Table 3 The list of medication for geriatric depression

	GD + Aβ	GD-Aβ
Antidepressants		
Amitriptyline	1	1
Duloxetine	0	2
Escitalopram	0	2
Fluvoxamine	1	1
Mianserin	0	1
Mirtazapine	4	2
Paroxetine	1	4
Sertraline	2	4
Trazodone	0	7
Other drugs		
Aripiprazole	1	0
Levothyroxine sodium	0	1
Lithium carbonate	0	1
Olanzapine	0	2
Quatiapine	2	4
Risperidone	1	1
Sodium valproate	0	2
Yokukansan	2	0
Anti-dementia drugs		
Donepezil	2	3
Memantine	0	1

GD, geriatric depression; Aβ, beta-amyloid

Aβ in the frequencies of current histories of hypertension, hyperlipidemia, and diabetes mellitus, nor in the presence of lacunar infarction, severity of PVH, and severity of DSWMH (Table 2).

GD + Aβ showed higher average ± SD SUVR than GD-Aβ in the medial orbital frontal lobe (1.18 ± 0.11 versus 0.99 ± 0.07, $z = 4.29$, $p < 0.0001$, $r = 0.75$), temporal lobe (1.30 ± 0.17 versus 1.06 ± 0.07, $z = 4.55$, $p < 0.0001$, $r = 0.79$), anterior cingulate (1.21 ± 0.17 versus 0.91 ± 0.12, $z = 4.26$, $p < 0.0001$, $r = 0.74$), posterior cingulate (1.14 ± 0.13 versus 0.94 ± 0.09, $z = 4.18$, $p < 0.0001$, $r = 0.73$), parietal lobe (1.15 ± 0.15 versus 0.93 ± 0.13, $z = 3.70$, $p < 0.0001$, $r = 0.65$), and precuneus (1.35 ± 0.22 versus 1.00 ± 0.09, $z = 4.62$, $p < 0.0001$, $r = 0.81$).

Comparison between late-onset and early-onset depression

ROC curve analysis for the onset age of MDE showed best sensitivity (92.3%) and specificity (60.0%) with a cut-off value of 69 years old for Aβ-positive (AUC 0.773, 95%CI 0.630 to 0.916), and for the time from the onset of first MDE showed best sensitivity (92.3%) and specificity (75.0%) with a cut-off value of 3 years for Aβ-positive (AUC 0.854, 95%CI 0.746 to 0.961). Then we divided the GD group by the cut-off age between the late-onset GD group (onset age was 69 years or older) and early-onset GD group (onset age was younger than 69 years). There was no significant difference between the late-onset GD group and early-onset GD group in terms of gender (18 females and 2 males versus 11 females and 2 males, Fisher's exact test $p = 0.64$, Cramer's $V = 0.08$), mean ± SD age (77.2 ± 4.3 versus 76.0 ± 4.1, $z = -0.80$; $p = 0.64$, $r = -0.14$), mean ± SD z-score of entorhinal cortex (1.4 ± 0.8 versus 1.1 ± 0.6, $z = -1.09$; $p = 0.27$, $r = -0.20$), mean ± SD score of MMSE (23.3 ± 3.5 versus 24.3 ± 3.6, $z = 0.80$; $p = 0.42$, $r = 0.14$), GDS (7.0 ± 3.8 versus 6.9 ± 4.1, $z = 0.04$; $p = 0.96$, $r = 0.01$), CDR (0.6 ± 0.3 versus 0.5 ± 0.2, $z = -0.57$; $p = 0.57$, $r = -0.10$), and frequency of current MDE (45.0% versus 53.9%, Fisher's exact test $p = 0.83$, Cramer's $V = 0.09$), but the late-onset GD group had a significantly higher rate of Aβ-positive (60.0% versus 7.7%, Fisher's exact test $p = 0.004$, Cramer's $V = 0.52$) and higher mean ± SD SUVR (1.13 ± 0.15 versus 0.98 ± 0.12, $z = -2.89$; $p = 0.003$, $r = -0.50$) than the early-onset GD group (Table 4). There was no significant difference between the late-onset GD group and early-onset GD group in the frequencies of current histories of hypertension, hyperlipidemia, and diabetes mellitus, nor in the presence of lacunar infarction, severity of PVH, and severity of DSWMH (Table 4).

Discussion

Our study showed that the prevalence of beta-amyloid positivity of GD + Aβ (39.4%) was comparable to the reported 45–50% in MCI patients without GD (Fleisher *et al.*, 2011; Camus *et al.*, 2012; Johnson *et al.*, 2013). Since positive Aβ is a strong predictor of the conversion of MCI to AD (Doraiswamy *et al.*, 2012), it could be said that GD + Aβ, which is amyloid-associated depression, is a risk factor much like MCI, which was reported repeatedly in previous studies.

The most important finding from the present study was the difference in the onset age of first MDE between GD + Aβ and GD-Aβ. There have been few studies on the association between GD and Aβ by PET. An earlier study reported that there was no significant difference between cortical Aβ and the lifetime history of MDE, but previous studies on the association between amyloid and depression reported that geriatric depression had significantly higher SUVR than healthy elders (Butters *et al.*, 2008; Wu *et al.*, 2014). This difference might have been influenced by the number, age, and onset age of first MDE of the participants. To our knowledge, our study was the first to compare GD + Aβ with GD-Aβ. In our study, there

Table 4 Comparison between late-onset (onset age ≥69 years old) and early-onset (onset age <69 years old) geriatric depression in the frequency of beta-amyloid-positive

	Late-onset GD	Early-onset GD	*p* value
N (f/m)	20 (18/2)	13 (11/2)	0.64
Age (years), mean ± SD	77.2 ± 4.3	76.0 ± 4.1	0.42
Hypertension, *N* (%)	9 (45.0)	8 (61.5)	0.35
Hyperlipidemia, *N* (%)	8 (40.0)	4 (30.8)	0.59
Diabetes mellitus, *N* (%)	1 (5.0)	4 (30.8)	0.04
N of Aβ-positive (%)	12 (60.0)	1 (7.7)	0.004
SUVR, mean ± SD	1.13 ± 0.15	0.98 ± 0.12	0.003
z-score of entorhinal cortex, mean ± SD	1.4 ± 0.8	1.1 ± 0.6	0.27
Presence of lacunar infarction, *N* (%)	14 (82.4)	13 (100.0)	0.11
Fazekas scale, *N* (%)			
PVH			0.98
Grade 0, *N* (%)	3 (17.7)	2 (15.4)	
Grade I, *N* (%)	10 (58.8)	8 (61.5)	
Grade II, *N* (%)	4 (23.5)	3 (23.1)	
Grade III, *N* (%)	0 (0.0)	0 (0.0)	
DSWMH			0.06
Grade 1, *N* (%)	2 (11.8)	0 (0.0)	
Grade 2, *N* (%)	9 (52.9)	12 (92.3)	
Grade 3, *N* (%)	6 (35.3)	1 (7.7)	
Grade 4, *N* (%)	0 (0.0)	0 (0.0)	
MMSE, mean ± SD	23.3 ± 3.5	24.3 ± 3.6	0.42
GDS, mean ± SD	7.0 ± 3.8	6.9 ± 4.1	0.96
CDR, mean ± SD	0.6 ± 0.3	0.5 ± 0.2	0.57
Frequency of current MDE, *N* (%)	9 (45.0)	7 (53.9)	0.62

GD, geriatric depression; Aβ, beta-amyloid; SUVR, standard uptake value ratio; PVH, Periventricular hyperintensity; DSWMH, Deep and subcortical white matter hyperintensity; *MMSE*, Mini-Mental State Examination; *GDS*, Geriatric Depression Scale; *MDE*, major depressive episode

was no significant difference in the level of cognitive function and ADL and the severity of depression between GD + Aβ and GD-Aβ, but GD + Aβ patients were significantly older at onset of MDE and had a shorter interval since the onset of first MDE than GD-Aβ. If the course of amyloid pathology among our subjects was the same as that of AD, the accumulation of Aβ might reach a plateau 10–20 years before symptoms of dementia occur (Jack *et al.*, 2009). Recent study could not find an association between 18F-florbetapir SUVR and prior MDE, age at onset of MDE, or time since onset of first MDE, but found higher SUVR in precuneus and parietal lobe where post-mortem studies found accumulated Aβ in early AD (Wu *et al.*, 2014). From the viewpoint of cognitive function, it could be said that our subjects showed more progression in the course of AD. Our results that the onset of MDE among GD + Aβ patients was within this range and SUVR was significantly correlated with the onset age of MDE might suggest that the higher the amyloid burden, the more likely is the start of GD.

The basic mechanism of the association of depression with Aβ is uncertain, although many hypothetical mechanisms underlying the association between depression and AD have been proposed (Caraci *et al.*, 2010). One of these was the dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, about which it was reported that it occurs early in AD and that cognitive decline was significantly correlated with the cortisol level in non-depressed AD patients (Belanoff *et al.*, 2001). This association might contribute to the mechanism of depression caused by AD. Second, brain-derived neurotrophic factor (BDNF) genetic variation causing the impairment of BDNF signaling by the presence of polymorphism may increase the risk of developing depression in AD (Borroni *et al.*, 2009). Third, concerning the disturbance of neurotransmitters, it has been reported that Aβ reduced the number of monoamine neurons (Hochstrasser *et al.*, 2013), serotonin reuptake transporters, and 5-HT_{1A} and 5-HT_{2A} receptor binding sites, and that neuronal loss in the locus coeruleus was correlated with the duration of AD (Zarow *et al.*, 2003; Sierksma *et al.*, 2010; Chen *et al.*, 2011). Taken together, these findings of monoamine neurons and transmitters, which appear early in the course of AD, have been reported to cause amyloid-associated depression. Another explanation for the association between depression and AD was inflammation. From the aspect that a history of depression was a risk factor of AD, there have been many reports of chronic inflammation being a common pathophysiological mechanism of both depression and AD (Caraci *et al.*, 2010). A recent study using mice reported that the

injection of Aβ oligomers induced depressive-like behavior and cognitive impairment (Ledo *et al.*, 2012). These changes were triggered by an inflammatory response in the mouse brain, since levels of interleukin-1β and tumor necrosis factor-α were significantly elevated after injection of Aβ oligomers in comparison to control (Ledo *et al.*, 2012). These findings might suggest that elevated brain levels of Aβ oligomers were a factor that was tied to depression and cognitive impairment in AD.

We should acknowledge several methodological limitations in our study. First, the sample size was relatively small. Thus, the findings may not be relevant to other populations or groups. A study with a larger number of participants would likely be more meaningful. Second, there has been much evidence that not only late-onset but also early-onset MDE was a risk factor of dementia in later life. However, we could not say whether early-onset or late-onset MDE was a risk factor of subsequent dementia or not. Third, we did not have any follow-up data, and therefore we could not predict with any precision whether GD + Aβ would convert to AD in the near future. However, many previous studies have revealed that MCI patients with positive Aβ tended to convert to AD (Doraiswamy *et al.*, 2012).

In conclusion, we examined the role of Aβ in MDE among elderly by [^{18}F]florbetapir PET. Although the mechanism underlying the association between AD and depression is still unclear, the Aβ pathology might play an important role in the mechanism of GD (e.g. the higher amyloid burden, the more likely is the start of GD). In our results, the rate of Aβ positivity was higher among late-onset GD and onset-age was associated with SUVR, suggesting that later GD onset was more affected by Aβ pathology.

Conflict of interest

All authors have read the journal's policy and have the following statement. YO has received grants or speaker's honoraria from the Ministry of Health, Labor, and Welfare, the Ministry of Education, Culture, Sport, Science and Technology, Japanese government, Dainippon Sumitomo Pharma, GlaxoSmithKline, Janssen Pharmaceutical, Otsuka, Pfizer, Eli Lilly, Astellas, Yoshitomi, and Meiji within the past 3 years. HS has received speaker's honoraria from Pfizer and Eisai within the past 3 years. For the remaining authors none were declared, and there were no other relationships or activities that could appear to have influenced the submitted work.

Key points

- When using a cut-off value for [^{18}F]florbetapir PET (SUVR > 1.08), 13 of 33 (39.4%) patients with mild cognitive impairment and a history of geriatric depression (GD) and 6 of 22 (27.3%) healthy controls were beta-amyloid-positive.
- Compared to GD-beta-amyloid (Aβ), GD + Aβ had significantly older average age at onset of major depressive episode (MDE) (73.6 ± 7.1 versus 58.7 ± 17.8) and had shorter average time since the onset of first MDE (3.1 ± 5.2 years versus 18.1 ± 18.6 years), despite no significant differences in age, cognitive function, severity of depression and activity of daily living (ADL), and brain atrophy.
- Our results indicated that the higher the amyloid burden is, the more likely is the start of GD, and the later the onset of GD, the more beta-amyloid pathology affected its onset.

Acknowledgements

We thank Kazuyoshi Honjo, Koji Nagaya, Koji Kanaya, Masaya Suda, Megumi Takei, and Minoru Sakurai (Clinical Imaging Center for Healthcare, Nippon Medical School, Tokyo, Japan) for their assistance in performing the PET experiments and MRI scanning, and Yoshitaka Kawashima, Reiko Otaki, Yumiko Nozu, and Maho Araki for their assistance in performing the neuropsychiatric tests.

Financial disclosure

This study was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japanese government, by a grant of Strategic Research Foundation Grant-aided Project for Private Universities from the Ministry of Education, Culture, Sport, Science, and Technology, Japan (MEXT), and by a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Ministry of Health, Labor, and Welfare, Japanese government. The radiotracer was provided at no cost to the study by Avid Radiopharmaceuticals Inc.

Authorship

AT designed the study, wrote the protocol, performed examinations and statistical analysis of the data, and wrote the manuscript. TS performed examinations and statistical analysis. MH, TS, and YO designed the study. KI and SK collected imaging data and revised the manuscript draft. HS and YO assisted in data collection, infrastructure and revising the manuscript draft. All authors contributed to and have approved the final manuscript.

References

Belanoff JK, Gross K, Yager A, Schatzberg AF. 2001. Corticosteroids and cognition. *J Psychiatr Res* **35**: 127–145.

Borroni B, Archetti S, Costanzi C, *et al.* 2009. Role of BDNF Val66Met functional polymorphism in Alzheimer's disease-related depression. *Neurobiol Aging* **30**: 1406–1412.

Butters MA, Klunk WE, Mathis CA, *et al.* 2008. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. *Alzheimer Dis Assoc Disord* **22**: 261–268.

Byers AL, Yaffe K. 2011. Depression and risk of developing dementia. *Nat Rev Neurol* **7**: 323–331.

Camus V, Payoux P, Barre L, *et al.* 2012. Using PET with 18F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment. *Eur J Nucl Med Mol Imaging* **39**: 621–631.

Caraci F, Copani A, Nicoletti F, Drago F. 2010. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *Eur J Pharmacol* **626**: 64–71.

Chen KH, Reese EA, Kim HW, Rapoport SI, Rao JS. 2011. Disturbed neurotransmitter transporter expression in Alzheimer's disease brain. *J Alzheimer Dis* **26**: 755–766.

Doraiswamy PM, Sperling RA, Coleman RE, *et al.* 2012. Amyloid-beta assessed by Florbetapir F 18 PET and 18-months cognitive decline. *Neurology* **79**: 1636–1644.

Elobeid A, Soininen H, Alafuzoff I. 2012. Hyperphosphorylated tau in young and middle-aged subjects. *Acta Neuropathol* **123**: 97–104.

Fazekas F, Kleinert R, Offenbacher H, *et al.* 1991. The morphologic correlate of incidental punctate white matter hyperintensities on MR images. *AJNR Am J Neuroradiol* **12**: 915–921.

Fleisher AS, Chen K, Liu X. 2011. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol* **68**: 1404–1411.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.

Geerlings MI, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. 2008. History of depression, depressive symptoms, and medical temporal lobe atrophy and the risk of Alzheimer disease. *Neurology* **70**: 1258–1264.

Hirata Y, Matsuda H, Nemoto K, *et al.* 2005. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. *Neurosci Lett* **382**: 269–274.

Hochstrasser T, Hohsfield LA, Sperner-Unterweger B, Humpel C. 2013. β-Amyloid induced effects on cholinergic, serotonergic, and dopaminergic neurons is differentially counteracted by anti-inflammatory drugs. *J Neurosci Res* **91**: 83–94.

Jack CR Jr, Lowe VJ, Weigand SD, *et al.* 2009. Serial PiB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological event in Alzheimer's disease. *Brain* **132**: 1355–1365.

Johnson KA, Sperling RA, Gidicsin CM, *et al.* 2013. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. *Alzheimers Dement* **9**: S72–S83.

Kramberger MG, Jelic V, Kåreholt I, *et al.* 2012. Cerebrospinal fluid Alzheimer markers in depressed elderly subjects with and without Alzheimer's disease. *Dement Geriatr Cogn Dis Extra* **2**: 48–56.

Kumar A, Kepe V, Barrio JR, *et al.* 2011. Protein binding in patients with late-life depression. *Arch Gen Psychiatry* **68**: 1143–1150.

Ledo JH, Azevedo EP, Clarke JR, *et al.* 2012. Amyloid-beta oligomers link depressive-like behavior and cognitive deficits in mice. *Mol Psychiatry* **18**: 1053–1054.

Madsen K, Hasselbalch BJ, Frederiksen KS, *et al.* 2008. Lack of association between prior depressive episodes and cerebral [11C]PiB binding. *Neurobiol Aging* **33**: 2334–2342.

Morris JC. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**: 2412–2414.

Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. 2006. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* **63**: 530–538.

Petersen RC, Morris JC. 2005. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* **62**: 1160–1163.

Pomara N, Bruno D, Sarreal AS, *et al.* 2012. Lower CSF amyloid beta peptides and higher F2-isoprostanes in cognitively intact elderly individuals with major depressive disorder. *Am J Psychiatry* **169**: 523–530.

Rapp MA, Schnaider-Beeri M, Purohit DP, *et al.* 2008. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. *Am J Geriatr Psychiatry* **16**: 168–174.

Sheikh JI, Yesavage JA. 1986. Geriatric Depression Scale (GDS) Recent evidence and development of a shorter version. In Clinical Gerontology: A Guide to Assessment and Intervention, Brink TL (ed.). The Haworth Press: New York; 165–173.

Sierksma AS, van den Hove DL, Steinbusch HW, Prickaerts J. 2010. Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? *Eur J Pharmacol* **626**: 72–82.

Starkstein SE, Dragovic M, Jorge R, Brockman S, Robinson RG. 2011. Diagnostic criteria for depression in Alzheimer disease: a study of symptom patterns using latent class analysis. *Am J Geriatr Psychiatry* **19**: 551–558.

Sun X, Steffens DC, Au R, *et al.* 2008. Amyloid-associated depression: a prodromal depression of Alzheimer disease? *Arch Gen Psychiatry* **65**: 542–550.

Tateno A, Sakayori T, Kawashima Y, *et al.* 2014. Comparison of imaging biomarkers for Alzheimer's disease: amyloid imaging with florbetapir F18 positron emission tomography and MRI voxel-based analysis for entorhinal cortex atrophy. *Int J Geriatr Psychiatry*. DOI: 10.1002/gps.4173 [Epub ahead of print].

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, *et al.* 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**: 273–289.

Wu KY, Hsiao IT, Chen CS, *et al.* 2014. Increased brain amyloid deposition in patients with a lifetime history of major depression: evidenced on 18F-florbetapir (AV-45/Amyvid) positron emission tomography. *Eur J Nucl Med Mol Imaging* **41**: 714–722.

Zarow C, Lyness SA, Mortimer JA, Chui HC. 2003. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch Neurol* **60**: 337–341.

General Hospital Psychiatry 37 (2015) 97.e7–97.e9

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Case Report

A case of Alzheimer's disease following mild traumatic brain injury

Amane Tateno, M.D., Ph.D., Takeshi Sakayori, M.D., Yuichi Takizawa, M.D., Ken Yamamoto, M.D., Kaoru Minagawa, M.D., Yoshiro Okubo, M.D., Ph.D. *

Department of Neuropsychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8602, Japan

ARTICLE INFO

Article history:
Received 23 June 2014
Revised 29 September 2014
Accepted 30 September 2014

Keywords:
Alzheimer's disease
Traumatic brain injury
Mild cognitive impairment
Beta-amyloid
Positron emission tomography

ABSTRACT

Objective: To report a case of Alzheimer's disease (AD) following mild traumatic brain injury (TBI).
Method: Case report.
Results: We report the time course of AD following mild TBI with evidence of AD pathology. A patient complained of minor memory disturbance 6 months after TBI and was diagnosed with mild cognitive impairment 1.5 years after TBI, and she was finally diagnosed as probable AD 4 years after TBI. Amyloid PET revealed brain accumulation of beta-amyloid at a pathological AD level.
Conclusion: Our case well illustrated how TBI can accelerate the AD process. Clinicians should carefully follow up patients with persistent cognitive impairment after TBI.

1. Introduction

Although recent studies reported that patients with traumatic brain injury (TBI) showed significantly more beta-amyloid accumulation than controls [1,2], the detailed role of TBI in the progression of Alzheimer's disease (AD) pathology has not been clearly understood. Case reports indicated that TBI induced rapid deterioration of cognition resembling AD [3,4], but those reports did not provide information about beta-amyloid pathology. It is difficult to know the cognitive function before TBI, since it is usually impossible to evaluate the subject before TBI. Thus, it is important to evaluate the changes of clinical symptoms in the stage after TBI as early as possible.

In the present article, we describe a previously healthy patient who developed AD after mild TBI in order to discuss the possible effect of TBI on the progress of AD, providing detailed information from mild cognitive impairment (MCI) to moderate AD.

2. Case report

The patient was a 48-year-old woman, living alone, who had been a full-time office worker of a publishing company since graduating from university. She had no history of TBI and no family history of dementia. At age 43, she was struck by a car while walking. Rescue staff reported that her Glasgow Coma Scale score was 15/15. She had experienced a brief period of loss of consciousness, for a few minutes, after the accident. She was brought to the emergency room because of injuries to her right shoulder and head. A skull X-ray and brain MRI were normal. She was diagnosed with a minor concussion and did not require hospital admission. She returned to work a few days after the accident without deterioration of cognitive function and had no trouble with activity of daily living (ADL). Six months later, she and her sister became aware of her minor memory disturbance. However, she did not want to go to the hospital, as she had no trouble with work.

One and a half years after TBI, she visited our psychiatric clinic because of memory disturbance exacerbation. There was no evidence of physical abnormalities, mood disorder, psychosis or drug abuse. Her sister said that she had no problems with memory and ADL prior to TBI. The Mini-Mental State Examination (MMSE) [5] score was 27/30, and Alzheimer's Disease Assessment Scale (ADAS) cognitive component Japanese version [6] score was 13 (ADAS range of 0–70 and AD cutoff score of 10). Wechsler Adult Intelligence Scale (3rd edition) (WAIS-III) [7] showed total-IQ 78, verbal-IQ 88 and performance-IQ 72. Neurobehavioral cognitive status examination (COGNISTAT) [8] showed severe memory disturbance. MRI showed slight enlargement of lateral cerebral ventricles. Thus, she was diagnosed with MCI as proposed by Petersen [9]. Amyloid positron emission tomography (PET) with [^{18}F] florbetapir showed that beta-amyloid accumulation was at a pathological AD level [10]. The apolipoprotein E (APOE) phenotype was E4/4.

Three years after TBI, she was still at work, but she became aware of difficulties in working due to memory and cognitive dysfunction. MMSE score was 23/30, ADAS score was 7 and COGNISTAT showed severe impairment of memory and orientation and moderate impairment of construction. The second PET scan showed the same results as the first one (Fig. 1).

* Corresponding author at: 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8602, Japan. Tel.: +81-3-3822-2131; fax: +81-3-5814-6287.
E-mail address: okubo-y@nms.ac.jp (Y. Okubo).

http://dx.doi.org/10.1016/j.genhosppsych.2014.09.016
0163-8343/

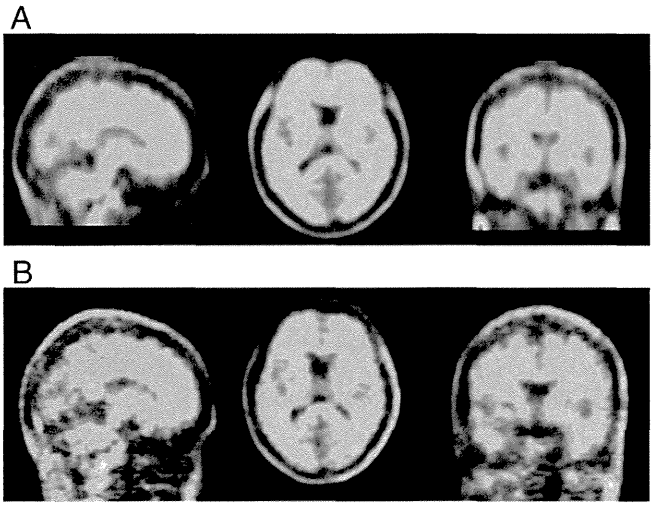

Fig. 1. Amyloid PET images 1.5 years (A) and 3 years (B) after brain injury. (A) 1.5 years after brain injury. SUVR=1.27; (B) 3 years after brain injury. SUVR=1.25. SUVR, standard uptake value ratios.

Table 1
Time-dependent changes by neuropsychological tests and brain imaging

Time since accident	2 years	3 years	5 years
WAIS-III			
Total IQ	78		52
Verbal Q	88		63
Performance IQ	72		47
MMSE	27	23	17
ADAS-cog	13	7	19
COGNISTAT			
Orientation	8	5	1
Attention	10	8	10
Comprehension	10	7	7
Repetition	11	11	10
Naming	10	10	7
Construction	8	6	5
Memory	4	5	4
Calculation	10	8	4
Similarities	10	10	9
Judgment	10	8	9
Amyloid PET			
SUVR	1.27	1.25	

ADAS-cog: Alzheimer's disease Assessment Scale cognitive component.

Four years after the TBI, she sometimes became confused when she was told to do several things at once. Her colleagues recognized that she had problems with memory and cognition. We judged that her social and occupational function had deteriorated to the same degree as AD. Then a diagnosis of probable AD [11] was made, and she was treated with donepezil, but she did not continue taking the medication, and her cognitive function deteriorated further.

She retired from her job 5 years after TBI. MMSE score was 17/30, ADAS score was 19 and COGNISTAT showed severe impairment of memory, orientation, construction and calculation. WAIS-III showed total-IQ 52, verbal-IQ 63 and performance-IQ 47. Compared to the prior MRI, brain MRI showed enlarged lateral cerebral ventricles. Time-dependent changes by neuropsychological examinations revealed rapid deteriorations (Table 1).

3. Discussion

We present a case of AD in a relatively young woman after she experienced mild TBI. The clinical symptoms of this case were similar to those of typical AD, which might start with "memory disturbance," then "orientation," "construction" and "similarities" deteriorating in the MCI stage of AD [12]. Clinical findings indicated that MCI appeared after TBI and that the onset of AD might have been affected by TBI. The accumulation of beta-amyloid might reach a plateau 10–20 years before symptoms of dementia appear [13], and in our case, the onset of AD was within this range (i.e., 4 years). Therefore, we cannot make the determination of whether TBI induced AD or the patient had already been suffering from early-onset AD at the time of the accident. As for the interaction between TBI and normal aging, Smith et al. hypothesized that TBI may cause an initial spike in AD pathology, which might then trigger accelerated accumulation of AD pathology, leading to earlier onset of AD [14]. The rapid worsening of her cognition after TBI and onset of AD at a younger-than-expected age might be well explained by this hypothesis. APOE E4 also may affect the pathway of beta-amyloid, as it has been reported that the presence of APOE ε4 allele was associated with increased beta-amyloid deposition and poor outcome after TBI [15]. Although there has been no information regarding how fast TBI hastens the accumulation of beta-amyloid, the unusually rapid cognitive deterioration of our patient might indicate that the impact of TBI at least accelerated the progression of AD.

In conclusion, to our knowledge, this is the first case report of the careful tracking of the time-course of AD following mild TBI before its actual onset with evidence of AD pathology. Our case well illustrated how TBI accelerates the process of AD, even if it is very mild. Clinicians should carefully follow up patients with mild TBI as they would for those with severe TBI if they complain of persistent cognitive impairment. Annual cognitive examination (e.g., MMSE and COGNISTAT) are recommended for the detection of AD at an earlier stage and particular if the deterioration of cognitive function is progressive. In addition, studies with larger numbers of participants should be conducted to better understand the effect of TBI on the course of AD.

Acknowledgment

This study was partly supported by a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Ministry of Health, Labor and Welfare, Japanese government.

References

[1] Kawai N, Kawanishi M, Kudomi N, Maeda Y, Yamamoto Y, Nishiyama Y, et al. Detection of brain amyloid beta deposition in patients with neuropsychological impairment after traumatic brain injury: PET evaluation using Pittsburgh Compound-B. Brain Inj 2013;27:1026–31.
[2] Hong YT, Veenith T, Dewar D, Outtrim JG, Mani V, Williams C, et al. Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. JAMA Neurol 2014;71:23–31.
[3] Nandoe RD, Scheltens P, Eikelenboom P. Head trauma and Alzheimer's disease. J Alzheimers Dis 2002;4:303–8.
[4] Kemp S, Goulding P, Spencer J, Mitchell AJ. Unusually rapid and severe cognitive deterioration after mild traumatic brain injury. Brain Inj 2005;19:1269–76.
[5] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[6] Homma A, Fukuzawa K, Tsukada Y. Development of a Japanese version of Alzheimer's disease assessment scale (ADAS). Jpn J Geriatr Psychiatry 1992;3:647–55.
[7] Wechsler D. Wechsler Adult Intelligence Scale-III. San Antonio: The Psychological Corporation; 1997.
[8] Kiernan RJ, Mueller J, Langston JW, Van Dyke C. The neurobehavioral cognitive status examination: a brief but differentiated approach to cognitive assessment. Ann Intern Med 1987;107:481–5.
[9] Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. JAMA Neurol 2005;62:1160–3.
[10] Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura R, Ayutyanont N, et al. Using positron emission tomography and florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol 2011;68:1404–11.
[11] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.

[12] Matsuda O, Saito M. Multiple cognitive deficits in patients during the mild cognitive impairment stage of Alzheimer's disease: how are cognitive domains other than episodic memory impaired? Int Psychogeriatr 2009;21:970–6.
[13] Jack Jr CR, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PiB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain 2009;132:1355–65.
[14] Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nat Rev Neurol 2013;9:211–21.
[15] Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci Biobehav Rev 2012;36:1376–81.

International Journal of Neuropsychopharmacology (2014), **17**, 697–703. © CINP 2014
doi:10.1017/S1461145713001612

ARTICLE

In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [^{18}F]FE-PE2I

WooChan Kim[1], Amane Tateno[1], Ryosuke Arakawa[1,2], Takeshi Sakayori[1], Yumiko Ikeda[3], Hidenori Suzuki[3] and Yoshiro Okubo[1]

[1] *Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan*
[2] *Department of Adult Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan*
[3] *Department of Pharmacology, Nippon Medical School, Tokyo, Japan*

Abstract

Modafinil, a wake-promoting drug used to treat narcolepsy, is a dopamine transporter inhibitor and is said to have very low abuse liability; this, however, is still up for debate. We conducted a dopamine transporter (DAT) occupancy study with modafinil (200 or 300 mg) in ten healthy volunteers using positron emission tomography (PET) with [^{18}F]FE-PE2I, a new PET radioligand with high affinity and selectivity for the dopamine transporter, to characterize its relation to abuse liability. Mean striatal DAT occupancies were 51.4% at 200 mg and 56.9% at 300 mg. There was a significant correlation between occupancy and plasma concentration, indicating dose dependency of DAT inhibition by modafinil in the striatum, and especially in the nucleus accumbens. This study showed that DAT occupancy by modafinil was close to that of methylphenidate, indicating that modafinil may be near the same level as methylphenidate in relation to abuse liability in terms of dopaminergic transmission.

Received 10 September 2013; Reviewed 27 October 2013; Revised 22 November 2013; Accepted 1 December 2013; First published online 21 January 2014

Key words: Abuse liability, dopamine transporter, [^{18}F]FE-PE2I, modafinil, positron emission tomography.

Introduction

Modafinil, which was first marketed nearly 20 years ago in Europe as an agent to offset excessive sleepiness associated with narcolepsy, was approved by the Food and Drug Administration (FDA) in 1998 and by the Pharmaceuticals and Medical Devices Agency (PMDA, Japan) in 2007. Modafinil may enhance cognition and is used off-label for the treatment of cognitive dysfunction in some psychiatric disorders (i.e. schizophrenia, attention-deficit/hyperactivity disorder [ADHD]) (Minzenberg and Carter, 2008). Modafinil is increasingly being diverted for nonmedical use by healthy individuals with the expectation of improving cognitive performance (Maher, 2008; Lynch et al., 2011). Although it is reported that modafinil has very low abuse liability (low reinforcing effects) in non-drug-abusing individuals (Jasinski and Kovacević-Ristanović, 2000; Myrick et al., 2004), the Physicians' Desk Reference (2006) cautions that it can produce psychoactive and euphoric effects typical of central nervous system (CNS) stimulant drugs (Physicians' Desk Reference, 2006), and there is debate about its potential for abuse (Kruszewski and Klotz, 2007). Amphetamine and methylphenidate are well-known typical stimulant drugs. Amphetamine acts by enhancing dopamine release and blocking dopamine transporter (DAT), resulting in dopamine increase, whereas methylphenidate acts mainly through blocking DAT at the synaptic clefts. Modafinil is known to have a blocking effect on DAT (IC_{50}=6.4 μM, Madras et al., 2006), thus increasing dopamine, in rhesus monkeys (Andersen et al., 2010). Although similar mechanisms are applicable to humans (Greenhill, 2006; Volkow et al., 2009b), the exact mechanism of the action of modafinil is not well known.

DAT plays a crucial role in the regulation of dopamine concentration in the synaptic cleft by dopamine reuptake. In the past, a study of modafinil use and DAT imaging with [^{11}C]cocaine was performed (Volkow et al., 2009b). However, [^{11}C]cocaine has various problems such as poor selectivity. Recently, a new ligand, N-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (PE2I), with high affinity and good selectivity for DAT, was developed (Emond et al., 1997; Halldin et al., 2003). In human positron emission tomography (PET) studies, [^{11}C]PE2I showed a high specific-to-nonspecific ratio (Halldin et al., 2003; Jucaite et al., 2006; Hirvonen et al., 2008; Seki et al., 2010). Further, a fluoroethyl analog of

Address for correspondence: Y. Okubo, Department of Neuropsychiatry, Nippon Medical School, 113-8602, Sendagi 1-1-5, Bunkyo-ku, Tokyo, Japan.
Tel.: +81-3-3822-2131 *Fax*: +81-3-5814-6280
Email: okubo-y@nms.ac.jp

PE2I, ^{18}F-(E)-N-(3-iodoprop-2E-enyl)-2β-carbofluoroethoxy-3β-(4-methylphenyl)nortropane ([^{18}F]FE-PE2I) (inhibition constant, 12 nM), has been developed (Varrone et al., 2009). The quantification of DAT with [^{18}F]FE-PE2I is less biased than that with [^{11}C]PE2I (Sasaki et al., 2012).

Volkow et al. reported that DAT occupancy was 53.8% in the caudate, 47.2% in the putamen, and 39.3% in the nucleus accumbens (NAcc) (modafinil at 200 or 400 mg, single) measured by [^{11}C]cocaine (Volkow et al., 2009b). Because cocaine binds other monoamine transporters besides DAT (Ritz et al., 1987), the data in Volkow's study may be biased. On the other hand, [^{18}F]FE-PE2I has good selectivity for DAT in comparison to norepinephrine transporter (NET) and serotonin transporter (SERT). *In vitro*, FE-PE2I showed ~10000 higher selectivity for DAT (Ki=12 nM) as compared with SERT (Ki>1 μM). In addition, the Ki value at rodent NET was not determined, as the NET inhibitor maprotiline at a concentration of 10 μM did not show any effect in autographic and PET studies (Varrone et al., 2009). In this study, we evaluated DAT occupancy of modafinil using PET with [^{18}F]FE-PE2I in healthy human subjects to assess its more precise pharmacokinetics.

Materials and methods

Subjects

Ten healthy volunteers (age range, 20–39 years; mean age±S.D., 34±1.6 years at 200 mg; 3 males, 2 females; 29.2±3.8 years at 300 mg; 2 males, 3 females) were enrolled in the study. We recruited ten subjects, and none were excluded due to drug usage. None had a history of present or past psychiatric, neurological or somatic disorders, or alcohol-related problems. All subjects were non-smokers and stopped caffeine intake 48 h prior to PET scan. The study was approved by the review board of Nippon Medical School Hospital, Japan. After thorough explanation of the study, written informed consent was obtained from all participants.

Study design

The experiments were designed as an open-label protocol. Two PET scans were performed, separated by an interval of more than 1 wk. The first PET scan was done prior to, and the second scan 2.5 h after taking modafinil. We planned the second scan to aim at the T_{max} of modafinil, which is 2.5 h, where T_{max} is the time after administration of a drug when the maximum plasma concentration is reached. Each subject underwent PET scan with one dose of modafinil, either 200 or 300 mg.

PET procedures

PET scans were carried out with an Eminence SET-3000GCT-X (Shimadzu Corp., Japan) scanner to measure regional brain radioactivity. A head fixation device was used during the scans. A 10-min transmission scan was done to correct for attenuation. Dynamic PET scan was performed for 60 min after intravenous bolus injection of [^{18}F]FE-PE2I. Injected radioactivity was 185.5–191.1 (mean±S.D.; 188.8±1.90) MBq at baseline condition and 179.0–190.8 (185.5±3.5) MBq at drug condition. Specific radioactivity was 100.1–253.2 (174.8±63.9) GBq/μmol at baseline condition and 95.6–398.4 (195.0±77.1) GBq/μmol at drug condition.

MRI procedures

Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Intera 1.5 T Achieve Nova (Philips Medical Systems, Best, Netherlands). T1-weighted MR images were obtained at 1-mm slices.

Plasma concentration of modafinil

The plasma concentration of modafinil was measured. Venous blood samples were taken 2.5 h after administration of modafinil (just before the second PET scan), collected in tubes containing EDTA-2Na, and centrifuged at 3000 rpm for 10 min at 4 °C. Separated plasma samples were stored at −80 °C until analysis. The plasma concentration of modafinil was measured by a validated method using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a target lower quantification limit of 0.1 μg/ml (Mitsubishi Chemical Medience Corp., Japan).

Data analysis

MR images were coregistered to summated PET images with the mutual information algorithm using PMOD (version 3.3; PMOD Technologies Ltd, Switzerland). Regions of interest (ROIs) were defined for the striatum (caudate, putamen, and NAcc) and cerebellar cortex. ROIs were drawn manually on overlaid summated PET and coregistered MR images of each subject. ROIs of caudate and putamen were drawn on horizontal slices, and that of NAcc was drawn on coronal slices, while also referring to the brain atlas.

The average values of right and left ROIs were used for the analysis. Group discussions were held between researchers and clinical technologists to confirm the scan quality. In fact, one participant (Subject 6) was re-scanned at baseline after a sufficient interval due to head motion. Data were not subjected to motion correction. DAT binding was quantified using a simplified reference tissue model (Lammertsma and Hume, 1996; Ito et al., 2001). The cerebellum was used as reference region because of its negligible DAT density (Sasaki et al., 2012).

These models allow the estimation of binding potential (BP_{ND}), which was defined as $f_{ND} \times B_{max}/K_d$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{max} is the transporter density, and K_d is the dissociation constant (Innis et al., 2007).

Table 1. Subject Characteristics, Binding Potential, and Dopamine Transporter Occupancy

Subject Number	Gender	Age, yr	Dose, mg	Plasma Concentration of MF, μg/mL	BP_{ND} at striatum		DAT occupancy, %			
					Baseline	Modafinil	Striatum	Caudate	Putamen	Nucleus Accumbens
1	Male	25	300	0.5	3.58	3.00	16.3	17.6	13.0	26.2
2	Female	34	300	12.4	3.61	1.00	72.3	76.5	70.0	74.2
3	Male	34	300	8.4	3.96	1.54	61.0	67.0	60.2	54.8
4	Female	24	300	10.5	3.87	1.14	70.5	75.1	69.8	68.0
5	Female	29	300	9.0	3.27	1.17	64.2	64.7	64.7	65.3
Mean (SD)		29.2 (4.3)		8.2 (3.1)	3.66 (0.20)	1.57 (0.57)	56.9 (16.2)	60.2 (17.0)	55.5 (17.0)	57.7 (13.8)
6	Male	36	200	4.0	2.73	1.16	57.6	60.1	56.7	61.1
7	Male	31	200	5.0	3.22	1.41	56.2	59.0	56.3	45.2
8	Male	35	200	5.4	2.87	1.51	47.4	47.8	47.1	48.8
9	Female	35	200	5.0	2.65	1.62	39.1	44.3	38.7	33.0
10	Female	33	200	5.4	3.01	1.29	57.1	59.0	53.2	69.5
Mean (SD)		34 (1.8)		5.0 (0.4)	2.90 (0.17)	1.40 (0.14)	51.4 (6.6)	54.5 (6.7)	51.2 (6.6)	51.5 (11.0)

BP_{ND}; Binding Potential; DAT, Dopamine Transporter; MF, Modafinil; SD, Standard Deviation.

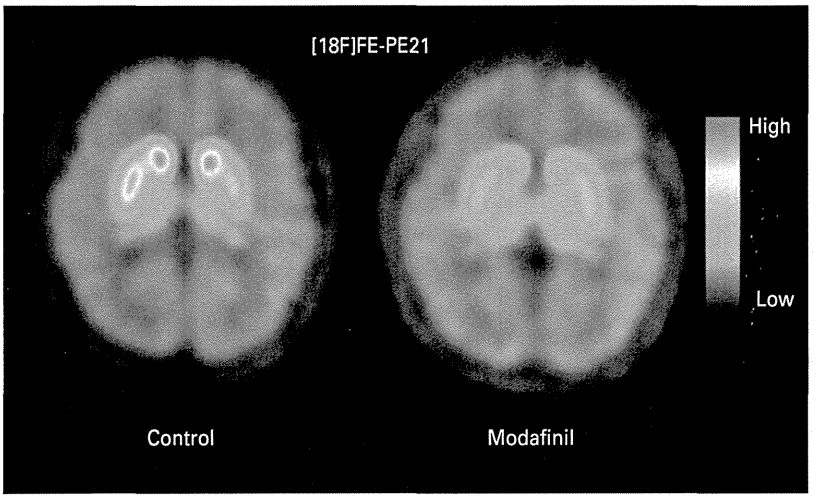

Fig. 1. Uptake of [^{18}F]FE-PE2I in a section of the striatum normalized to cerebellar uptake at baseline (left) and 2.5 h after the administration of modafinil (right) in subject 2.

DAT occupancy by modafinil in the striatum was calculated by the following equation:

$$\text{Occupancy}\,(\%) = (BP_{base} - BP_{drug})/BP_{base} \times 100,$$

where Occupancy is DAT occupancy, BP_{base} is BP_{ND} under drug-free condition, and BP_{drug} is BP_{ND} under drug-taking condition.

The relationship between dose or plasma concentration and DAT occupancy by modafinil is shown by the following equation:

$$\text{Occupancy}\,(\%) = D/(ED_{50} + D) \times 100 \text{ or } C/(EC_{50} + C) \times 100.$$

D is the dose of modafinil, C is the concentration of modafinil, ED_{50} is the dose required to achieve 50% occupancy, and EC_{50} is the plasma concentration required to achieve 50% occupancy (Arakawa et al., 2010; Tateno et al., 2013). Correlations between dose or plasma concentration of modafinil and DAT occupancy in the striatum were examined.

Results

Figure 1 depicts the uptake of [^{18}F]FE-PE2I at baseline and post-dose scans for subject 2, whose data were typical of those of the other subjects. Subject characteristics, binding potentials, striatal DAT occupancies, and plasma concentrations are shown in Table 1. Subject 1, who had a very low plasma concentration, showed low DAT occupancy. Mean striatal occupancies were 51.4±6.6% at 200 mg and 56.9±16.2% at 300 mg. Plasma concentrations were 5.0±0.4 μg/ml at 200 mg and 8.2±3.1 μg/ml at 300 mg. Correlations between dose or plasma concentration of modafinil and DAT occupancy in the striatum

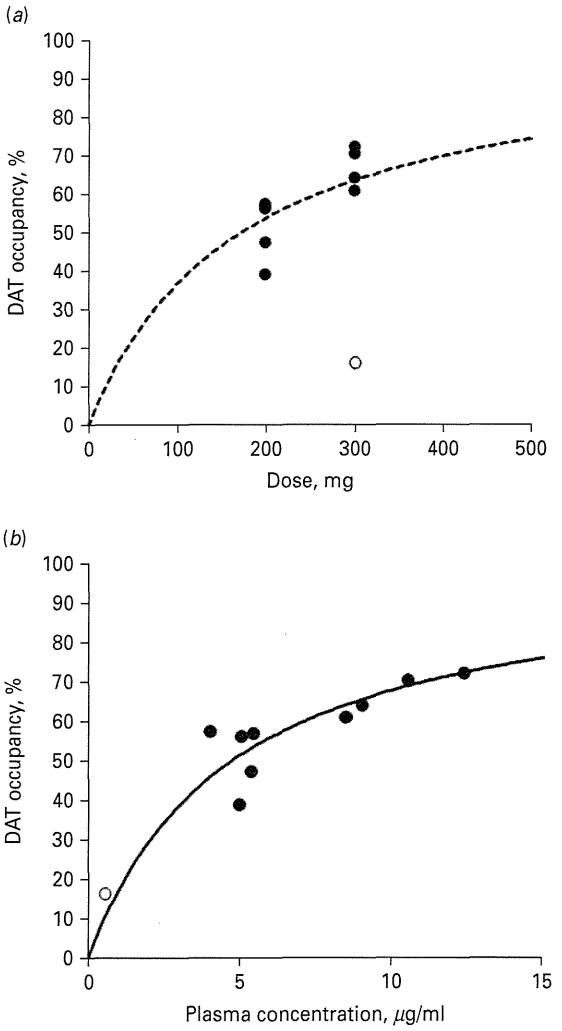

Fig. 2. (*a*) DAT occupancy in the striatum with [^{18}F]FE-PE2I and one dose of modafinil. Dotted line is fitted while excluding one sample for subject 1 (open circle) that showed extremely low occupancy. ED_{50} was 170.9 mg (r=0.72) except for one sample showing extremely low occupancy. (*b*) DAT occupancy in the striatum with [^{18}F]FE-PE2I and plasma concentration of modafinil. EC_{50} was 4.7 μg/ml (r=0.92). DAT=dopamine transporter.

are shown in Fig. 2*a*, *b*. There was a significant correlation between DAT occupancy and plasma concentration. The EC_{50} value was 4.7 μg/ml (r=0.92). Furthermore, when we viewed the three striatal regions separately, EC_{50} was 4.1 μg/ml (r=0.93) in the caudate, 4.9 μg/ml (r=0.93) in the putamen, and 4.7 μg/ml (r=0.70) in the NAcc. With the exception of the single data set of subject 1, showing extremely low plasma concentration and DAT occupancy, DAT occupancy correlated well with the modafinil dose, and the ED_{50} value was 170.9 mg (r=0.72).

Discussion

DAT occupancy was 51.4% (39.1–57.6%) at 200 mg and 56.9% (16.3–72.3%) at 300 mg in the striatum after single modafinil administration. Mean occupancy at 300 mg was 67.0±4.3% when we excluded the data of subject 1, who showed an irregularly low value of 16.3%. DAT occupancy at 300 mg was much higher than that at 200 mg except for that single sample with extremely low DAT occupancy. Furthermore, the correlation between DAT occupancy and the plasma concentration of modafinil was significant. As mentioned above, we confirmed that DAT occupancy by modafinil increased in a dose-dependent manner.

This is the first study of pharmacological PET with [^{18}F]FE-PE2I. Most PET studies of DAT in the past were performed with ([^{11}C]or[^{18}F])CFT (Wong et al., 1993; Laakso et al., 1998), [^{11}C]altropane (Madras et al., 1998), [^{11}C]cocaine (Fowler et al., 1989), [^{11}C]β-CIT (Farde et al., 1994), and other radioligands. Those radioligands have a rather low affinity, which is reflected by a low uptake in the striatum (Fowler et al., 1989). Additionally, they are not selective for DAT, having relatively high affinity for SERT and NET (Ritz et al., 1987). The pharmacological properties of PE2I have demonstrated that it has high affinity for DAT (Ki=17 nM) and is one of the most selective DAT ligands (Emond et al., 2008). [^{11}C]PE2I and [^{18}F]FE-PE2I have been utilized for PET studies (Seki et al., 2010; Varrone et al., 2011, 2012; Odano et al., 2012; Sasaki et al., 2012). Varrone et al. confirmed *in vivo* that [^{18}F]FE-PE2I, developed from [^{11}C]PE2I, has high affinity and selectivity for DAT and shows faster kinetics and more favorable metabolism than [^{11}C]PE2I, with less production of radiometabolites that could interfere with the quantification (Varrone et al., 2011). Quantification of DAT with [^{18}F]FE-PE2I should be able to produce less biased results compared to studies using [^{11}C]PE2I (Sasaki et al., 2012).

Only one PET study of modafinil was performed in the past. Volkow et al. reported DAT occupancy of 53.8% in the caudate, 47.2% in the putamen, and 39.3% in the NAcc (modafinil at 200 or 400 mg, single) as measured by [^{11}C]cocaine (Volkow et al., 2009b). In addition to obtaining almost the same occupancy in the caudate and putamen, we could calculate ED_{50} and confirm dose dependency in the striatum, and especially in the NAcc. There might be two reasons for this result. First, although the value of BP_{ND} by [^{11}C]cocaine is <1, that by [^{18}F]FE-PE2I is 2–4 at baseline. Second, because SERT exists, as does DAT, in the striatum, the binding of [^{11}C]cocaine does not precisely reflect the quantity of DAT (Staley et al., 1995; Gurevich and Joyce, 1996; Varnas et al., 2004). Based on the above-mentioned data, DAT occupancy as measured by [^{18}F]FE-PE2I in our study could possibly be the most precise figure to date.

Modafinil is increasingly being diverted for nonmedical use by healthy individuals with the expectation that it will improve cognitive performance (Lynch et al., 2011), although the degree of abuse liability of modafinil is controversial and there is debate surrounding its

potential for abuse (Kruszewski and Klotz, 2007). There are some arguments regarding the relationship between abuse liability and dopamine increase by blocking dopamine transporters (Greenhill, 2006; Volkow et al., 2009a). The dopamine-enhancing effects of modafinil in the striatum may help explain reports of its abuse, since this pharmacological effect is considered crucial for drug reinforcement (Myrick et al., 2004). Therefore, it is important to measure occupancy in the striatum (especially NAcc) for evaluating the degree of abuse.

Modafinil is used in doses ranging from 200 to 600 mg (Schwartz et al., 2005), and the dosage in our and Volkow's studies was within the clinical dosage range. Spencer et al. also reported that the DAT occupancy of armodafinil (optical isomer of modafinil) was 40.4% at 100 mg and 65.2% at 250 mg in the striatum measured by [^{11}C]altropane (Spencer et al., 2010). From these reports, we can say with confidence that the DAT occupancy of modafinil (or armodafinil) at a clinical dose is approximately 40–70%. Additionally, the occupancies of methylphenidate and bupropion, representative of DAT inhibitors, have been measured by PET with various radioligands. As for bupropion, Meyer et al. reported its DAT occupancy (300 mg p.o.) as less than 22% in the striatum with [^{11}C]RTI32 (Meyer et al., 2002), Learned-Coughlin et al. reported a DAT occupancy of bupropion sustained-release (SR) (150 mg p.o.) of 26% in the striatum with [^{11}C]βCIT-FE (Learned-Coughlin et al., 2003), and Volkow et al. also reported a DAT occupancy of radafaxine ((+)-isomer of hydroxybupropion, 40 mg p.o) of 20% in the striatum with [^{11}C]cocaine (Volkow et al., 2005). As for methylphenidate, Volkow et al. reported a DAT occupancy of 12–74% in the striatum with [^{11}C]cocaine at clinically relevant doses of 5–60 mg (Volkow et al., 1998). Spencer et al. reported a DAT occupancy of dexmethylphenidate of 48–67% in the striatum with [^{11}C] altropane at clinically relevant doses of 20–40 mg (Spencer et al., 2012). In general, it is said that abuse of methylphenidate is most common (Kollins et al., 2001; Maher, 2008; Bruggisser et al., 2012; Sembower et al., 2013), and a low risk of abuse by bupropion has been reported (Chevassus et al., 2012). The degree of abuse risk seems to correspond with DAT occupancy, considering the data of these two stimulants. Our study showed that DAT occupancy of modafinil was near that of methylphenidate at a clinical dose. So, we suggest that modafinil is at a level similar to methylphenidate with respect to abuse liability; modafinil may have not a little risk of abuse. Stimulant abuse is a serious public health problem that affects almost every community, and this also points to some potential adverse consequences for the modafinil user (Greenhill, 2006). This study suggests that the measurement of DAT occupancy by PET with [^{18}F]FE-PE2I may be able to evaluate the risk of abuse by stimulants.

There are several limitations to the current study, urging caution in how these results are interpreted. First, in our study one sample showed an extremely low plasma concentration. This result may be ascribable to a personal diversity of absorption, distribution, metabolism and excretion (Robertson and Hellriegel, 2003). However, this subject also showed low DAT occupancy, and the data, in total, had no effect on our interpretation of this study. Second, in this study we measured DAT occupancy alone. Madras et al. reported that modafinil is a dopamine (IC_{50}=6.4 μM) serotonin (IC_{50}=35.6 μM) norepinephrine (IC_{50}>500 μM) reuptake inhibitor (Madras et al., 2006). Abuse is considered to have a relation with dopamine, but we should investigate the occupancy of SERT/NET to learn the properties of modafinil. Third, we measured drug concentrations in plasma only before PET-scan in this study. As the drug concentrations in plasma can change rapidly in time periods close to T_{max}, it might have been suitable to measure drug concentrations directly before and after the PET-scan for the purpose of assessing their more precise pharmacokinetics. Fourth, because we did not perform any respective motion corrections in the process analyzing the data, although we did confirm the scan quality, head motion may have had some influence on the data. Fifth, we performed PET-scan once only for a single administration. The relationship between chronic dosing and occupancy is unclear. There is a difference in abuse liability between short- and long-acting oral methylphenidate (Spencer et al., 2006). Therefore, we might be able to evaluate abuse liability better by measuring the time-course of DAT occupancy. Finally, this study was conducted with both genders as subjects. Modafinil is considered to have a gender effect mainly during the clearance process (Wong et al., 1999). In this regard, we must evaluate the abuse risk related to plasma concentration and/or DAT occupancy under strict consideration of the gender difference.

In conclusion, this is the first study of pharmacological PET by [^{18}F]FE-PE2I. Modafinil blocked DAT dose-dependently in the human brain with similar numerical values of earlier literature, but our data suggest that the present results with [^{18}F]FE-PE2I are more precise. There was a significant correlation between DAT occupancy and plasma concentration of modafinil, and DAT occupancy by modafinil was at almost the same level as that of methylphenidate, so we suggest that modafinil may resemble methylphenidate in terms of abuse liability. By this study, we found with considerable certainty the possibility that the DAT occupancy of stimulants may reflect abuse liability at a clinical dose.

Acknowledgments

The authors thank Dr Kiichi Ishiwata (Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan) and Dr Shinji Kageyama (Mitsubishi Chemical Medience Corp., Tokyo, Japan), Mr Koji Nagaya, Mr Koji Kanaya, Mr Masaya Suda,

Ms Megumi Takei, Mr Kazuyoshi Honjo, and Mr Minoru Sakurai (Clinical Imaging Center for Healthcare, Nippon Medical School, Tokyo, Japan) for their assistance with this study.

Statement of Interest

This work was partially supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology (MEXT, Japan). Dr Suzuki has received speaker's honoraria from Pfizer and Eisai within the past 3 years. Dr Okubo has received grants or speaker's honoraria from Dainippon Sumitomo Pharma, GlaxoSmithKline, Janssen Pharmaceutical, Otsuka, Pfizer, Eli Lilly, Astellas, Yoshitomi and Meiji within the past 3 years. For the remaining authors none were declared.

References

Andersen ML, Kessler E, Murnane KS, McClung JC, Tufik S, Howell LL (2010) Dopamine transporter-related effects of modafinil in rhesus monkeys. Psychopharmacology (Berl) 210:439–448.

Arakawa R, Okumura M, Ito H, Takano A, Takahashi H, Takano H, Maeda J, Okubo Y, Suhara T (2010) Positron emission tomography measurement of dopamine D_2 receptor occupancy in the pituitary and cerebral cortex: relation to antipsychotic-induced hyperprolactinemia. J Clin Psychiatry 71:1131–1137.

Bruggisser M, Bodmer M, Liechti ME (2012) [Methylphenidate misuse]. Praxis (Bern 1994) 101:299–305.

Chevassus H, Farret A, Gagnol JP, Ponçon CA, Costa F, Roux C, Galtier F, Petit P (2012) Psychological and physiological effects of bupropion compared to methylphenidate after prolonged administration in healthy volunteers (NCT00285155). Eur J Clin Pharmacol 69:779–787.

Emond P, Garreau L, Chalon S, Boazi M, Caillet M, Bricard J, Frangin Y, Mauclaire L, Besnard JC, Guilloteau D (1997) Synthesis and ligand binding of nortropane derivatives: N-substituted 2beta-carbomethoxy-3beta-(4′-iodophenyl)nortropane and N-(3-iodoprop-(2E)-enyl)-2beta-carbomethoxy-3beta-(3′, 4′-disubstituted phenyl)nortropane. New high-affinity and selective compounds for the dopamine transporter. J Med Chem 40:1366–1372.

Emond P, Guilloteau D, Chalon S (2008) PE2I: a radiopharmaceutical for *in vivo* exploration of the dopamine transporter. CNS Neurosci Ther 14:47–64.

Farde L, Halldin C, Muller L, Suhara T, Karlsson P, Hall H (1994) PET study of [11C]beta-CIT binding to monoamine transporters in the monkey and human brain. Synapse 16:93–103.

Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, Macgregor RR, Hitzemann R, Logan J, Bendriem B, Gatley SJ, Christman D (1989) Mapping cocaine binding sites in human and baboon brain *in vivo*. Synapse 4:371–377.

Greenhill LL (2006) The science of stimulant abuse. Pediatr Ann 35:552–556.

Gurevich EV, Joyce JN (1996) Comparison of [3H]paroxetine and [3H]cyanoimipramine for quantitative measurement of serotonin transporter sites in human brain. Neuropsychopharmacology 14:309–323.

Halldin C, Erixon-Lindroth N, Pauli S, Chou YH, Okubo Y, Karlsson P, Lundkvist C, Olsson H, Guilloteau D, Emond P, Farde L (2003) [(11)C]PE2I: a highly selective radioligand for PET examination of the dopamine transporter in monkey and human brain. Eur J Nucl Med Mol Imaging 30:1220–1230.

Hirvonen J, Johansson J, Teräs M, Oikonen V, Lumme V, Virsu P, Roivainen A, Någren K, Halldin C, Farde L, Hietala J (2008) Measurement of striatal and extrastriatal dopamine transporter binding with high-resolution PET and [11C]PE2I: quantitative modeling and test-retest reproducibility. J Cereb Blood Flow Metab 28:1059–1069.

Innis RB et al. (2007) Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539.

Ito H, Sudo Y, Suhara T, Okubo Y, Halldin C, Farde L (2001) Error analysis for quantification of [(11)C]FLB 457 binding to extrastriatal D(2) dopamine receptors in the human brain. Neuroimage 13:531–539.

Jasinski DR, Kovacević-Ristanović R (2000) Evaluation of the abuse liability of modafinil and other drugs for excessive daytime sleepiness associated with narcolepsy. Clin Neuropharmacol 23:149–156.

Jucaite A, Odano I, Olsson H, Pauli S, Halldin C, Farde L (2006) Quantitative analyses of regional [11C]PE2I binding to the dopamine transporter in the human brain: a PET study. Eur J Nucl Med Mol Imaging 33:657–668.

Kollins SH, MacDonald EK, Rush CR (2001) Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. Pharmacol Biochem Behav 68:611–627.

Kruszewski SP, Klotz SG (2007) Modafinil: mischaracterization. J Clin Psychiatry 68:970–971; author reply 971–972.

Laakso A, Bergman J, Haaparanta M, Vilkman H, Solin O, Hietala J (1998) [18F]CFT [(18F)WIN 35428], a radioligand to study the dopamine transporter with PET: characterization in human subjects. Synapse 28:244–250.

Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158.

Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B (2003) *In vivo* activity of bupropion at the human dopamine transporter as measured by positron emission tomography. Biol Psychiatry 54:800–805.

Lynch G, Palmer LC, Gall CM (2011) The likelihood of cognitive enhancement. Pharmacol Biochem Behav 99:116–129.

Madras BK, Meltzer PC, Liang AY, Elmaleh DR, Babich J, Fischman AJ (1998) Altropane, a SPECT or PET imaging probe for dopamine neurons: I. Dopamine transporter binding in primate brain. Synapse 29:93–104.

Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, Johnson R, Livni E, Spencer TJ, Bonab AA, Miller GM, Fischman AJ (2006) Modafinil occupies dopamine and norepinephrine transporters *in vivo* and modulates the transporters and trace amine activity *in vitro*. J Pharmacol Exp Ther 319:561–569.

Maher B (2008) Poll results: look who's doping. Nature 452:674–675.

Meyer JH, Goulding VS, Wilson AA, Hussey D, Christensen BK, Houle S (2002) Bupropion occupancy of the dopamine transporter is low during clinical treatment. Psychopharmacology (Berl) 163:102–105.

Minzenberg MJ, Carter CS (2008) Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33:1477–1502.

Myrick H, Malcolm R, Taylor B, LaRowe S (2004) Modafinil: preclinical, clinical, and post-marketing surveillance–a review of abuse liability issues. Ann Clin Psychiatry 16:101–109.

Odano I, Varrone A, Savic I, Ciumas C, Karlsson P, Jucaite A, Halldin C, Farde L (2012) Quantitative PET analyses of regional [11C]PE2I binding to the dopamine transporter–application to juvenile myoclonic epilepsy. Neuroimage 59:3582–3593.

PDR Network (2006) Provigil (modafinil). In: Chesanow N, Fleming H (eds) Physicians' desk reference, 60th edn, pp1002–1007. New Jersey: Thompson PDR.

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223.

Robertson P Jr., Hellriegel ET (2003) Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 42:123–137.

Sasaki T, Ito H, Kimura Y, Arakawa R, Takano H, Seki C, Kodaka F, Fujie S, Takahata K, Nogami T, Suzuki M, Fujiwara H, Takahashi H, Nakao R, Fukumura T, Varrone A, Halldin C, Nishikawa T, Suhara T (2012) Quantification of dopamine transporter in human brain using PET with 18F-FE-PE2I. J Nucl Med 53:1065–1073.

Schwartz JR, Feldman NT, Bogan RK (2005) Dose effects of modafinil in sustaining wakefulness in narcolepsy patients with residual evening sleepiness. J Neuropsychiatry Clin Neurosci 17:405–412.

Seki C, Ito H, Ichimiya T, Arakawa R, Ikoma Y, Shidahara M, Maeda J, Takano A, Takahashi H, Kimura Y, Suzuki K, Kanno I, Suhara T (2010) Quantitative analysis of dopamine transporters in human brain using [11C]PE2I and positron emission tomography: evaluation of reference tissue models. Ann Nucl Med 24:249–260.

Sembower MA, Ertischek MD, Buchholtz C, Dasgupta N, Schnoll SH (2013) Surveillance of diversion and nonmedical use of extended-release prescription amphetamine and oral methylphenidate in the United States. J Addict Dis 32:26–38.

Spencer TJ, Biederman J, Ciccone PE, Madras BK, Dougherty DD, Bonab AA, Livni E, Parasrampuria DA, Fischman AJ (2006) PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 163:387–395.

Spencer TJ, Madras BK, Bonab AA, Dougherty DD, Clarke A, Mirto T, Martin J, Fischman AJ (2010) A positron emission tomography study examining the dopaminergic activity of armodafinil in adults using [^{11}C]altropane and [^{11}C]raclopride. Biol Psychiatry 68:964–970.

Spencer TJ, Bonab AA, Dougherty DD, Mirto T, Martin J, Clarke A, Fischman AJ (2012) Understanding the central pharmacokinetics of spheroidal oral drug absorption system (SODAS) dexmethylphenidate: a positron emission tomography study of dopamine transporter receptor occupancy measured with C-11 altropane. J Clin Psychiatry 73:346–352.

Staley JK, Boja JW, Carroll FI, Seltzman HH, Wyrick CD, Lewin AH, Abraham P, Mash DC (1995) Mapping dopamine transporters in the human brain with novel selective cocaine analog [125I]RTI-121. Synapse 21:364–372.

Tateno A, Arakawa R, Okumura M, Fukuta H, Honjo K, Ishihara K, Nakamura H, Kumita S, Okubo Y (2013) Striatal and extrastriatal dopamine D2 receptor occupancy by a novel antipsychotic, Blonanserin: a PET study with [11C]Raclopride and [11C]FLB 457 in schizophrenia. J Clin Psychopharmacol 33:162–169.

Varnas K, Halldin C, Hall H (2004) Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum Brain Mapp 22:246–260.

Varrone A, Steiger C, Schou M, Takano A, Finnema SJ, Guilloteau D, Gulyas B, Halldin C (2009) *In vitro* autoradiography and *in vivo* evaluation in cynomolgus monkey of [18F] FE-PE2I, a new dopamine transporter PET radioligand. Synapse 63:871–880.

Varrone A, Tóth M, Steiger C, Takano A, Guilloteau D, Ichise M, Gulyás B, Halldin C (2011) Kinetic analysis and quantification of the dopamine transporter in the nonhuman primate brain with 11C-PE2I and 18F-FE-PE2I. J Nucl Med 52:132–139.

Varrone A, Gulyás B, Takano A, Stabin MG, Jonsson C, Halldin C (2012) Simplified quantification and whole-body distribution of [18F]FE-PE2I in nonhuman primates: prediction for human studies. Nucl Med Biol 39:295–303.

Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, Hitzemann R, Pappas N (1998) Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 155:1325–1331.

Volkow ND, Wang GJ, Fowler JS, Learned-Coughlin S, Yang J, Logan J, Schlyer D, Gatley JS, Wong C, Zhu W, Pappas N, Schueller M, Jayne M, Carter P, Warner D, Ding YS, Shea C, Xu Y (2005) The slow and long-lasting blockade of dopamine transporters in human brain induced by the new antidepressant drug radafaxine predict poor reinforcing effects. Biol Psychiatry 57:640–646.

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009a) Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56 (Suppl. 1):3–8.

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang GJ, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K (2009b) Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301:1148–1154.

Wong DF, Yung B, Dannals RF, Shaya EK, Ravert HT, Chen CA, Chan B, Folio T, Scheffel U, Ricaurte GA, Neumeyer JL, Wagner HN Jr., Kuhar MJ (1993) *In vivo* imaging of baboon and human dopamine transporters by positron emission tomography using [11C]WIN 35428. Synapse 15:130–142.

Wong YN, King SP, Simcoe D, Gorman S, Laughton W, McCormick GC, Grebow P (1999) Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 39:281–288.

Psychopharmacology (2014) 231:3217–3228
DOI 10.1007/s00213-014-3499-0

ORIGINAL INVESTIGATION

Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens

Takuya Funayama · Yumiko Ikeda · Amane Tateno · Hidehiko Takahashi · Yoshiro Okubo · Haruhisa Fukayama · Hidenori Suzuki

Received: 14 September 2013 / Accepted: 8 February 2014 / Published online: 28 February 2014

Abstract
Rationale The nucleus accumbens (NAc) works as a key brain structure of the reward system, in which reward-related neural activity is well correlated with dopamine release from mesolimbic dopaminergic neurons.
Objectives Since modafinil can modulate dopaminergic transmission through re-uptake inhibition of dopamine, we investigated whether modafinil affects the reward-related brain activity in the NAc in healthy subjects.
Methods Twenty healthy participants underwent two series of functional magnetic resonance imaging while performing monetary incentive delay task in which they were cued to anticipate and respond to a rapidly presented target to gain or avoid losing varying amounts of money, under modafinil or placebo condition. Blood oxygenation-level dependent (BOLD) activation signals during gain and loss anticipations were analyzed in the NAc as an a priori region of interest as well as the whole brain.
Results Modafinil significantly changed subjective feelings toward positive ones. The activation of BOLD signals was observed during gain anticipation under the placebo and modafinil conditions in the left and bilateral NAc, respectively. The modafinil condition showed significantly higher BOLD signal change at the highest gain (+¥500) cue compared to the placebo condition.
Conclusions The present study showed that modafinil affects reward processing in the NAc in healthy subjects through enhancing more positive anticipation, and it may provide a basis for the use of this drug for treating anhedonia observed in psychiatric disorders.

Keywords Mesolimbic dopaminergic neuron · fMRI · Modafinil · Monetary incentive delay task · Nucleus accumbens · Reward

T. Funayama · H. Fukayama
Anesthesiology and Clinical Physiology, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8549, Japan

Y. Ikeda · H. Suzuki (✉)
Department of Pharmacology, Graduate School of Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan
e-mail: hsuzuki@nms.ac.jp

A. Tateno · Y. Okubo
Department of Neuropsychiatry, Graduate School of Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan

H. Takahashi
Department of Psychiatry, Graduate School of Medicine, Kyoto University, 54 Shogoin-kawaharamachi, Sakyo-ku, Kyoto 606-8507, Japan

Introduction

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide) is a psychostimulant approved for the treatment of excessive somnolence in narcolepsy worldwide, and may also be used off-label as a cognitive enhancer to treat cognitive dysfunction in patients with psychiatric disorders such as schizophrenia and major depression (Minzenberg and Carter 2008). Pharmacological effects of modafinil on cognitive functions have been examined in humans (Minzenberg and Carter 2008), although there is conflicting literature on these effects (Lynch et al. 2011). In healthy humans, working memory and sustained attention are reportedly enhanced by modafinil (Minzenberg and Carter 2008; Müller et al. 2004; Randall et al. 2005). In patients with schizophrenia, who show cognitive impairment as a core symptom, modafinil improves cognitive functions such as working memory, problem solving, control, and flexibility, as well as emotion, suggesting that

modafinil acts on the prefrontal and limbic brain areas (Scoriels et al. 2011, 2013; Turner et al. 2004). Therefore, modafinil seems to affect specific cognitions dependent on psychological states of subjects rather than having widespread effects evenly across the brain through its arousal effect (Lynch et al. 2011; Minzenberg and Carter 2008). Modafinil exerts its effects on a number of neurotransmitter systems. Administration of modafinil causes significantly elevated levels of extracellular dopamine, noradrenaline, serotonin, glutamate, and histamine as well as decreased extracellular GABA in various brain regions, although the effects on dopamine and noradrenaline appear to be primary, and serotonin, glutamate, histamine, GABA, and orexin may be secondary to catecholamine (Minzenberg and Carter 2008). In animal studies, blockade of dopamine receptors (Qu et al. 2008) or dopamine transporter knockout (Wisor et al. 2001) abolishes or blunts the arousal effects of modafinil. In addition, modafinil has been shown to have reinforcing effects in addictive drug-experienced rhesus monkeys (Andersen et al. 2010) and rats (Gold and Balster 1996), increase locomotor activity (Zolkowska et al. 2009), and improve working memory (Piérard et al. 2007) through the interaction with dopamine transporters (see Scoriels et al. 2013 for review). Modafinil reportedly has rewarding properties through binding dopamine receptors and dopamine transporters in the prefrontal cortex, the caudate putamen, and the nucleus accumbens (NAc; Nguyen et al. 2011). In a positron emission tomography (PET) study in nonhuman primates, it was reported that modafinil occupies substantial DAT sites in the striatum (Madras et al. 2006). A human PET study also showed that modafinil at a therapeutic dose decreases [^{11}C]cocaine binding potential in the NAc, indicating that modafinil occupies dopamine transporters (Volkow et al. 2009). Collectively, modafinil enhances dopamine neurotransmission by at least partly inhibiting dopamine transporters (Madras et al. 2006; Minzenberg and Carter 2008).

Midbrain dopaminergic neurons are well known for their crucial roles in reward processing (Bromberg-Martin et al. 2010; Haber and Knutson 2010; Schultz 1997). Reward delivery or reward-predicting cue activates dopaminergic neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA; Bromberg-Martin et al. 2010; Haber and Knutson 2010; Schultz 1997), which then send their information to the dorsal and ventral striatum and prefrontal cortex. The NAc, a part of the ventral striatum, works as a key brain structure of reward processing (Bromberg-Martin et al. 2010; Chau et al. 2004; Haber and Knutson 2010; Knutson and Greer 2008; Peters and Büchel 2011; Schultz 1997). The NAc receives input from the medial and orbital prefrontal cortex, amygdale, and hippocampus, as well as the VTA, and projects to the ventral pallidum, VTA, SN, the bed nucleus of stria terminalis, and the lateral hypothalamus (Bromberg-Martin et al. 2010; Haber and Knutson 2010; Peters and Büchel 2011). In human studies using PET or functional MRI (fMRI), exposure to both primary (pleasant tastes and sound) and secondary (monetary gain) rewards increases ventral striatum activation (Haber and Knutson 2010). Further, reward-related neural activity in the ventral striatum/NAc is well correlated with dopamine release in the ventral striatum (Buckholtz et al. 2010; Schott et al. 2008). Abnormality of the reward circuitry is observed in patients with psychiatric disorders, including substance use disorders, schizophrenia, depression, and pathological gambling (Chau et al. 2004; Reuter et al. 2005; Russo and Nestler 2013), who also show dysfunction of mesolimbic dopaminergic systems (Chau et al. 2004).

Modafinil at therapeutic doses binds to the dopamine transporters (Madras et al. 2006; Zolkowska et al. 2009) and inhibits dopamine reuptake, resulting in significant dopamine release in the NAc (Volkow et al. 2009). Given that reward-related neural activity in the ventral striatum/NAc is well correlated with dopamine release in the ventral striatum (Buckholtz et al. 2010; Schott et al. 2008), modafinil could also modulate the reward system by at least enhancing dopaminergic transmission in humans. Actually, armodafinil is reported to improve negative symptoms such as anhedonia caused by dysfunction of the reward system in patients with schizophrenia (Bobo et al. 2011). The monetary incentive delay (MID) task is designed to elicit neural responses to monetary incentive anticipation (Knutson et al. 2001). The MID task with fMRI allows us to separately visualize brain activity in response to incentive anticipation. Previous imaging studies showed that NAc activation clearly increased in proportion to the magnitude of the anticipated monetary reward (Knutson et al. 2001; Yacubian et al. 2006). In the present study, we therefore adopted the MID task to examine the effect of modafinil on reward processing in the NAc in healthy subjects.

Materials and methods

Participants

Twenty physically and psychiatrically healthy volunteers over 20 years of age (12 males and 8 non-pregnant females; mean age, 29.90 years) participated in the study. Participants did not suffer from diseases such as hypertension, hepatic disorder, and renal dysfunction and had taken no medication such as contraceptives, vasopressor, monoamine oxidase inhibitor, warfarin, or phenobarbital for at least 2 weeks prior to the experiment, and they had no history of psychiatric disorders, cardiac disorders, epilepsy, or allergy to modafinil. The baseline mood and subjective states of the participants were assessed and the participants were excluded according to criteria as described below in the "Subjective ratings" section.

They did not have any contraindications to fMRI including cardiac pacemaker, mechanical heart valve, metal implants, potential pregnancy, tattoo, or claustrophobia. For assessment of baseline mood and subjective state, the participants underwent various psychological tests: Beck Depression Inventory (BDI; Beck et al. 1996; Kojima and Furukawa 2003), Epworth Sleepiness Scale (ESS; Johns 1991; Takegami et al. 2009), and State–Trait Anxiety Inventory (STAI; Hidano et al. 2000). These tests consisted of 21, 8, and 40 question items rated by 4-point scales, respectively. We selected subjects whose scores were below set criteria (BDI< 10, ESS<9, STAI-state<41, and STAI-trait<44). Data of participants whose head movements were excessive (more than 2 mm of translation or 2 degrees of rotation) during fMRI acquisition were excluded. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971). All subjects provided written informed consent before the experiments, and the present study was approved by the ethics committee of Nippon Medical School (approval number 223019).

Experimental design

A randomized single-blind placebo-controlled within-subjects cross-over design was applied. Each participant came to the imaging center for two series separated by a 2-week wash-out period. Modafinil (200 mg as a Modiodal 100-mg tablet formula, Alfresa Pharma, Japan; Minzenberg et al. 2011) or placebo was administered orally with water in the first series, and the second compound (modafinil or placebo) was administered in the second series of the study. The order of drug administration was randomly allocated with equal probability. Medication was administered 2.5 h prior to the start of the fMRI scan. Timing of the scan was based on pharmacokinetic data indicating that the 200-mg dose of modafinil reaches the peak plasma level at 2.5 h after oral administration (Robertson and Hellriegel 2003). The participants took part in the fMRI scan during the MID task as described below.

The task was presented on a personal computer using E-prime (version 2.0; Psychology Software Tools, USA) and viewed by the participants on a monitor at the foot of the scanner bed via mirrors mounted on the head coil. We recorded their behavioral responses using an MRI-compatible keypad and calculated their accuracy and reaction times with E-prime.

Subjective ratings

Before, 2 h (just before MRI scanning) after the drug administration in each series, transient subjective emotional states were also evaluated with Profile of Mood States (POMS; McNair et al. 1992; Yokoyama et al. 1990), Hamilton Depression Scale (HAM-D; Nakane and Williams 2003; Williams et al. 1988) and Hamilton Anxiety Scale (HAM-A; Inada 2010; Shear et al. 2001), and visual analogue scales (VAS for feeling; Norris 1971). A questionnaire of POMS consists of 65 adjectives rated by the participants on a 5-point scale. HAM-D and HAM-A included 21 and 14 question items, respectively. A researcher asked participants these questions and scored answers on a 3- or 5-point scale. VAS for feeling involved 10-cm lines with opposing feeling and mood adjectives at each end, and included 16 dimensions (Norris 1971). The measures used in this study were as follows: 1—alert–drowsy, 2—calm–excited, 3—strong–feeble, 4—muzzy–clear-headed, 5—well-coordinated–clumsy, 6—lethargic–energetic, 7—contented–discontented, 8—troubled–tranquil, 9—mentally slow–quick-witted, 10—tense–relaxed, 11—attentive–dreamy, 12—incompetent–proficient, 13—happy–sad, 14—antagonistic–amicable, 15—interested–bored, and 16—withdrawn–gregarious. The items were divided into the following four domains of effects: (a) mental awareness (items 1, 4, 9, and 11); (b) physical energy (items 3, 5, 6, and 12); (c) tranquility (items 2, 7, 8, and 10); and (d) sociability (items 13, 14, 15, and 16). The position of each mark was measured by ruler to the nearest mm. Items 1, 3, 5, 8, 10, 11, 13, and 15 were measured right-to-left and the others left-to-right (Norris 1971). Following the scanning, the participants rated on 10-cm VAS scales how much effort they put in when they saw each of the cues during the task (VAS for effort, Stoy et al. 2011) for assessing their subjective eagerness to achieve monetary incentives.

Statistical analyses of behavioral data and psychological measures

Values were expressed as median (interquartile range). The Wilcoxon signed-rank test was used to compare values in POMS, HAM-D, HAM-A, VAS for feeling, VAS for effort, hit rate, and reaction time during a series of the fMRI study between the placebo and modafinil treatments. Values of $p<0.05$ were considered to indicate statistical significance.

Monetary incentive delay task

Participants performed a slightly modified MID task (Knutson et al. 2008; Saji et al. 2013) to examine neural responses to monetary anticipation. Before entering the scanner, participants received a verbal description of the task and completed a 6-min practice version. This practice task minimized later learning effects and provided an estimate of mean reaction time for individually standardizing the task difficulty among all participants. Participants were informed that they would receive a gift voucher according to the amount of money they could earn by the end of the second series. Participants' monetary gain depended on their performance in a simple reaction time task at the end of each trial, which required

pressing a button upon the brief presentation of a visual target. Prior to executing the task, a photograph of cash was shown to the participants via the monitor in the scanner.

The MID task was run twice, making a total of 180 trials (Fig. 1). During each trial, participants saw one of nine geometric figures (cue) for 2,000 ms, which indicated that they could either gain or avoid losing different amounts of money (¥0, ¥20, ¥100, or ¥500) if they pressed the response button during the target presentation. Participants were instructed to respond as fast as possible. A cue signaled the potential reward (number of total signals presented in two sessions, $n=72$; denoted by circles), potential punishment ($n=72$; denoted by squares), or no response requirement ($n=36$; denoted by triangles). Reward cues (circles) consisted of four signals with the possibility of gaining ¥0 ($n=18$; no lines), ¥20 ($n=18$; one horizontal line), ¥100 ($n=18$; two horizontal lines), or ¥500 ($n=18$; three horizontal lines). Similarly, punishment cues (squares) were further divided into four signals with the possibility of losing ¥0 ($n=18$; no lines), ¥20 ($n=18$; one horizontal line), ¥100 ($n=18$; two horizontal lines), or ¥500 ($n=18$; three horizontal lines). No response trials ($n=36$; triangles) indicated that the subject should not respond during that trial and instead should wait until the appearance of the cue signaling the next trial. Trial types were pseudo-randomly ordered within each session. Between cues and target, an x-shaped fixation cross was inserted for a variable anticipation delay period (2,000–2,500 ms). Then a solid white target square appeared for a variable length of time (160–470 ms; target) urging the participants to press a button. Feedback (1,900 ms) following the disappearance of the second delay (1,130–1,940 ms) notified the participant how much money they had gained or lost during the preceding trial and the cumulative amount of money they had earned by that time point during the session. Due to the application of an adaptive algorithm for target duration, task difficulty was standardized to a hit rate of approximately 66 % for all participants.

MRI data acquisition

Imaging was performed with Intera Achieva 1.5 T Nova (Phillips Electronics, The Netherlands). For the acquisition of high-resolution T1-weighted anatomical images, the following parameters were used: repetition time (TR)=9.3 ms, echo time (TE)=4.6 ms, flip angle=8°, field of view (FOV)=250 mm, matrix=256×256, slice thickness=1.2 mm, number of slices=160. Functional images were acquired with the following parameters: TR=2,000 ms, TE=40 ms, flip angle=90°, FOV=256 mm, matrix=64×64. A total of 740 functional images were acquired from each participant with a T2*-weighted gradient-echo echo-planer imaging sequence sensitive to blood oxygenation level-dependent (BOLD) contrast. Whole brain coverage was obtained with 5-mm slice thickness and 28 axial slices.

fMRI data analysis

The analyses focused on changes in BOLD activation occurring during the anticipatory period and were conducted with SPM8 (Wellcome Department of Imaging Neuroscience, UK) running with MATLAB (Mathworks, USA). The anatomical T1 image and the functional images were manually reoriented to the anterior commissure–posterior commissure line. Slice-time correction was performed to adjust for time differences due to multi-slice imaging acquisition. To correct for between-

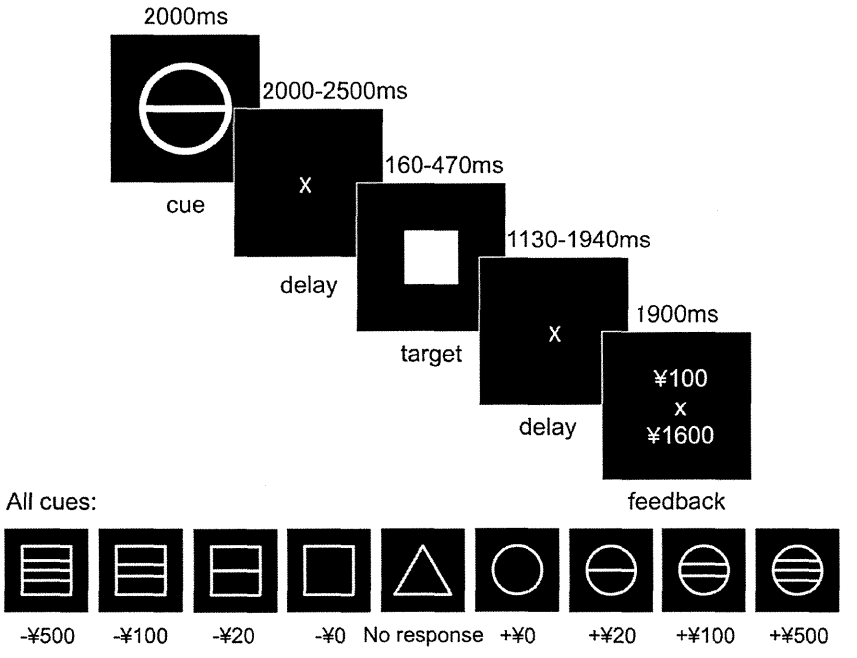

Fig. 1 Task structure for representative trial in the monetary incentive delay task. The procedure is described in the text. All cues in the task are shown as follows: *no line square* ¥0 loss, *square with one horizontal line* ¥20 loss, *square with two horizontal lines* ¥100 loss, *square with three horizontal lines* ¥500 loss, *no line circle* ¥0 gain, *circle with one horizontal line* ¥20 gain, *circle with two horizontal lines* ¥100 gain, *circle with three horizontal lines* ¥500 gain, *triangle* no response

scan movements, the functional images were realigned to the first image of the session and again realigned to the mean image created after the first realignment. The individual anatomical T1 image was then co-registered to the mean functional image. The transformed anatomical image was then segmented to create spatial normalization parameters that were applied to functional images in the next normalization step. The functional images were spatially normalized into the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans were resampled at a resolution of 2×2×2 mm. The functional images were spatially smoothed with an isotropic Gaussian kernel (full width at half maximum of 8 mm) to increase the signal-to-noise ratio. For subject-level statistical analyses, the functional images were analyzed using the general linear model. Hemodynamic responses to each stimulus were modeled with a δ function convolved with a synthetic hemodynamic response function time-locked to the onset time of delay following the cue and feedback. Low frequency noise was removed by applying a high-pass filter (cutoff period, 128 s) to the fMRI time-series data of each voxel. The statistical parametric map for each contrast, (a) gain anticipation (+¥20, +¥100, and +¥500>+¥0) and (b) loss anticipation (−¥20, −¥100, and −¥500>−¥0) of the *t* statistic, was calculated on a voxel×voxel basis.

For group-level analyses, the one-sample *t* test was performed to determine group-level activation for each effect. Then, for group comparisons, paired *t* test was performed to assess the difference between the placebo and modafinil administrations. The contrast images obtained from subject-level statistical analyses were entered into paired *t* test analyses. All results on activation in the whole brain were reported at $p<0.001$ uncorrected with a minimum cluster size of 63 voxels. The cluster size threshold was determined using a cluster-extent correction procedure as implemented in SPM8. Only results surviving the cluster-correction ($p<0.05$) were reported. For anatomical location, peak voxels were converted from MNI to Talairach coordinates (Talairach and Tournoux 1988). Based on previous fMRI studies using the MID task by other researchers and us (Saji et al. 2013), we set the NAc as an *a priori* region of interest (ROI) for incentive anticipation. The bilateral NAc ROIs were anatomically defined by the left and right NAc templates using the Wake Forest University (WFU) PickAtlas and were analyzed at familywise error (FWE)-corrected $p<0.05$. The percent signal change within the ROI was calculated for the anticipatory period using MarsBar. Because the values of percent signal change were not subject to normal distribution, they were analyzed using the Wilcoxon signed-rank test with incentive valence (gain, loss) and magnitude (¥0, ¥20, ¥100, and ¥500) between placebo and modafinil treatments.

Results

Effects of drugs on subjective emotional states

Table 1 shows the mean scores of each test before the drug treatments (HAM-D, HAM-A, and POMS), indicating that the subjects enrolled in this study showed no tendency to have psychotic features, and their mood states were almost comparable between the two series of fMRI studies. Table 2 shows the values calculated by subtracting the scores before the drug administration from those 2 h after the drug administration. As for VAS for feeling, the subjects were significantly more alert ($p=0.026$), clearer-headed ($p=0.012$), more energetic ($p=0.020$), more attentive ($p=0.029$), and more gregarious ($p=0.036$) with the modafinil treatment compared to the placebo treatment. Among the 4 domains for feeling, modafinil significantly increased the mental awareness of subjects ($p<0.001$).

Effects of modafinil on task performance and VAS for effort

We then examined the effects of modafinil on reaction times in response to cues and VAS effort scores. Median reaction times for each cue did not differ significantly between placebo and modafinil (Table 3). On the other hand, VAS effort scores for +¥500 and −¥500 cues were significantly higher under modafinil than placebo conditions (+¥500, $p=0.025$; −¥500, $p=0.023$; Table 3). The hit rates were standardized to 66 % for all participants, as described, so that the actual median values of the hit rate were 64.60 % with placebo and 64.25 % with modafinil, showing no difference. We analyzed behavioral differences in the commission error to the no-response trials between under modafinil and placebo conditions. Modafinil significantly decreased the commission error compared to placebo (mean error rates, placebo, 1.11 %, modafinil, 0.14 %; $p=0.038$).

Table 1 Baseline rating of subjective mood

	Placebo mean (SEM)	Modafinil mean (SEM)
HAM-D	0.90 (0.26)	0.60 (0.21)
HAM-A	0.55 (0.25)	0.50 (0.20)
POMS		
Tension–Anxiety	3.35 (0.70)	3.45 (0.77)
Depression–Dejection	2.05 (1.03)	2.75 (1.16)
Anger–Hostility	2.30 (0.76)	2.90 (1.01)
Vigor	17.90 (1.45)	17.80 (1.77)
Fatigue	3.15 (1.05)	3.15 (0.95)
Confusion	3.75 (0.79)	2.90 (0.62)

HAM-D Hamilton Depression Scale, *HAM-A* Hamilton Anxiety Scale, *POMS* Profile of Mood States, *SEM* standard error of the mean

Table 2 Subjective ratings of emotional states

	Placebo median (IQR)	Modafinil median (IQR)
HAM-D	0 (−1.00–0)	0 (0–1.00)
HAM-A	0 (0–0)	0 (0–0)
POMS		
Tension–Anxiety	0 (−2.25–0)	0 (−1.00–1.00)
Depression–Dejection	0 (0–0)	0 (−1.00–0)
Anger–Hostility	0 (−1.25–0)	0 (−1.00–0)
Vigor	−1.00 (−2.50–0)	0 (−2.00–2.25)
Fatigue	0 (−1.00–0)	0 (−1.25–0)
Confusion	0 (−1.00–0)	0 (0–0)
VAS for feeling		
1. Alert–drowsy*	1.00 (−16.50–14.25)	1.00 (−1.25–18.50)
2. Calm–excited	3.00 (−0.50–15.25)	0 (−2.25–17.75)
3. Strong–feeble	1.00 (−1.00–2.75)	0.50 (−1.00–8.00)
4. Muzzy–clear-headed*	0.50 (−10.25–5.75)	11.00 (−2.00–26.25)
5. Well-coordinated–clumsy	0 (−1.25–5.25)	2.00 (−0.25–6.75)
6. Lethargic–energetic*	−4.00 (−11.00–3.25)	2.50 (−1.25–11.75)
7. Contented–discontented	0 (−5.75–4.00)	−2.00 (−8.50–8.25)
8. Troubled–tranquil	−2.00 (−7.50–3.25)	1.00 (−7.50–8.25)
9. Mentally slow–quick-witted	−0.50 (−6.50–2.25)	3.50 (−2.50–10.75)
10. Tense–relaxed	−1.50 (−7.25–7.25)	−0.50 (−8.25–14.00)
11. Attentive–dreamy*	−1.50 (−10.75–2.50)	7.00 (1.00–10.50)
12. Incompetent–proficient	0 (−6.25–2.00)	−0.50 (−7.25–3.25)
13. Happy–sad	0 (−3.00–4.00)	0.50 (−3.25–3.25)
14. Antagonistic–amicable	1.00 (−3.00-6.25)	0 (−4.50–4.00)
15. Interested–bored	0.50 (−4.75–3.50)	4.00 (−1.00–9.25)
16. Withdrawn–gregarious*	−2.00 (−7.75–3.00)	6.00 (0.50–10.50)
Mental awareness*** (1, 4, 9, 11)	0 (−10.25–5.25)	6.00 (−2.00–17.25)
Physical energy (3, 5, 6, 12)	0 (−4.25–4.00)	1.00 (−2.00–7.25)
Tranquility (2, 7, 8, 10)	0 (−5.50–6.25)	0 (−8.00–12.00)
Sociability (13, 14, 15, 16)	0 (−5.00–3.25)	2.00 (−2.25–9.00)

HAM-D Hamilton Depression Scale, *HAM-A* Hamilton Anxiety Scale, *IQR* interquartile range, *POMS* Profile of Mood States, *VAS* visual analogue scale

*$p<0.05$ between placebo and modafinil treatments; ***$p<0.001$ between placebo and modafinil treatments

Whole brain analysis during gain and loss anticipations in the MID task under the placebo and modafinil conditions

Activations under the placebo condition

Consistent with previous studies (Saji et al. 2013), the contrast of gain anticipation showed a significant increase in BOLD signal in the left NAc ($p<0.05$ FWE-corrected for NAc ROI). Other activated areas during gain anticipation were observed in the bilateral insula and medial frontal gyri, right inferior frontal gyrus, bilateral thalamus and precentral gyri, right postcentral gyrus, right paracentral lobule and precuneus, bilateral middle occipital gyri and right cerebellum ($p<0.001$ uncorrected). The contrast of loss anticipation showed a significant increase in BOLD signal in the left putamen, left insula, left cingulated and precentral gyri, and right precuneus ($p<0.001$ uncorrected; Table 4).

Activations under the modafinil condition

The contrast of gain anticipation showed increased BOLD signal in the bilateral NAc, left middle frontal and precentral gyri, and left cuneus. The contrast of loss anticipation showed BOLD signal activation in the bilateral putamen, right thalamus, bilateral insula, right superior and middle frontal gyri, left medial and right inferior frontal gyri, right precentral gyrus, bilateral superior temporal gyri, left inferior occipital gyrus, right inferior parietal lobule, bilateral cuneus, and right cerebellum ($p<0.001$ uncorrected; Table 4).

Direct dose-wise differences

Group-level analyses the whole brain revealed no differences in BOLD response between the placebo and modafinil