, or has served as a consultant to, Abbvie, Asahi Kasei Pharma, Astellas, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Meiji Seika Pharma, Mochida, MSD, Novartis Pharma, Ono, Otsuka, Pfizer, Shionogi, Takeda, Tanabe Mitsubishi, Sanofi, and Yoshitomi. The other authors have no conflict of interest to declare. The drug companies had no role in study design; in supply of necessary materials; in the collection, analysis and interpretation of data; in writing and submitting the manuscript.

ACKNOWLEDGMENTS

We sincerely thank the volunteers for participating in this study. This work was supported in part by research grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Ministry of Health, Labour and Welfare of Japan, the Academic Frontier Project for Private Universities, Comparative Cognitive Science Institutes, Meijo University, Grant-in-Aid for “Center of Innovation for Personalized and Diverse Society” carried out under the Center of Innovation Program from Japan Science and Technology Agency, JST, Grant-in-Aid for Scientific Research on Innovative Areas (JP15H05935), the Research on Regulatory Science of Pharmaceuticals and Medical Devices from Japan Agency for Medical Research and development, AMED (JP18mk0101055), the foundation of NEXCO’s affiliates for Expressway Disaster Prevention Countermeasures, the General Insurance Association of Japan, the Daiwa Syoken Health Foundation, the Mitsui-Sumitomo Wellness Foundation, and the Japan Foundation for Neuroscience and Mental Health.

REFERENCES

Barker, M. J., Greenwood, K. M., Jackson, M., & Crowe, S. F. (2004). Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs, 18*(1), 37-48.

Clay, E., Falissard, B., Moore, N., & Toumi, M. (2013). Contribution of prolonged-release melatonin and anti-benzodiazepine campaigns to the reduction of benzodiazepine and Z-drugs consumption in nine European countries. *Eur J Clin Pharmacol, 69*(4), 1-10. doi:10.1007/s00228-012-1424-1

Hampson, E. (1990). Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn, 14*(1), 26-43.

Herrmann, M. J., Langer, J. B., Jacob, C., Ehlis, A. C., & Fallgatter, A. J. (2008). Reduced prefrontal oxygenation in Alzheimer disease during verbal fluency tasks. *Am J Geriatr Psychiatry, 16*(2), 125-135. doi:10.1097/JGP.0b013e3180cc1fbc

Herrmann, M. J., Walter, A., Ehlis, A. C., & Fallgatter, A. J. (2006). Cerebral oxygenation changes in the prefrontal cortex: effects of age and gender. *Neurobiol Aging, 27*(6), 888-894. doi:10.1016/j.neurobiolaging.2005.04.013

Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., & Dement, W. C. (1973). Quantification of sleepiness: a new approach. *Psychophysiology, 10*(4), 431-436.

Johnson, M. W., Suess, P. E., & Griffiths, R. R. (2006). Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. *Arch Gen Psychiatry, 63*(10), 1149-1157. doi:10.1001/archpsyc.63.10.1149

Kameyama, M., Fukuda, M., Uehara, T., & Mikuni, M. (2004). Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. *Neuroimage, 22*(4), 1715-1721. doi:10.1016/j.neuroimage.2004.03.050

Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., . . . Mikuni, M. (2006). Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. *Neuroimage, 29*(1), 172-184. doi:10.1016/j.neuroimage.2005.07.025

Katayama, H., Kohmura, K., Tanaka, S., Imaeda, M., Kawano, N., Noda, Y., . . . Ozaki, N. (2014). Social insecurity in relation to orbitofrontal activity in patients with eating disorders: a near-infrared spectroscopy study. *BMC Psychiatry, 14*, 173. doi:10.1186/1471-244X-14-173

Kato, K., Iwamoto, K., Kawano, N., Noda, Y., Ozaki, N., & Noda, A. (2018). Differential effects of physical activity and sleep duration on cognitive function in young adults. *Journal of Sport and Health Science, 7*, 227-236.

doi:10.1016/j.jshs.2017.01.005

Kohmura, K., Iwamoto, K., Aleksic, B., Sasada, K., Kawano, N., Katayama, H., . . . Ozaki, N. (2013). Effects of sedative antidepressants on prefrontal cortex activity during verbal fluency task in healthy subjects: a near-infrared spectroscopy study. *Psychopharmacology (Berl), 226*(1), 75-81. doi:10.1007/s00213-012-2885-8

Kono, T., Matsuo, K., Tsunashima, K., Kasai, K., Takizawa, R., Rogers, M. A., . . . Kato, N. (2007). Multiple-time replicability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. *Neurosci Res, 57*(4), 504-512. doi:10.1016/j.neures.2006.12.007

Licata, S. C., Lowen, S. B., Trksak, G. H., Maclean, R. R., & Lukas, S. E. (2011). Zolpidem reduces the blood oxygen level-dependent signal during visual system stimulation. *Prog Neuropsychopharmacol Biol Psychiatry, 35*(7), 1645-1652. doi:10.1016/j.pnpbp.2011.05.015

Maki, P. M., Rich, J. B., & Rosenbaum, R. S. (2002). Implicit memory varies across the menstrual cycle: estrogen effects in young women. *Neuropsychologia, 40*(5), 518-529.

Mataix-Cols, D., Alonso, P., Pifarre, J., Menchon, J. M., & Vallejo, J. (2002).

Neuropsychological performance in medicated vs. unmedicated patients with obsessive-compulsive disorder. *Psychiatry Res, 109*(3), 255-264.

McCabe, R. T., & Wamsley, J. K. (1986). Autoradiographic localization of subcomponents of the macromolecular GABA receptor complex. *Life Sci, 39*(21), 1937-1945.

McKean, A., & Vella-Brincat, J. (2011). Ten-year dispensing trends of hypnotics in New Zealand. *N Z Med J, 124*(1331), 108-110.

Mets, M. A., de Vries, J. M., de Senerpont Domis, L. M., Volkerts, E. R., Olivier, B., & Verster, J. C. (2011). Next-day effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on highway driving performance, memory functioning, psychomotor performance, and mood in healthy adult subjects. *Sleep, 34*(10), 1327-1334. doi:10.5665/SLEEP.1272

Mintzer, M. Z., Griffiths, R. R., Contoreggi, C., Kimes, A. S., London, E. D., & Ernst, M. (2001). Effects of triazolam on brain activity during episodic memory encoding: a PET study. *Neuropsychopharmacology, 25*(5), 744-756. doi:10.1016/S0893-133X(01)00280-9

Mintzer, M. Z., Kuwabara, H., Alexander, M., Brasic, J. R., Ye, W., Ernst, M., . . . Wong, D. F. (2006). Dose effects of triazolam on brain activity during episodic memory

encoding: a PET study. *Psychopharmacology (Berl), 188*(4), 445-461. doi:10.1007/s00213-006-0446-8

Miyata, A., Iwamoto, K., Kawano, N., Kohmura, K., Yamamoto, M., Aleksic, B., . . . Ozaki, N. (2015). The effects of acute treatment with ramelteon, triazolam, and placebo on driving performance, cognitive function, and equilibrium function in healthy volunteers. *Psychopharmacology (Berl), 232*(12), 2127-2137. doi:10.1007/s00213-014-3843-4

Miyata, S., Noda, A., Iwamoto, K., Kawano, N., Banno, M., Tsuruta, Y., . . . Ozaki, N. (2015). Impaired cortical oxygenation is related to mood disturbance resulting from three nights of sleep restriction. *Sleep Biol Rhythms, 13*(4), 387-394. doi:DOI: 10.1111/sbr.12130

Miyata, S., Noda, A., Ozaki, N., Hara, Y., Minoshima, M., Iwamoto, K., . . . Koike, Y. (2010). Insufficient sleep impairs driving performance and cognitive function. *Neurosci Lett, 469*(2), 229-233. doi:10.1016/j.neulet.2009.12.001

Nishida, M., Kikuchi, S., Matsumoto, K., Yamauchi, Y., Saito, H., & Suda, S. (2017). Sleep complaints are associated with reduced left prefrontal activation during a verbal fluency task in patients with major depression: A multi-channel near-infrared spectroscopy study. *J Affect Disord, 207*, 102-109.

doi:10.1016/j.jad.2016.09.028

Ohayon, M. M., Lemoine, P., Arnaud-Briant, V., & Dreyfus, M. (2002). Prevalence and consequences of sleep disorders in a shift worker population. *J Psychosom Res*, *53*(1), 577-583.

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., . . . Dan, I. (2004). Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. *Neuroimage, 21*(1), 99-111.

Pandi-Perumal, S. R., Srinivasan, V., Poeggeler, B., Hardeland, R., & Cardinali, D. P. (2007). Drug Insight: the use of melatonergic agonists for the treatment of insomnia-focus on ramelteon. *Nat Clin Pract Neurol*, *3*(4), 221-228. doi:10.1038/ncpneuro0467

Phillips, S. M., & Sherwin, B. B. (1992). Variations in memory function and sex steroid hormones across the menstrual cycle. *Psychoneuroendocrinology, 17*(5), 497-506.

Report of the International Narcotics Control Board for 2015. (2015). Retrieved from https://www.incb.org/documents/Publications/AnnualReports/AR2015/English/Supplement-AR15_availability_English.pdf

Schecklmann, M., Ehlis, A. C., Plichta, M. M., Boutter, H. K., Metzger, F. G., & Fallgatter, A. J. (2007). Altered frontal brain oxygenation in detoxified alcohol dependent patients with unaffected verbal fluency performance. *Psychiatry Res, 156*(2), 129-138. doi:10.1016/j.pscychresns.2007.01.009

Strangman, G., Culver, J. P., Thompson, J. H., & Boas, D. A. (2002). A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *Neuroimage, 17*(2), 719-731.

Suda, M., Sato, T., Kameyama, M., Ito, M., Suto, T., Yamagishi, Y., . . . Mikuni, M. (2008). Decreased cortical reactivity underlies subjective daytime light sleepiness in healthy subjects: a multichannel near-infrared spectroscopy study. *Neurosci Res, 60*(3), 319-326. doi:10.1016/j.neures.2007.12.001

Suda, M., Uehara, T., Fukuda, M., Sato, T., Kameyama, M., & Mikuni, M. (2010). Dieting tendency and eating behavior problems in eating disorder correlate with right frontotemporal and left orbitofrontal cortex: a near-infrared spectroscopy study. *J Psychiatr Res, 44*(8), 547-555. doi:10.1016/j.jpsychires.2009.11.005

Suto, T., Fukuda, M., Ito, M., Uehara, T., & Mikuni, M. (2004). Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. *Biol Psychiatry, 55*(5), 501-511.

doi:10.1016/j.biopsych.2003.09.008

Suzuki, Y., Sakakibara, M., Shiraishi, N., Hirose, T., Akishita, M., & Kuzuya, M. (2018). Prescription of potentially inappropriate medications to older adults. A nationwide survey at dispensing pharmacies in Japan. *Arch Gerontol Geriatr, 77*, 8-12. doi:10.1016/j.archger.2017.12.010

Takahashi, M., Iwamoto, K., Kawamura, Y., Nakamura, Y., Ishihara, R., Uchiyama, Y., . . . Ozaki, N. (2010). The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers. *Hum Psychopharmacol, 25*(3), 260-267. doi:10.1002/hup.1105

Takamiya, A., Hirano, J., Ebuchi, Y., Ogino, S., Shimegi, K., Emura, H., . . . Mimura, M. (2017). High-dose antidepressants affect near-infrared spectroscopy signals: A retrospective study. *Neuroimage Clin, 14*, 648-655. doi:10.1016/j.nicl.2017.02.008

Takizawa, R., Fukuda, M., Kawasaki, S., Kasai, K., Mimura, M., Pu, S., . . . Joint Project for Psychiatric Application of Near-Infrared Spectroscopy, G. (2014). Neuroimaging-aided differential diagnosis of the depressive state. *Neuroimage, 85 Pt 1*, 498-507. doi:10.1016/j.neuroimage.2013.05.126

Tsuzuki, D., Jurcak, V., Singh, A. K., Okamoto, M., Watanabe, E., & Dan, I. (2007).

Virtual spatial registration of stand-alone fNIRS data to MNI space. *Neuroimage, 34*(4), 1506-1518. doi:10.1016/j.neuroimage.2006.10.043

Urata, J., Uchiyama, M., Iyo, M., Enomoto, T., Hayakawa, T., Tomiyama, M., . . . Okawa, M. (1996). Effects of a small dose of triazolam on P300 and resting EEG. *Psychopharmacology (Berl), 125*(2), 179-184.

Vermeeren, A. (2004). Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs, 18*(5), 297-328.

Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci, 11*(8), 589-599. doi:10.1038/nrn2868

Zezula, J., Cortes, R., Probst, A., & Palacios, J. M. (1988). Benzodiazepine receptor sites in the human brain: autoradiographic mapping. *Neuroscience, 25*(3), 771-795.

Table1. Number of words correctly generated and subjective sleepiness (mean ± SD)

Measure	Test Time	Mean (SD)		
		Placebo	Ramelteon 8mg	Triazolam 0.125 mg
Behavioral performance	Baseline	13.4 (5.0)	13.3 (4.1)	12.5 (3.9)
	1h	14.6 (5.5)	13.9 (4.4)	16.4 (4.4)
	4h	14.4 (5.1)	14.1 (4.5)	16.7 (4.2)
Stanford Sleepiness Scale	Baseline	1.6 (0.5)	1.9 (0.5)	1.8 (0.7)
	1h	2.1 (0.8)	2.8 (1.0)	2.8 (1.2)
	4h	2.3 (0.9)	2.8 (0.9)	2.9 (1.0)

Figure legend

Figure 1 Placement of NIRS shells

Figure 2 Positions of NIRS channels in prefrontal area according to the International 10-20 system

Figure 3 Oxy-Hb concentration change during the whole 150-s period (left) and averaged oxy-Hb concentration change during post-task period (right)

*$p<0.05$ (*post hoc* test; PLSD)