Table 1. Demographic Data of the Participants and Neuropsychological Test Results.[a]

	NL Group	AD Group	*P* Value	Successful AD Subgroup	Unsuccessful AD Subgroup	*P* Value
Number	18	47		15	32	
Age (65-89)	75.1 ± 5.2	77.9 ± 5.2	.054	78.7 ± 5.1	77.6 ± 5.2	.474
Education	13.4 ± 2.5	13.5 ± 2.8	.975	13.2 ± 2.6	13.6 ± 2.9	.654
GDS (0-15)	5.7 ± 4.2	4.8 ± 3.6	.390	5.1 ± 4.4	4.6 ± 3.3	.693
MMSE (0-30)	28.6 ± 1.1	22.0 ± 3.5	<.001	22.7 ± 3.2	21.7 ± 3.7	.335
RCPM (0-36)	31.6 ± 3.5	25.5 ± 5.0	<.001	27.1 ± 4.4	24.7 ± 5.2	.121
RAVLT (0-15)	11.1 ± 2.4	2.7 ± 2.6	<.001	3.3 ± 3.0	2.4 ± 2.4	.306
ROCFT copy (0-36)	35.0 ± 0.9	33.2 ± 4.1	.124	33.8 ± 1.7	32.9 ± 4.9	.509
ROCFT recall (0-36)	17.8 ± 5.3	5.5 ± 4.7	<.001	6.1 ± 4.8	5.2 ± 4.8	.579
LM II (0-25)	9.6 ± 2.4	1.6 ± 1.6	<.001	1.8 ± 1.3	1.5 ± 1.8	.644
TMT-B	173 ± 54	336 ± 137	<.001	357 ± 145	326 ± 135	.496
mST	27.9 ± 10.2	52.8 ± 32.4	.009	40.5 ± 14.1	58.9 ± 37.1	.082
VFT initial	25.0 ± 5.9	17.2 ± 7.6	.001	19.1 ± 6.8	16.3 ± 8.0	.265
VFT category	42.6 ± 7.2	24.1 ± 7.2	<.001	26.5 ± 3.8	23.0 ± 8.1	.129
Z score of VSRAD	0.89 ± 0.52	1.72 ± 1.11	.001	1.64 ± 1.39	1.75 ± 0.99	.766

Abbreviations: AD, Alzheimer's disease; NL, cognitively and neuroradiologically normal individuals with subjective memory impairment; GDS, shorter version of geriatric depression scale; MMSE, Mini-Mental State Examination; RCPM, Raven's colored progressive matrices; RAVLT, Rey auditory verbal learning test; ROCFT, Rey-Osterrieth complex figure test; LM II, delayed recall in logical memory subtest of the Wechsler memory scale-revised; TMT-B, trail making test B; mST, modified Stroop test; VFT, verbal fluency test; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SD, standard deviation.
[a] Values are mean ± SD.

Magnetic Resonance Imaging and SPECT

All participants underwent brain MRI and N-isopropyl-p-(123I) iodoamphetamine (IMP) SPECT. The MRI studies were performed using a 1.5T GE scanner (General Electric 1.5-Tesla scanner). Axial and sagittal T1-weighted, axial T2-weighted, and axial fluid-attenuated inversion recovery images were acquired for all participants. To assess the extent of hippocampal atrophy, we used voxel-based specific regional analysis system for AD software (VSRAD).[16] This software automatically evaluates the severity of gray matter loss in the entorhinal cortex by comparing a patient's gray matter volume with the original normal database template, and the extent of atrophy is expressed as a *Z* score relative to the normal range.

All the SPECT studies were performed using triple-head rotating gamma camera (Toshiba GXA-9300A/DI; Toshiba Corporation, Tokyo, Japan) mounted with ultra high-resolution fan-beam collimators. The imaging was started 30 minutes after intravenous injection of 222 MBq of N-isopropyl-p-(123I) iodoamphetamine (IMP). Comparison of brain perfusion on SPECT was performed using the 3-dimensional stereotactic surface projection (3D-SSP) technique.[17] Three-dimensional stereotactic surface projection images were created with the NEUROSTAT image analysis program, which is suitable for an anatomical standardization of atrophic brains.[18]

Results

Table 1 shows the demographic data and the results of neuropsychological testing for the AD and NL groups. Alzheimer's disease performed significantly worse on almost all the neuropsychological tests than NL. Regarding the relation between the outcome of the Reverse Fox test and the results of neuropsychological testing, no significant differences were observed between the successful and unsuccessful AD subgroups. The mean *Z* score of VSRAD was significantly higher in the AD group than in the NL group, while no significant difference was observed between the successful and unsuccessful AD subgroups.

Table 2. Results of the "Reverse Fox" Test in the AD Group.

	Sensitivity (Success Rate)	Specificity	Positive Predictive Value	Negative Predictive Value
AD	68.1% (31.9%)	94.4%	97.0%	53.1%

Abbreviations: AD, Alzheimer's disease; Specificity, success rate in the NL group.

The success rate in the Reverse Fox test was 31.9% (15 of 47) for the AD group and 94.4% (17 of 18) for the NL group. The positive predictive value of the test for AD was 97.0%, while the negative predictive values were 53.1% (Table 2). The most frequent error pattern was touching both index fingers together and both little fingers together without twisting either hand. In the AD group, 3 (30%) of 10 patients taking donepezil and 12 (32.4%) of 37 patients not taking donepezil succeeded in the Reverse Fox test. Pearson's chi-square test indicated that donepezil did not affect the performance on the Reverse Fox test (chi-square = .021, $P = .884$). In all, 2 patients were given memantine in the AD group, only 1 patient succeeded the test and another did not, suggesting no effect of memantine on the results of this test.

As compared with the NL group, the AD group demonstrated decreased perfusion over a wide range of brain regions, including the temporoparietal region, parahippocampal gyrus,

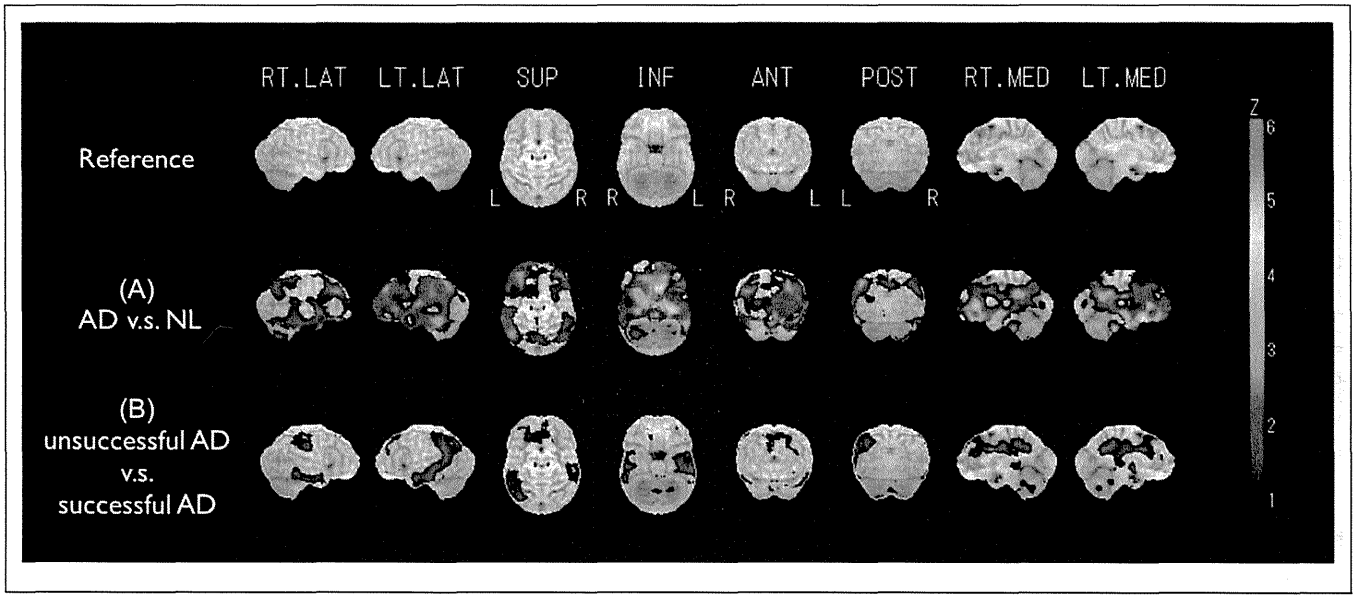

Figure 2. Images reconstructed by the 3D-SSP technique. After global normalization to the mean blood flow of the entire brain, rCBF was compared using the *Z* test. Color coding indicates the statistical significance (*Z* score) of the decrease in rCBF with red representing a more significant rCBF reduction. Anatomic reference maps for the right lateral, left lateral, superior, Foxinferior, anterior, posterior, right medial, and left medial views (from left to right). A, Reduction in rCBF in the AD group compared with the NL group. B, Reduction in rCBF in the unsuccessful AD subgroup compared with the successful AD subgroup. AD indicates Alzheimer's disease; 3D-SSP, 3-dimensional stereotactic surface projection; rCBF, regional cerebral blood flow.

precuneus, and posterior cingulate cortex (PCC; Figure 2A). Moreover, 3D-SSP SPECT analyses demonstrated that the unsuccessful AD subgroup had lower perfusion of the medial parietal region (including the precuneus and PCC) than the successful AD subgroup. The unsuccessful AD subgroup also had lower perfusion of the bilateral temporoparietal regions especially on the left side (Figure 2B).

Discussion

The present study investigated the usefulness of the Reverse Fox test for detecting parietal hypofunction in early stage AD at the outpatient clinic. Although the sensitivity (error rate) of 68.1% for mild AD was not sufficient, the high specificity (94.4%) combined with high-positive predictive values (97.0%) indicated that this test might be a clinically useful supporting tool for detecting mild AD. Persons who fail in this test are very unlikely to be "normal."

The unsuccessful AD subgroup showed lower perfusion of the bilateral temporoparietal regions and medial parietal region (including the precuneus and PCC) compared with the successful AD subgroup. These findings are compatible with the well-known concept that the temporoparietal region has a crucial role in visuoconstructive ability.[19,20] Some researchers have proposed that visuospatial deficits can precede typical memory impairment in the very prodromal phase of AD,[21,22] and recent studies have suggested that deficits of visuospatial function might be an early predictor of AD.[23,24] Accordingly, impaired performance in the Reverse Fox test might be a very early predictor of pathological cognitive decline in patients with AD.

In addition, a longitudinal SPECT study has shown that reduction of rCBF in the temporoparietal region and PCC is significantly associated with subsequent rapid cognitive deterioration.[25] Thus, the Reverse Fox test may be available for predicting a potential risk of progression in patients with AD, which is an intriguing topic for future study.

The Reverse Fox test is very simple and rapid to perform, allowing it to be done in the daily memory clinic. Moreover, this test does not tax the memory of the patient, which is advantageous in the clinical setting since persons with mild AD are often unwilling to receive memory tests. When diagnosing early dementia at the outpatient clinic, it is desirable to evaluate cognitive function with simple and rapid tasks that assess particular cognitive domains.[26] The deficits of gesture imitation in AD have often been documented in relation to apraxia.[27,28] Our Reverse Fox test is a test for imitation of meaningless gesture, which is considered a form of praxis and also evaluates visuospatial and visuomotor ability based on the copying of hand positions.

In the present study, there were no significant differences in the performances in neuropsychological testing between the successful and unsuccessful AD subgroups. Visuospatial manipulation often be examined using the task of coping figures,[29,30] whereas no significant differences were observed in scores of copying ROCFT between the successful and unsuccessful AD subgroups. The fact that the mean score of AD of copying ROCFT was as high as the mean score of NL (33.2 $\pm$ 4.1 in AD and 35.0 $\pm$ 0.9 in NL, $P = .124$) and clustered toward the top of score of copying ROCFT (ceiling effect) might be accountable for the present result.

The present study had a number of limitations. First, the total number of participants included in the study was relatively small. Moreover, the NL group was actually composed of "CDR 0" individuals, that is, "cognitively" preserved and "neuroradiologically" normal persons. We thought that it was useful to compare performance in the Reverse Fox test between mild AD and the NL groups in the present study, but it would be better to investigate a larger number of "healthy" individuals. Second, the Reverse Fox test should also be performed in patients with other types of dementia (eg, dementia with Lewy bodies, vascular dementia, and/or frontotemporal lobar degeneration). Third, the present study only examined the participants at 1 time point. Accordingly, we need the longitudinal data to determine whether the Reverse Fox test is useful for predicting cognitive decline.

In conclusion, our present findings suggest that the Reverse Fox test is a clinically useful and simple tool for the rapid detection of parietal hypofunction in patients with mild AD. Individuals with early AD who failed this simple test had lower rCBF in the bilateral temporoparietal and medial parietal regions (including the precuneus and PCC) than those who passed it. Furthermore, our findings suggest that the Reverse Fox test may be one of the useful supporting tools for detecting mild AD at outpatient clinic.

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Declaration of Conflicting Interests

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References

1. Almkvist O. Neuropsychological features of early Alzheimer's disease: preclinical and clinical stages. *Acta Neurol Scand Suppl.* 1996;165:63-71.
2. Hodges JR. Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain.* 2006;129(11):2811-2822.
3. Tippett WJ, Sergio LE. Visuomotor integration is impaired in early stage Alzheimer's disease. *Brain Res.* 2006;1102(1):92-102.
4. Rousseaux M, Rénier J, Anicet L, Pasquier F, Mackowiak-Cordoliani MA. Gesture comprehension, knowledge and production in Alzheimer's disease. *Eur J Neurol.* 2012;19(7):1037-1044.
5. Yamaguchi H, Maki Y, Yamagami T. Yamaguchi fox-pigeon imitation test: a rapid test for dementia. *Dement Geriatr Cogn Disord.* 2010;29(3):254-258.
6. Bakchine S, Lacomblez L, Palisson E, Laurent M, Derouesne C. Relationship between primitive reflexes, extra-pyramidal signs, reflective apraxia and severity of cognitive impairment in dementia of the Alzheimer type. *Acta Neurol Scand.* 1989;79(1):38-46.
7. Austin BP, Nair VA, Meier TB, Xu G, et al. Effects of hypoperfusion in Alzheimer's disease. *J Alzheimers Dis.* 2011;26(S3): 123-133.
8. Alegret M, Vinyes-Junqué G, Boada M, et al. Brain perfusion correlates of visuoperceptual deficits in mild cognitive impairment and mild Alzheimer's disease. *J Alzheimers Dis.* 2010;21(2): 557-567.
9. Matsuda H. Role of neuroimaging in Alzheimer's disease, with emphasis on brain perfusion SPECT. *J Nucl Med.* 2007;48(8): 1289-1300.
10. 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(7):939-944.
11. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43(11):2412-2414.
12. Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *Int Psychogeriatrics.* 2008;20(1):1-16.
13. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):280-292.
14. Lezak MD. *Nuropsychological assessment.* 3rd ed. New York: Oxford UP; 1996.
15. Sheik JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol.* 1986;5(1-2):165-172.
16. Hirata Y, Matsuda H, Nemoto K, et al. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. *Neurosci Lett.* 2005;382(3):269-274.
17. Minoshima S, Berger KL, Lee KS, Mintun MA. An automated method for rotational correction and centering of three-dimensional functional brain images. *J Nucl Med.* 1992;33(8): 1579-1585.
18. Ishii K, Willoch F, Minoshima S, et al. Statistical brain mapping of 18F-FDG PET in Alzheimer's disease: Validation of anatomic standardization for atrophied brains. *J Nucl Med.* 2001;42(4):548-557.
19. Kravitz DJ, Saleem KS, Baker CI, Mishkin M. A new neural framework for visuospatial processing. *Nat Rev Neurosci.* 2011; 12(4):217-230.
20. Melrose RJ, Ettenhofer ML, Harwood D, et al. Cerebral metabolism, cognition, and functional abilities in Alzheimer's disease. *J Geriatr Psychiatry Neurol.* 2011;24(3):127-134.
21. Alescio-Lautier B, Michel BF, Herrera C, et al. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. *Neuropsychologia.* 2007;45(8): 1948-1960.
22. Hort J, Laczò J, Vyhnàlek M, Bojar M, Bure J, Vlek K. Spatial navigation deficit in amnestic mild cognitive impairment. *Proc Natl Acad Sci U S A.* 2007;104(10):4042-4047.
23. Chapman RM, Mapstone M, McCrary JW, et al. Predicting conversion from mild cognitive impairment to Alzheimer's disease

using neuropsychological tests and multivariate methods. *J Clin Exp Neuropsychol*. 2011;33(2):187-199.
24. Iachini I, Iavarone A, Senese VP, Ruotolo F, Ruggiero G. Visuospatial memory in healthy elderly, AD and MCI: a review. *Curr Aging Sci*. 2009;2(1):43-59.
25. Hanyu H, Sato T, Hirao K, Kanetaka H, Iwamoto T, Koizumi K. The progression of cognitive deterioration and regional cerebral blood flow patterns in Alzheimer's disease: a longitudinal SPECT study. *J Neurol Sci*. 2010;290(1-2):96-101.
26. Kashima H. Small test for dementia of Alzheimer's type. *Psychogeriatics*. 2007;7(1):1-3.
27. Crutch SJ, Rossor MN, Warrington EK. The quantitative assessment of apraxic deficits in Alzheimer's disease. *Cortex*. 2007; 43(7):976-986.
28. Parakh R, Roy E, Koo E, Black S. Pantomime and imitation of limb gestures in relation to the severity of Alzheimer's disease. *Brain Cogn*. 2004;55(2):272-274.
29. Binetti G, Cappa SF, Magni E, Padovani A, Bianchetti A, Trabucchi M. Visual and spatial perception in the early phase of Alzheimer's disease. *Neuropsychology*. 1998;12(1):29-33.
30. Kramer JH, Wells AM. The role of perceptual bias in complex figure recall. *J Clin Exp Neuropsychol*. 2004;26(6):838-845.

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PET neuroimaging of extrastriatal dopamine receptors and prefrontal cortex functions

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ABSTRACT

The role of prefrontal dopamine D1 receptors in prefrontal cortex (PFC) functions, including working memory, is widely investigated. However, human (healthy volunteers and schizophrenia patients) positron emission tomography (PET) studies about the relationship between prefrontal D1 receptors and PFC functions are somewhat inconsistent. We argued that several factors including an inverted U-shaped relationship between prefrontal D1 receptors and PFC functions might be responsible for these inconsistencies. In contrast to D1 receptors, relatively less attention has been paid to the role of D2 receptors in PFC functions. Several animal and human pharmacological studies have reported that the systemic administration of D2 receptor agonist/antagonist modulates PFC functions, although those studies do not tell us which region(s) is responsible for the effect. Furthermore, while prefrontal D1 receptors are primarily involved in working memory, other PFC functions such as set-shifting seem to be differentially modulated by dopamine. PET studies of extrastriatal D2 receptors including ours suggested that orchestration of prefrontal dopamine transmission and hippocampal dopamine transmission might be necessary for a broad range of normal PFC functions. In order to understand the complex effects of dopamine signaling on PFC functions, measuring a single index related to basic dopamine tone is not sufficient. For a better understanding of the meanings of PET indices related to neurotransmitters, comprehensive information (presynaptic, postsynaptic, and beyond receptor signaling) will be required. Still, an interdisciplinary approach combining molecular imaging techniques with cognitive neuroscience and clinical psychiatry will provide new perspectives for understanding the neurobiology of neuropsychiatric disorders and their innovative drug developments.

1. Introduction

The prefrontal cortex (PFC) receives dense dopaminergic input originating in the ventral tegmental area. Due to the fact that dopamine D1 receptors in PFC are several times more abundant than D2 receptors (Hall et al., 1994), the roles of D1 receptors in PFC functions have been widely investigated. It has been demonstrated that local administration of D1 receptor antagonists into PFC induced impairment in working memory task in non-human primate (Sawaguchi and Goldman-Rakic, 1991). In human, positron emission tomography (PET) has been utilized to quantify prefrontal D1 receptors in vivo, and their role in human PFC functions has been studied. In contrast to D1 receptors, initial PET studies of D2 receptors were limited to the striatal region because of a lack of appropriate PET ligands for measuring D2 receptors outside the striatum where their expression is very low (Hall et al., 1994). With the introduction of high-affinity PET radioligands such as [^{11}C]FLB457 (Halldin et al., 1995) and [^{18}F]-fallypride (Mukherjee et al., 1996), it has become possible to quantify extrastriatal D2 receptors by PET. In this short review, we summarize PET studies investigating the role of extrastriatal dopamine D1 and D2 receptors in PFC functions.

2. PET imaging of D1 receptors and PFC functions

2.1. PET imaging of prefrontal D1 receptors in schizophrenia

Because schizophrenia patients are known to have impairments of PFC functions including working memory and set-shifting (Kalkstein et al., 2010), prefrontal D1 receptors in schizophrenia have been investigated using PET. An initial PET study with [^{11}C]SCH23390 revealed that D1 receptors in PFC were decreased in schizophrenia, which was associated with poor performance on the Wisconsin Card Sorting Test (WCST), a test requiring working memory and set-shifting abilities (Okubo et al., 1997). However, another PET study using [^{11}C]NNC112 reported that increased D1 receptors in PFC were associated with working memory deficits in schizophrenia (Abi-Dargham et al., 2002). The same research group recently replicated increased D1 receptors in PFC of

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drug-naïve schizophrenia patients. The interpretation was that the increase is related to compensatory up-regulation in response to lower dopamine tone in PFC (Abi-Dargham et al., 2012). In support of their interpretation, they investigated the effect of a functional polymorphism in the catechol O-methyltransferase (COMT) gene, which has been shown to modulate the prefrontal dopamine level, on prefrontal D1 receptors (Slifstein et al., 2008). The COMT gene contains a common polymorphism, a valine (Val)-to-methionine (Met) substitution at codon 158 (Val158Met). The Val allele is associated with higher activity, whereas the Met allele is associated with lower enzymatic activity (Lachman et al., 1996). Consequently, individuals with the val/val genotype have a lower level of extracellular dopamine in PFC. Using [^{11}C]NNC112 PET, they demonstrated that individuals with the val/val genotype show significantly higher cortical D1 receptor binding than individuals with the met/met genotype, suggesting a mechanism by which a lower level of extracellular dopamine in PFC induces up-regulation of D1 receptors in individuals with the val/val genotype (Slifstein et al., 2008).

It has been discussed that these inconsistent results might stem from differences in radioligands, but our more recent PET study measuring cortical D1 receptors with both [^{11}C]SCH23390 and [^{11}C]NNC112 in the same schizophrenia sample demonstrated that prefrontal D1 receptors were decreased in chronic schizophrenia regardless of the radioligands used (Kosaka et al., 2010).

2.2. An inverted U-shaped relationship between prefrontal D1 receptors and PFC functions

In order to partly reconcile the inconsistency that Okubo et al. (1997) (Abi-Dargham et al. (2002)) showed that too low (high) prefrontal D1 receptors in schizophrenia were associated with poor PFC function, we focused on an inverted U-shaped relationship between prefrontal D1 receptors and PFC functions (Takahashi et al., 2008b). A body of animal studies has indicated that stimulation of D1 receptors in PFC produces an inverted U-shaped dose-response curve, such that too little or too much D1 receptor stimulation impairs PFC functions (Cools and D'Esposito, 2011; Goldman-Rakic et al., 2000; Williams and Castner, 2006). Primal animal studies indicated that stimulation of D1 receptors in PFC produces an inverted U-shaped response in working memory, with the response being optimized within a narrow range of D1 receptor stimulation (Castner and Goldman-Rakic, 2004; Lidow et al., 2003; Seamans and Yang, 2004; Vijayraghavan et al., 2007). Subsequent human studies have investigated the effect of a functional polymorphism in the COMT gene on PFC functions. Individuals with the val/val genotype show lower performance and increased (inefficient) PFC activation during completion of cognitive tasks related to PFC functions (WCST and N-back task) (Egan et al., 2001; Goldberg et al., 2003). It was reported that amphetamine challenge in individuals with the val/val genotype induced improvement in the performance of WCST and decreased (efficient) PFC activation during N-back task, whereas that in individuals with the met/met genotype caused deterioration in the performance of WCST and increased (inefficient) PFC activation, indicating that too little or too much dopamine signaling would impair PFC functions, although these studies could not identify the receptor subtype that plays a central role in this effect (Mattay et al., 2003).

We thought that this model might account for PFC function deficits in schizophrenia patients, regardless of whether D1 receptors in PFC are increased or decreased in patients. D1 receptor binding, indices proportional to receptor density, was measured using [^{11}C]SCH23390 in healthy male subjects, and the relationship between prefrontal D1 receptors and neurocognitive performance including PFC functions was examined. Quadratic regression analysis was conducted to reveal the putative "U-shaped" relation between D1 receptor binding in PFC and its functions. Although standard linear regression analysis revealed a trend-level negative correlation between D1 receptor binding in PFC and total error of WCST, a quadratic regression model better predicted the relationship (Takahashi et al., 2008b). That is, we found a significant "U-shaped" relationship between D1 receptor binding in PFC and total error of WCST (because total error of WCST is a negative measure of frontal lobe function, the relation is not "inverted") (Fig. 1).

An inverted U-shaped response has been suggested based on cognitive and behavioral studies (Williams and Castner, 2006), but the exact physiological mechanism of this effect has not yet been fully understood. A monkey electrophysiology study has demonstrated a neuron-level mechanism that constitutes the inverted U-shaped response whereby too much or too little stimulation of prefrontal D1 receptors leads to working memory deficits (Vijayraghavan et al., 2007). D1 receptor stimulation had a suppressive effect on the PFC neural activities involved in a spatial working memory task. Moderate D1 receptor stimulation spatially tunes PFC neurons that process target signals by preferentially suppressing non-target (noisy) neural activities, whereas excessive D1 receptor stimulation induces non-selective suppression of PFC neural activities irrespective of whether the neural activities are task-related or not (Vijayraghavan et al., 2007). Supporting this notion, a PET study investigated the relation between cortical D1 receptors and intra-individual variability, that is, within-person fluctuations in cognitive performance. The study reported that age-related increase in intra-individual variability in performance was associated with low-level cortical D1 receptors in aged subjects (MacDonald et al., 2012). Low-level cortical D1 receptors might lead to a decreased signal-to-noise ratio in the cortex, then possibly resulting in increased fluctuations in performance.

2.3. Other factors to be considered for measurement of prefrontal D1 receptors in human

The inverted U-model is not a perfect explanation for the inconsistent findings of D1 receptors and PFC dysfunction in schizophrenia, and a recent PET study did not find linear or quadratic relationships between D1 receptors in PFC and performance in cognitive tasks that are dependent on PFC (Karlsson et al., 2011). More importantly, although the inverted U-model tells us that altered (extreme) prefrontal D1 receptors will lead to poor PFC functions in schizophrenia regardless of whether prefrontal D1 receptors are increased or decreased in schizophrenia, the model per se does not tell us why some studies reported decreased prefrontal D1 receptors in schizophrenia (Okubo et al., 1997) and others reported increased (Abi-Dargham et al., 2002) or unchanged (Karlsson et al., 2002) prefrontal D1 receptors in schizophrenia. Thus, other factors should be considered to explain these inconsistencies. D1 receptors are known to decrease with age in healthy controls (Kosaka et al., 2010). A recent study demonstrated that age-related reduction in D1 receptors in PFC was associated with age-related reduction in working memory performance and PFC activation during working memory task (Bäckman et al., 2011). That study tells us that other factors besides D1 receptors, such as pre-synaptic dopamine synthesis and cerebrovascular pathology, could influence PFC functions and PFC activation in older adults, and interaction between groups (schizophrenia patients versus controls) and age, i.e., illness-specific reduction in D1 receptors, should also be considered. Thus, the design and performance of longitudinal studies of prefrontal D1 receptors in schizophrenia are strongly recommended.

Furthermore, although [^{11}C]SCH23390 and [^{11}C]NNC112 are selective radioligands for D1 receptors, they have some affinity for 5HT2A receptors. 5HT2A receptor density in the striatum is negligible compared to D1 receptor density, whereas 5HT2A

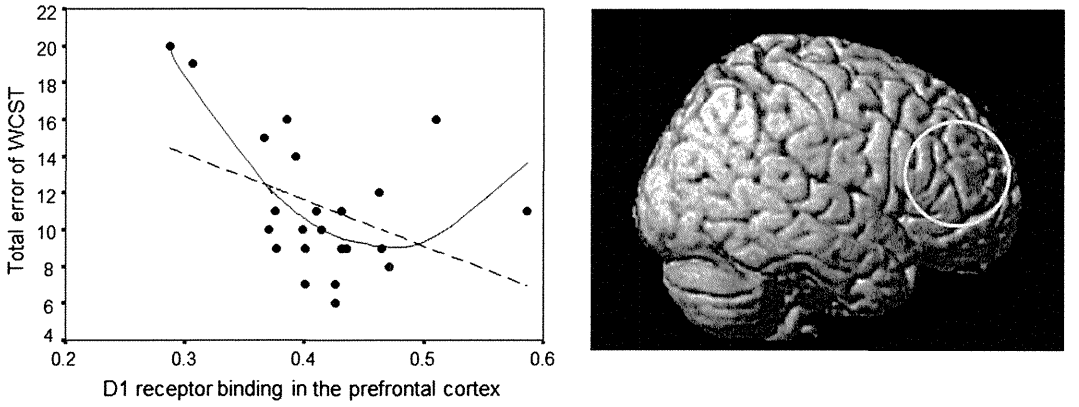

Fig. 1. Quadratic (inverted U-shaped) relationship between D1 receptor binding in PFC and performance of WCST. ROI analysis revealed a significant quadratic regression between D1 receptor binding in PFC and total error of WCST. Red solid line: quadratic regression, black broken line: linear regression (left panel). SPM analysis also revealed significant quadratic regression between prefrontal D1 receptor binding and total error of WCST (right panel).

receptor density is not negligible in extrastriatal regions. Previous reports have indicated that their affinity for 5HT2A receptors relative to D1 receptors is negligible. However, recent in vivo studies reported that D1 to 5-HT2A selectivity of these radioligands was in a range of approximately 5- to 14-fold and 10–25% of the cortical signals of these radiologands was due to binding to 5HT2A receptors (Ekelund et al., 2007; Slifstein et al., 2007). Thus, cautious interpretation of the extrastriatal findings regarding these radioligands is recommended. Another related problem is that selective D1 agonist/antagonist is not available for human use. A body of data from animal studies supports the utility of the D1 agonist for the treatment of cognitive impairments in schizophrenia (Buchanan et al., 2007). In human, a mixed D1 and D2 agonist, pergolide, was reported to have a positive effect on working memory (Müller et al., 1998). However, it is not clear whether this effect was attributable to D1 receptor stimulation because the affinity of pergolide for D1 receptors is lower than for D2 receptors, and it was reported that it may not stimulate D1 receptors in vivo at doses used to activate D2 receptors (Fuller and Clemens, 1991; Mehta and Riedel, 2006). More recently, a selective D1/D5 agonist, dihydrexidine, has been a target for improving cognitive deficit in schizophrenia (George et al., 2007; Mu et al., 2007). However, the efficacy of this compound on cognitive impairments has so far not been proven due to several practical issues concerning drug development (poor oral bioavailability, short half-life, and adverse effects) (Ye et al., 2013). For instance, George et al. (2007) reported that a single low dose of dihydrexidine administered subcutaneously is safe and tolerated in patients with schizophrenia, but did not produce delayed clinical or neuropsychological improvements.

However, the efficacy of D1 agonists on cognitive impairments has so far not been proven due to several practical issues concerning drug development. Not only clinical psychiatry but also basic human neurosciences have been eagerly awaiting the development of selective D1 agonist/antagonist.

3. PET imaging of D2 receptors and PFC functions

3.1. Central D2 receptors stimulation and PFC functions

In contrast to D1 receptors, relatively less attention has been paid to the role of prefrontal D2 receptors in cognitive functions partly because their density in extrastriatal regions is very low (Suhara et al., 1999). It was reported that blockade of D2 receptors in PFC did not impair working memory in non-human primate (Sawaguchi and Goldman-Rakic, 1991). Müller et al. (1998) reported that the systemic administration of the mixed D1/D2 receptor agonist pergolide facilitated working memory while the selective D2 receptor agonist bromocriptine had no effect. However, there is converging evidence from human and animal studies to suggest the involvement of D2 receptors in cognitive functions. In an animal study, mice lacking D2 receptors were reported to have a working memory deficit (Glickstein et al., 2002). It was reported that the systemic administration of bromocriptine in human improved cognitive functions including working memory and executive functions (Luciana et al., 1992; McDowell et al., 1998), and the administration of the D2 receptor antagonist sulpiride impaired those functions (Mehta et al., 1999). Moreover, pharmacological studies in human have shown that the effect of systemic bromocriptine administration depends on baseline working memory capacity. Bromocriptine improved working memory in low-capacity subjects, while impairing it in high-capacity subjects (Kimberg et al., 1997), suggesting that D2 receptor stimulation also might have inverted U-shaped action on PFC functions (Cools and D'Esposito, 2011). These studies, however, did not reveal the regions most responsible for these effects. Because the density of D2 receptors in PFC is very low, D2 receptors outside the PFC could be candidates. The striatum, where D2 receptors are abundant, has been a straightforward candidate, and the role of dopamine in the striatum-PFC loop and PFC functions is widely acknowledged. This topic has been nicely reviewed elsewhere (Cools and D'Esposito, 2011). Another potential substrate for the modulatory effects of D2 agonist/antagonist is the hippocampus (HPC), based on the fact that the density of D2 receptors in the medial temporal cortex is relatively high in the cortical regions (Suhara et al., 1999). In addition to the PFC functions, systemic administration of D2 receptor agonist (antagonist) improved (impaired) episodic memory in older healthy human subjects (Morcom et al., 2010).

3.2. D2 receptors in HPC and PFC functions

While it is likely that prefrontal D1 receptors predominantly modulate PFC functions, we hypothesize that the combination of prefrontal D1 receptors and D2 receptor stimulation outside PFC is most effective. Therefore, in the aforementioned study (Takahashi et al., 2008b), we investigated extrastriatal D2 receptor binding using [^{11}C]FLB457 PET in the same sample. Neither linear nor quadratic relation was found between D2 receptor binding in PFC and any neuropsychological measures. However, in line with our previous study (Takahashi et al., 2007), we found that D2 receptor binding in HPC was positively correlated not only with episodic memory ability but also with WCST performance (Takahashi et al., 2008b) (Fig. 2).

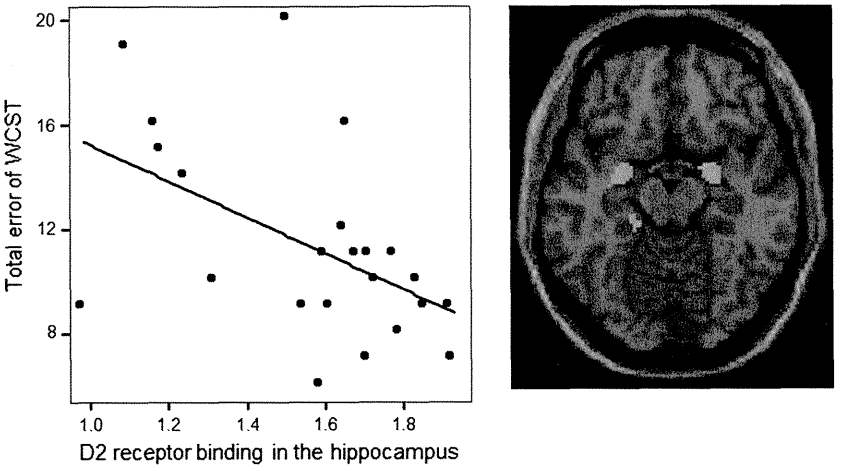

Fig. 2. Linear relationship between D2 receptor binding in HPC and performance of WCST. ROI analysis revealed positive linear correlation between D2 receptor binding in HPC and total error of WCST (left panel). SPM analysis also revealed similar correlation between hippocampal D2 receptor binding and total error of WCST (right panel).

Patients with lesions in HPC sometimes show deficits in WCST (Corkin, 2001; Igarashi et al., 2002). It was reported that infusion of the D2 receptor agonist quinpirole in HPC of rats improved working memory performance in the radial-arm maze, while ventral hippocampal infusion of the D2 receptor antagonist raclopride in HPC impaired performance (Wilkerson and Levin, 1999). These observations suggest that hippocampal D2 receptors could modulate PFC activity by the HPC–PFC pathway, which plays a significant role in the cognitive process (Laroche et al., 2000; Thierry et al., 2000). Accumulating evidence has suggested the modulatory effects of dopamine on HPC–PFC interactions (Goto and Grace, 2008; Seamans et al., 1998; Tseng et al., 2007). Supporting the importance of hippocampal D2 receptors in PFC functions, using [^{11}C]FLB 457 PET, Aalto et al. (2005) demonstrated a reduction of D2 receptor binding in HPC during working memory task compared to control condition, suggesting HPC D2 receptor stimulation during working memory load. In addition, MacDonald et al. (2009) reported that lower D2 receptor binding in HPC was associated with greater intra-individual variability in episodic memory and executive function, indicating that lower D2 receptor-mediated transmission in HPC leads to noisy neural information processing and results in unstable episodic memory and executive functions. Recently, other PET studies reported the importance of prefrontal D1 receptors (Karlsson et al., 2011) or prefrontal D2 receptors (Ko et al., 2012) in executive functions.

WCST is a test for executive functions or PFC functions that include working memory process and set-shifting (behavioral flexibility). Based on rat studies, Floresco and Magyar (2006) suggested that, while prefrontal D1 receptors are primarily involved in working memory, comparative actions of D1 and D2 receptors are necessary for set-shifting. Furthermore, they noted that the "inverted U-shaped" relationship between prefrontal D1 receptors and PFC function is limited to working memory and does not necessarily apply to other PFC functions such as set-shifting. Inhibitory GABAergic inputs to pyramidal neurons in PFC were enhanced and attenuated through D1 receptor and D2 receptor activations, respectively (Seamans et al., 2001). It is expected that D1 and D2 activations might contribute to making the PFC network stable and vulnerable, respectively (Seamans and Yang, 2004). In the process of set-shifting, one needs to disengage from the previous attentional set and represent multiple stimuli and strategies. Animal studies and human PET findings including ours suggested that orchestration of prefrontal dopamine transmission and hippocampal dopamine transmission might be necessary for a broad range of normal PFC functions.

4. PET imaging before and beyond receptors

4.1. Measurements of tonic and phasic dopamine transmission

First, for a better understanding of the role of dopamine in PFC functions, we should consider the fact that dopamine neurons are known to show tonic (basic) firing and phasic (burst) firing and that, in turn, tonic and phasic dopamine release is induced, respectively (Grace, 1991; Grace et al., 2007). Although the release of both tonic and phasic dopamine is necessary for PFC functions, phasic dopamine release plays a crucial role in working memory and set-shifting (Braver et al., 1999; Phillips et al., 2004). Standard PET indices (dopamine receptors, dopamine transporters, dopamine synthesis) are related to dopamine transmission during resting state without any cognitive load (Ito et al., 2011). These indices are considered to reflect basic dopamine tone (Ito et al., 2008, 2011). On the other hand, PET can be used for the indirect measurement of changes in synaptic dopamine concentration in vivo. [^{11}C]raclopride has been used for measuring dopamine release in the striatum in response to addictive drugs like cocaine, amphetamine and nicotine (Dewey et al., 1993; Takahashi et al., 2008a) and even in response to cognitive load (Koepp et al., 1998). Dopamine is thought to compete with [^{11}C]raclopride at the D2 receptor, and dopamine release is associated with a reduction in [^{11}C]raclopride binding (Dewey et al., 1993). Because of its low affinity, [^{11}C]raclopride is not suitable for measuring dopamine release in the extrastriatal regions, where the D2 receptor density is much lower than in the striatum. High-affinity PET radioligands such as [^{11}C]FLB457 and [^{18}F]-*fallypride* were reported to be capable of detecting dopamine release in the cortical regions by amphetamine challenge or cognitive task (Aalto et al., 2005; Buckholtz et al., 2010). However, several studies failed to detect the expected effect in the cortical regions (Cropley et al., 2008; Slifstein et al., 2010). This is thought to stem from the fact that the signal-to-noise ratio of D2 receptor binding in the cortical regions is relatively low even if high-affinity radioligands are used. Hence, indirect measures of dopamine release, a subtraction of binding potential between two (on and off) PET scans, are very sensitive to noise (Lataster et al., 2013). Furthermore, careful consideration for the timing of task or drug challenge is needed, because different uptake and washout kinetics across various brain regions due to the difference in receptor density would result in inconsistent results across the brain regions (Ceccarini et al., 2012). In contrast to D2 receptors, D1 receptors are moderately expressed in the cortical regions, and both striatal and extrastriatal D1 receptors

can be measured by a single D1 antagonist radioligand (Farde et al., 1987). However, D1 antagonist radioligands such as [^{11}C]SCH23390 and [^{11}C]NNC112 (Abi-Dargham et al., 1999) are not sensitive to endogenous dopamine release even in the striatum. It is conceivable that several factors contribute to the insensitivity of D1 receptors to the dopamine concentration in the synaptic cleft, but the exact reasons for the insensitivity are as yet unknown. It has been shown that D1 receptors have much less affinity for endogenous dopamine than D2 receptors (Richfield et al., 1989). Furthermore, cortical and striatal D1 receptors are known to be predominantly extrasynaptic (Smiley et al., 1994; Caille et al., 1996). Thus, it is difficult to measure prefrontal D1 receptor stimulation by phasic dopamine release during working memory or set-shifting. Recently, McNab et al. (2009) investigated the effect of intensive working memory training on D1 receptors in PFC. They demonstrated the quadratic relation between the improvement of working memory capacity by training and the change in D1 receptor binding induced by training, although greater reduction in D1 receptor binding was associated with greater improvements in working memory capacity within the measured range (McNab et al., 2009). This might reflect down-regulation of D1 receptors in response to a prolonged phasic dopamine release during working memory training. If a D1 receptor antagonist/agonist radioligand with sensitivity for endogenous dopamine release in PFC is developed, a more direct relationship between D1 receptors and PFC functions will be clarified. A D1 receptor agonist radioligand such as [^{11}C]SKF 82957 is thought to be more sensitive to endogenous dopamine release, but in vivo imaging has so far not been successful (Palner et al., 2010).

4.2. Measurements of dopamine transmission beyond the synapse

Second, we should also consider beyond receptors. There have been some attempts to investigate second-messenger signaling beyond synapse by PET. Cyclic adenosine monophosphate (cAMP) is one of the second messengers, and it plays an important role in neuronal signal transmission and transduction in the brain. Stimulation of D1 receptors elevates the level of cAMP by stimulating adenylate cyclase to convert adenosine triphosphate (ATP) to cAMP, while stimulation of D2 receptors decreases the level of cAMP by inhibiting adenylate cyclase. cAMP-mediated signal transduction is terminated by degradation of cAMP to AMP by phosphodiesterase (PDE). Among subtypes of PDE, PDE4 selectively metabolizes cAMP in the brain (Greengard, 1976). An inhibitor of PDE4, 4-[3-(cyclopentoxyl)-4-methoxyphenyl]-2-pyrrolidone (rolipram) has been used as a radiotracer for the quantification of PDE4 levels in the brain (Fujita et al., 2005). A previous study demonstrated that methamphetamine increased PDE4 activity measured by [^{11}C]rolipram in the striatum of conscious monkey brain by stimulating D1 receptors (Tsukada et al., 2001). Recently, [^{11}C]rolipram has been utilized to investigate PDE4 activity in neuropsychiatric disorders. Using [^{11}C]rolipram PET, widespread (including cerebral cortex and striatum) lower levels of PDE4 were reported in unmedicated depression patients (Fujita et al., 2012). A previous [^{11}C]SCH23390 PET study (Suhara et al., 1992) reported decreased prefrontal D1 receptors, and a [^{11}C]NNC112 study (Cannon et al., 2009) reported decreased striatal D1 receptors in depressed patients. We previously reported the relationship between dopamine receptors and presynaptic dopamine synthesis in the striatum combining [^{11}C]raclopride and L-[β-^{11}C]DOPA PET (Ito et al., 2011). A negative correlation was observed between the binding potential of dopamine D2 receptors and endogenous dopamine synthesis rate in the striatum. Thus, this points to the necessity of investigating the relationship between dopamine receptor density and second-messenger signaling beyond receptors as well.

5. Conclusion

In conclusion, in order to understand the complex effects of dopamine signaling on PFC functions, not only multi-faceted assessment of PFC functions containing various components with substantial overlaps, but also clever extraction and delineation of each component are needed. Equally, it certainly does not seem enough just to measure a single index related to basic dopamine tone. For a better understanding of the meanings of the PET indices related to neurotransmitters, comprehensive information (presynaptic, postsynaptic, and beyond receptor signaling) will be required. Still, an interdisciplinary approach combining molecular imaging techniques with cognitive neuroscience and clinical psychiatry will provide new perspectives for understanding the neurobiology of neuropsychiatric disorders and their innovative drug developments.

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References

Aalto, S., Bruck, A., Laine, M., Nagren, K., Rinne, J.O., 2005. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [^{11}C]FLB 457. J. Neurosci. 25, 2471–2477.

Abi-Dargham, A., Simpson, N., Kegeles, L., Parsey, R., Hwang, D.R., Anjilvel, S., Zea-Ponce, Y., Lombardo, I., Van Heertum, R., Mann, J.J., Foged, C., Halldin, C., Laruelle, M., 1999. PET studies of binding competition between endogenous dopamine and the D1 radiotracer [^{11}C]NNC 756. Synapse 32, 93–109.

Abi-Dargham, A., Mawlawi, O., Lombardo, I., Gil, R., Martinez, D., Huang, Y., Hwang, D.R., Keilp, J., Kochan, L., Van Heertum, R., Gorman, J.M., Laruelle, M., 2002. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J. Neurosci. 22, 3708–3719.

Abi-Dargham, A., Xu, X., Thompson, J.L., Gil, R., Kegeles, L.S., Urban, N., Narendran, R., Hwang, D.R., Laruelle, M., Slifstein, M., 2012. Increased prefrontal cortical D1 receptors in drug naive patients with schizophrenia: a PET study with [^{11}C]NNC112. J. Psychopharmacol. 26, 794–805.

Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., Rieckmann, A., MacDonald, S.W., Farde, L., Nyberg, L., 2011. Dopamine D1 receptors and age differences in brain activation during working memory. Neurobiol. Aging 32, 1849–1856.

Braver, T.S., Barch, D.M., Cohen, J.D., 1999. Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol. Psychiatry 46, 312–328.

Buchanan, R.W., Freedman, R., Javitt, D.C., Abi-Dargham, A., Lieberman, J.A., 2007. Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. Schizophr. Bull. 33, 1120–1130.

Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Kessler, R.M., Zald, D.H., 2010. Dopaminergic network differences in human impulsivity. Science 329, 532.

Caille, I., Dumartin, B., Bloch, B., 1996. Ultrastructural localization of D1 dopamine receptor immunoreactivity in rat striatonigral neurons and its relation with dopaminergic innervation. Brain Res. 730, 17–31.

Cannon, D.M., Klaver, J.M., Peck, S.A., Rallis-Voak, D., Erickson, K., Drevets, W.C., 2009. Dopamine type-1 receptor binding in major depressive disorder assessed using positron emission tomography and [^{11}C]NNC-112. Neuropsychopharmacology 34, 1277–1287.

Castner, S.A., Goldman-Rakic, P.S., 2004. Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. J. Neurosci. 24, 1446–1450.

Ceccarini, J., Vrieze, E., Koole, M., Muylle, T., Bormans, G., Claes, S., Van Laere, K., 2012. Optimized in vivo detection of dopamine release using 18F-fallypride PET. J. Nucl. Med. 53, 1565–1572.
Cools, R., D'Esposito, M., 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69, e113–125.
Corkin, S., 2001. Beware of frontal lobe deficits in hippocampal clothing. Trends Cogn. Sci. 5, 321–323.
Cropley, V.L., Innis, R.B., Nathan, P.J., Brown, A.K., Sangare, J.L., Lerner, A., Ryu, Y.H., Sprague, K.E., Pike, V.W., Fujita, M., 2008. Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. Synapse 62, 399–408.
Dewey, S.L., Smith, G.S., Logan, J., Brodie, J.D., Fowler, J.S., Wolf, A.P., 1993. Striatal binding of the PET ligand ^{11}C-raclopride is altered by drugs that modify synaptic dopamine levels. Synapse 13, 350–356.
Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R., 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. USA 98, 6917–6922.
Ekelund, J., Slifstein, M., Narendran, R., Guillin, O., Belani, H., Guo, N.N., Hwang, Y., Hwang, D.R., Abi-Dargham, A., Laruelle, M., 2007. In vivo DA D 1 receptor selectivity of NNC 112 and SCH 23390. Mol. Imaging Biol. 9, 117–125.
Farde, L., Halldin, C., Stone-Elander, S., Sedvall, G., 1987. PET analysis of human dopamine receptor subtypes using 11C-SCH 23390 and 11C-raclopride. Psychopharmacology 92, 278–284.
Floresco, S.B., Magyar, O., 2006. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology 188, 567–585.
Fujita, M., Zoghbi, S.S., Crescenzo, M.S., Hong, J., Musachio, J.L., Lu, J.Q., Liow, J.S., Seneca, N., Tipre, D.N., Cropley, V.L., Imaizumi, M., Gee, A.D., Seidel, J., Green, M.V., Pike, V.W., Innis, R.B., 2005. Quantification of brain phosphodiesterase 4 in rat with (R)-[^{11}C]Rolipram-PET. Neuroimage 26, 1201–1210.
Fujita, M., Hines, C.S., Zoghbi, S.S., Mallinger, A.G., Dickstein, L.P., Liow, J.S., Zhang, Y., Pike, V.W., Drevets, W.C., Innis, R.B., Zarate Jr., C.A., 2012. Downregulation of brain phosphodiesterase type IV measured with ^{11}C-(R)-rolipram positron emission tomography in major depressive disorder. Biol. Psychiatry 72, 548–554.
Fuller, R.W., Clemens, J.A., 1991. Pergolide: a dopamine agonist at both D1 and D2 receptors. Life Sci. 49, 925–930.
George, M.S., Molnar, C.E., Grenesko, E.L., Anderson, B., Mu, Q., Johnson, K., Nahas, Z., Knable, M., Fernandes, P., Juncos, J., 2007. A single 20 mg dose of dihydrexidine (DAR-0100), a full dopamine D1 agonist, is safe and tolerated in patients with schizophrenia. Schizophr. Res. 93, 42–50.
Glickstein, S.B., Hof, P.R., Schmauss, C., 2002. Mice lacking dopamine D2 and D3 receptors have spatial working memory deficits. J. Neurosci. 22, 5619–5629.
Goldberg, T.E., Egan, M.F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B.S., Goldman, D., Weinberger, D.R., 2003. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch. Gen. Psychiatry 60, 889–896.
Goldman-Rakic, P.S., Muly 3rd, E.C., Williams, G.V., 2000. D1 receptors in prefrontal cells and circuits. Brain Res. Brain Res. Rev. 31, 295–301.
Goto, Y., Grace, A.A., 2008. Dopamine modulation of hippocampal-prefrontal cortical interaction drives memory-guided behavior. Cereb. Cortex 18, 1407–1414.
Grace, A.A., 1991. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41, 1–24.
Grace, A.A., Floresco, S.B., Goto, Y., Lodge, D.J., 2007. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 30, 220–227.
Greengard, P., 1976. Possible role for cyclic nucleotides and phosphorylated membrane proteins in postsynaptic actions of neurotransmitters. Nature 260, 101–108.
Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., Farde, L., 1994. Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology 11, 245–256.
Halldin, C., Farde, L., Hogberg, T., Mohell, N., Hall, H., Suhara, T., Karlsson, P., Nakashima, Y., Swahn, C.G., 1995. Carbon-11-FLB 457: a radioligand for extrastriatal D2 dopamine receptors. J. Nucl. Med. 36, 1275–1281.
Igarashi, K., Oguni, H., Osawa, M., Awaya, Y., Kato, M., Mimura, M., Kashima, H., 2002. Wisconsin card sorting test in children with temporal lobe epilepsy. Brain Dev. 24, 174–178.
Ito, H., Takahashi, H., Arakawa, R., Takano, H., Suhara, T., 2008. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. Neuroimage 39, 555–565.
Ito, H., Kodaka, F., Takahashi, H., Takano, H., Arakawa, R., Shimada, H., Suhara, T., 2011. Relation between presynaptic and postsynaptic dopaminergic functions measured by positron emission tomography: implication of dopaminergic tone. J. Neurosci. 31, 7886–7890.
Kalkstein, S., Hurford, I., Gur, R.C., 2010. Neurocognition in schizophrenia. Curr. Top. Behav. Neurosci. 4, 373–390.
Karlsson, P., Farde, L., Halldin, C., Sedvall, G., 2002. PET study of D1 dopamine receptor binding in neuroleptic-naive patients with schizophrenia. Am. J. Psychiatry 159, 761–767.
Karlsson, S., Rieckmann, A., Karlsson, P., Farde, L., Nyberg, L., Bäckman, L., 2011. Relationship of dopamine D1 receptor binding in striatal and extrastriatal regions to cognitive functioning in healthy humans. Neuroimage 57, 346–351.
Kimberg, D.Y., D'Esposito, M., Farah, M.J., 1997. Effects of bromocriptine on human subjects depend on working memory capacity. NeuroReport 8, 3581–3585.
Ko, J.H., Antonelli, F., Monchi, O., Ray, N., Rusjan, P., Houle, S., Lang, A.E., Christopher, L., Strafella, A.P., 2012. Prefrontal dopaminergic receptor abnormalities and executive functions in Parkinson's disease. Hum. Brain Mapp. [Epub ahead of print].
Koepp, M.J., Gunn, R.N., Lawrence, A.D., Cunningham, V.J., Dagher, A., Jones, T., Brooks, D.J., Bench, C.J., Grasby, P.M., 1998. Evidence for striatal dopamine release during a video game. Nature 393, 266–268.
Kosaka, J., Takahashi, H., Ito, H., Takano, A., Fujimura, Y., Matsumoto, R., Nozaki, S., Yasuno, F., Okubo, Y., Kishimoto, T., Suhara, T., 2010. Decreased binding of [^{11}C] NNC112 and [^{11}C] SCH23390 in patients with chronic schizophrenia. Life Sci. 86, 814–818.
Lachman, H.M., Papolos, D.F., Saito, T., Yu, Y.M., Szumlanski, C.L., Weinshilboum, R.M., 1996. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6, 243–250.
Laroche, S., Davis, S., Jay, T.M., 2000. Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. Hippocampus 10, 438–446.
Lataster, J., Collip, D., Ceccarini, J., Hernaus, D., Haas, D., Booij, L., van Os, J., Pruessner, J., Van Laere, K., Myin-Germeys, I., 2013. Familial liability to psychosis is associated with attenuated dopamine stress signaling in ventromedial prefrontal cortex. Schizophr. Bull. [Epub ahead of print].
Lidow, M.S., Koh, P.O., Arnsten, A.F., 2003. D1 dopamine receptors in the mouse prefrontal cortex: immunocytochemical and cognitive neuropharmacological analyses. Synapse 47, 101–108.
Luciana, M., Depue, R.A., Arbisi, P., Leon, A., 1992. Facilitation of working memory in humans by a D2 dopamine receptor agonist. J. Cogn. Sci. 4, 58–68.
MacDonald, S.W., Cervenka, S., Farde, L., Nyberg, L., Bäckman, L., 2009. Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. Neuropsychologia 47, 2299–2304.
MacDonald, S.W., Karlsson, S., Rieckmann, A., Nyberg, L., Bäckman, L., 2012. Aging-related increases in behavioral variability: relations to losses of dopamine D1 receptors. J. Neurosci. 32, 8186–8191.
Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., Weinberger, D.R., 2003. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc. Natl. Acad. Sci. USA 100, 6186–6191.
McDowell, S., Whyte, J., D'Esposito, M., 1998. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain 121, 1155–1164.
McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., Klingberg, T., 2009. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 323, 800–802.
Mehta, M.A., Riedel, W.J., 2006. Dopaminergic enhancement of cognitive function. Curr. Pharm. Des. 12, 2487–2500.
Mehta, M.A., Sahakian, B.J., McKenna, P.J., Robbins, T.W., 1999. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology 146, 162–174.
Morcom, A.M., Bullmore, E.T., Huppert, F.A., Lennox, B., Praseedom, A., Linnington, H., Fletcher, P.C., 2010. Memory encoding and dopamine in the aging brain: a psychopharmacological neuroimaging study. Cereb. Cortex 20, 743–757.
Mu, Q., Johnson, K., Morgan, P.S., Grenesko, E.L., Molnar, C.E., Anderson, B., Nahas, Z., Kozel, F.A., Kose, S., Knable, M., 2007. A single 20 mg dose of the full D1 dopamine agonist dihydrexidine (DAR-0100) increases prefrontal perfusion in schizophrenia. Schizophr. Res. 94, 332–341.
Mukherjee, J., Yang, Z.Y., Brown, T., Roemer, J., Cooper, M., 1996. 18F-desmethoxyfallypride: a fluorine-18 labeled radiotracer with properties similar to carbon-11 raclopride for PET imaging studies of dopamine D2 receptors. Life Sci. 59, 669–678.
Müller, U., von Cramon, D.Y., Pollmann, S., 1998. D1- versus D2-receptor modulation of visuospatial working memory in humans. J. Neurosci. 18, 2720–2728.
Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., Someya, Y., Sassa, T., Sudo, Y., Matsushima, E., Iyo, M., Tateno, Y., Toru, M., 1997. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385, 634–636.
Palner, M., McCormick, P., Parkes, J., Knudsen, G.M., Wilson, A.A., 2010. Systemic catechol-O-methyl transferase inhibition enables the D1 agonist radiotracer R-[^{11}C]SKF 82957. Nucl. Med. Biol. 237, 837–843.
Phillips, A.G., Ahn, S., Floresco, S.B., 2004. Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. J. Neurosci. 24, 547–553.
Richfield, E.K., Penney, J.B., Young, A.B., 1989. Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. Neuroscience 30, 767–777.
Sawaguchi, T., Goldman-Rakic, P.S., 1991. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251, 947–950.
Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1–58.
Seamans, J.K., Floresco, S.B., Phillips, A.G., 1998. D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J. Neurosci. 18, 1613–1621.

Seamans, J.K., Gorelova, N., Durstewitz, D., Yang, C.R., 2001. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J. Neurosci. 21, 3628–3638.

Slifstein, M., Kegeles, L.S., Gonzales, R., Frankle, W.G., Xu, X., Laruelle, M., Abi-Dargham, A., 2007. [^{11}C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects. J. Cereb. Blood Flow Metab. 27, 1733–1741.

Slifstein, M., Kolachana, B., Simpson, E.H., Tabares, P., Cheng, B., Duvall, M., Frankle, W.G., Weinberger, D.R., Laruelle, M., Abi-Dargham, A., 2008. COMT genotype predicts cortical-limbic D1 receptor availability measured with [^{11}C]NNC112 and PET. Mol. Psychiatry 13, 821–827.

Slifstein, M., Kegeles, L.S., Xu, X., Thompson, J.L., Urban, N., Castrillon, J., Hackett, E., Bae, S.A., Laruelle, M., Abi-Dargham, A., 2010. Striatal and extrastriatal dopamine release measured with PET and [(18)F] fallypride. Synapse 64, 350–362.

Smiley, J.F., Levey, A.I., Ciliax, B.J., Goldman-Rakic, P.S., 1994. D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. Proc. Natl. Acad. Sci. USA 91, 5720–5724.

Suhara, T., Nakayama, K., Inoue, O., Fukuda, H., Shimizu, M., Mori, A., Tateno, Y., 1992. D 1 dopamine receptor binding in mood disorders measured by positron emission tomography. Psychopharmacology 106, 14–18.

Suhara, T., Sudo, Y., Okauchi, T., Maeda, J., Kawabe, K., Suzuki, K., Okubo, Y., Nakashima, Y., Ito, H., Tanada, S., Halldin, C., Farde, L., 1999. Extrastriatal dopamine D2 receptor density and affinity in the human brain measured by 3D PET. Int. J. Neuropsychopharmacol. 2, 73–82.

Takahashi, H., Kato, M., Hayashi, M., Okubo, Y., Takano, A., Ito, H., Suhara, T., 2007. Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. Neuroimage 34, 1643–1649.

Takahashi, H., Fujimura, Y., Hayashi, M., Takano, H., Kato, M., Okubo, Y., Kanno, I., Ito, H., Suhara, T., 2008a. Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study. Int. J. Neuropsychopharmacol. 11, 413–417.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., Hayashi, M., Okubo, Y., Ito, H., Suhara, T., 2008b. Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. J. Neurosci. 28, 12032–12038.

Thierry, A.M., Gioanni, Y., Degenetais, E., Glowinski, J., 2000. Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. Hippocampus 10, 411–419.

Tseng, K.Y., Lewis, B.L., Lipska, B.K., O'Donnell, P., 2007. Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. Biol. Psychiatry 62, 730–738.

Tsukada, H., Harada, N., Ohba, H., Nishiyama, S., Kakiuchi, T., 2001. Facilitation of dopaminergic neural transmission does not affect [^{11}C]SCH23390 binding to the striatal D1 dopamine receptors, but the facilitation enhances phosphodiesterase type-IV activity through D1 receptors: PET studies in the conscious monkey brain. Synapse 42, 258–265.

Vijayraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., Arnsten, A.F., 2007. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat. Neurosci. 10, 376–384.

Wilkerson, A., Levin, E., 1999. Ventral hippocampal dopamine D1 and D2 systems and spatial working memory in rats. Neuroscience 89, 743.

Williams, G.V., Castner, S.A., 2006. Under the curve: critical issues for elucidating D1 receptor function in working memory. Neuroscience 139, 263–276.

Ye, N., Neumeyer, J.L., Baldessarini, R.J., Zhen, X., Zhang, A., 2013. Update 1 of: recent progress in development of dopamine receptor subtype-selective agents: potential therapeutics for neurological and psychiatric disorders. Chem. Rev. 113, 123–178.

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Molecular neuroimaging of emotional decision-making

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ABSTRACT

With the dissemination of non-invasive human neuroimaging techniques such as fMRI and the advancement of cognitive science, neuroimaging studies focusing on emotions and social cognition have become established. Along with this advancement, behavioral economics taking emotional and social factors into account for economic decisions has been merged with neuroscientific studies, and this interdisciplinary approach is called neuroeconomics. Past neuroeconomics studies have demonstrated that subcortical emotion-related brain structures play an important role in "irrational" decision-making. The research field that investigates the role of central neurotransmitters in this process is worthy of further development. Here, we provide an overview of recent molecular neuroimaging studies to further the understanding of the neurochemical basis of "irrational" or emotional decision-making and the future direction, including clinical implications, of the field.

1. Introduction

With the dissemination of non-invasive human neuroimaging techniques such as fMRI and the advancement of cognitive science, neuroimaging studies regarding emotions, social cognition (Theory of Mind) and moral cognition became established from the late 1990s (Adolphs, 2002; Frith and Frith, 2003; Lamm et al., 2011; Moll et al., 2005; Takahashi et al., 2004). This general period was also an important time for the advancement of behavioral or experimental economics. In normative economics theory, decision makers are assumed to be "rational" and purely self-interested. However, we are not always rational, and sometimes show other regarding preference (e.g. charity, moral decision etc.). Laboratory and field evidence from behavioral economics has shown that decision-makers systematically depart from normative theory (Camerer and Loewenstein, 2004; Camerer and Fehr, 2006; Tversky and Kahneman, 1992). Because behavioral economics deals with the effects of emotional and social factors on economic decisions, not surprisingly, it has been merged with neuroscientific studies about emotions or social cognition, and this interdisciplinary approach is called neuroeconomics (Fehr and Camerer, 2007; Levallois et al., 2012). Since Daniel Kahneman and Vernon Smith were awarded the Nobel Prize in Economics for their contributions to the establishment of behavioral or experimental economics in 2002, neuroeconomics research has been accelerating (Fehr and Camerer, 2007; Glimcher et al., 2005; Sanfey et al., 2003; Takahashi et al., 2009). Past neuroeconomics studies have investigated the neural basis of "irrational" or "emotional" decision-making that violates normative theory, demonstrating that, in addition to cortical regions such as the prefrontal cortex (PFC), subcortical emotion-related brain structures play a major role in "irrational" decision-making (Fehr and Camerer, 2007). The next question then is how modulatory neurotransmission is involved in these central processes (Rangel et al., 2008). Here, we provide an overview of recent efforts to understand the neurochemical basis of "emotional" decision-making under risks.

2. Emotional decision-making under risks

2.1. Neuroscientific studies of nonlinear probability weighting

Normative economics theory in decision-making under risks assumes that decision-makers combine probabilities and valuation (utility) of possible outcomes in some way, most typically by taking the probability-weighted expectation over possible utilities. However, our daily experiences and empirical evidence tell us that we systematically violate the normative theory. One type of systematic violation of normative economics theory is that people tend to weight objective probabilities nonlinearly. Decision-makers often overestimate low probabilities (e.g. playing lotteries) and

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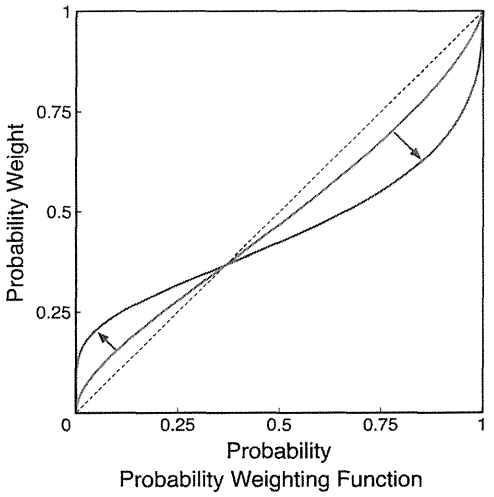

Fig. 1. Hypothesized model showing the contribution of central DA tone to nonlinear probability weighting. A smaller value of α (closer to 0) means a more nonlinear inflected weighting function and a higher value (closer to 1) means a more linear weighting function. At $\alpha = 1$ the function is linear. DA tone might play a central role in distorting probability weighting function nonlinearly. Excessive DA tone might cause exaggerated overestimation of low probability and underestimation of moderate to high probabilities.

underestimate high probabilities. A leading alternative to normative theory (expected utility theory) is the prospect theory (Tversky and Kahneman, 1992). One of the important components of the prospect theory is nonlinear probability weighting, where objective probabilities, p, are transformed nonlinearly into decision weights $w(p)$ by a weighting function (Fig. 1).

From a psychological point of view, the overweighting of low-probability gains may reflect the hope of winning, and underweighting of high-probability gains may reflect the fear of losing a "near sure thing". In this sense, nonlinear probability weighting is called "emotional" decision-making. Experimental studies suggest that the weighting function is regressive, asymmetric, and inverse S-shaped, crossing the diagonal from above at an inflection point (around 1/3) where $p = w(p)$. Although several functions have been proposed to express nonlinear probability weighting, the one-parameter function derived axiomatically by Prelec (1998), $w(p) = \exp\{-(\ln(1/p))^{\alpha}\}$ with $0 < \alpha < 1$, is widely used. In an inverse S-shaped nonlinear weighting function, low probabilities are overweighted and moderate to high probabilities are underweighted. The function neatly explains the typically observed pattern of risk-seeking for low probability gain and risk aversion toward high probability gain.

The neural correlates related to nonlinear probability transformation were investigated using fMRI with a certainty equivalent procedure (Paulus and Frank, 2006). During this procedure, a gamble's certainty equivalent, the amount of sure payoff at which a player is indifferent between the sure payoff and the gamble, was determined. It was reported that differential anterior cingulate activation during estimation of high probabilities relative to low probabilities was positively correlated with Prelec's nonlinearity parameter α across subjects. Another fMRI study with risks of negative outcomes (electric shocks) found similar nonlinear response in brain regions including the caudate/subgenual anterior cingulate (Berns et al., 2008). Tobler et al. (2008) reported that the dorsolateral PFC was involved in overweighting low probabilities and underweighting high probabilities, and that the ventral frontal regions showed the opposite pattern. However, more recently, the degree of nonlinearity in the striatal response to anticipated reward was shown to reflect the nonlinearity parameter as estimated behaviorally (Hsu et al., 2009). The discrepancies regarding the loci of activation are thought to stem from differences in the task (probability range, context, etc.) and parameter estimation method. However, elucidating the role of the dopamine (DA) system in nonlinear probability weighting would seem promising, considering the fact that DA is linked to risk-seeking behavior (Leyton et al., 2002) and excessive DA release was observed in pathological gambling in Parkinson's disease patients (Steeves et al., 2009). Trepel et al. (2005) hypothesized in an insightful review that DA transmission in the striatum might be involved in shaping probability weighting. Taking advantage of in vivo molecular neuroimaging, we investigated the relationship between central DA transmission and nonlinear probability weighting by positron emission tomography (PET).

Using a certainty equivalent procedure, we estimated probability weighting with Prelec's one-parameter function outside the PET scanner. There was positive correlation between striatal D1 receptor binding measured by [^{11}C]SCH23390 PET and the nonlinearity parameter α of weighting function (Fig. 2) (Takahashi et al., 2010a). No correlation was found between D2 receptor binding measured by [^{11}C]raclopride PET and nonlinearity parameter α. That is, subjects with lower striatal D1 receptor binding tend to show more pronounced overestimation of low probabilities and underestimation of high probabilities. Although [^{11}C]SCH23390 is a selective radioligand for D1 receptors, it also has some affinity for serotonin (5-HT) 2A receptors. 5HT2A receptor density in the striatum is negligible compared to D1 receptor density. However, 5HT2A receptor density is never negligible in extrastriatal regions, and it was reported that approximately one-fourth of the cortical signal of [^{11}C]SCH23390 was due to binding to 5HT2A receptors (Ekelund et al., 2007). Future studies with a more selective radioligand are recommended to test the role of extrastriatal (cortical) D1 receptors in nonlinear weighting.

Mis-estimation of probabilities, especially of low probabilities, might be related to some problematic behaviors in neuropsychiatric disorders. Clinical studies have reported the emergence of pathological gambling in Parkinson's disease patients taking DA agonist medication (Dagher and Robbins, 2009; Gallagher et al., 2007), and such patients showed exaggerated DA release in the ventral striatum measured by [^{11}C]raclopride PET during gambling (Steeves et al., 2009). Although pathological gambling is a heterogeneous disorder and cannot be solely attributed to mis-estimating probability, these observations can lead to the hypothesis that excessive DA transmission might cause distortion of subjective probability weights for gains (positive outcomes) (Fig. 1). On the basis of this hypothesis, circumstantial evidence can lead us to the conjecture of a vicious-cycle mechanism for developing drug/gambling addiction as follows: Reduced striatal D1 binding (which might in part be determined by genetic information) is linked to a risk-seeking trait. The risk-seeking trait is linked to enhanced activation and DA release in the striatum during risk-seeking behavior (Leyton et al., 2002; St Onge and Floresco, 2009). Chronic exposure to unusually high release of DA might lead to down-regulation of D1 receptors (Moore et al., 1998; Yasuno et al., 2007). Further decrease in D1 receptor binding would then lead to further risk-seeking. Reduced striatal D1 binding could therefore be a gateway to a vicious cycle, creating a predisposition to drug addiction and pathological gambling. In fact, a recent study suggested that reduced D1 receptor binding may be associated with an increased risk of relapse in drug addiction (Martinez et al., 2009).

However, nonlinear probability weighting is a combination of risk-seeking (overestimation of low probability) and risk-aversion (underestimation of high probability). In fact, a recent study reported that pathological gamblers demonstrated an overall shift toward risk, rather than excessive distortion of nonlinear probability weighting in decision-making under risks (Ligneul et al., 2012). Thus, the shape of weighting function, especially in the

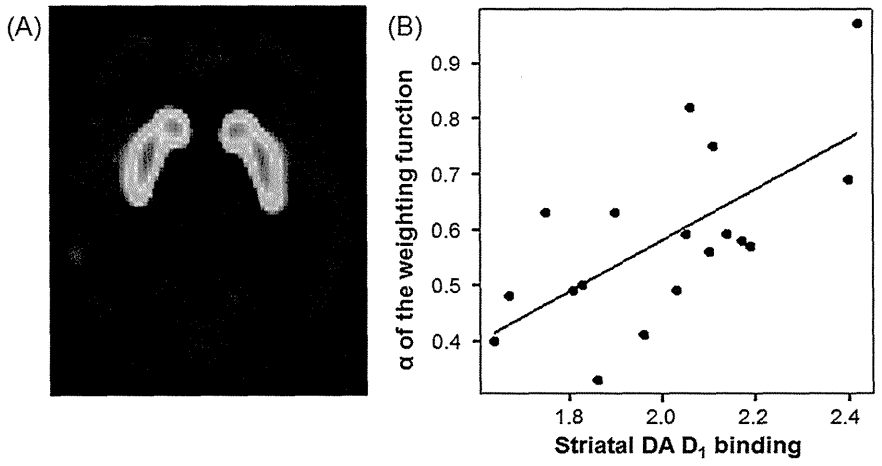

Fig. 2. Relationship between striatal DA D1 receptors and nonlinear probability weighting: (A) parametric image of DA D1 receptor binding potential measured by [^{11}C]SCH23390 is shown and (B) positive correlation between striatal D1 receptor binding and α of weighting function is shown.

high-probability portion, should be determined by multiple neurotransmitters other than DA (Takahashi et al., 2010b), such as 5-HT (Takahashi et al., 2005) and NE (Onur et al., 2009), which are also known to modulate the emotional reaction of fear. Furthermore, the role of modulatory neurotransmitters in shaping weighting function for losses (negative outcomes) should be tested as well.

2.2. Neuroscientific studies of loss aversion

Distaste derived from losing a certain amount of money appears to be greater than the pleasure derived from gaining the equivalent amount. Imagine having a chance to participate in a coin-flip game of chance. Using a fair coin, if the result is heads, you will win \$100, and if the result is tails, you will lose \$100. Are you willing to participate in this gamble? Typically, most people would say "no". Well, how about the following gamble? If the winning prize is increased to \$200, while the potential loss remains \$100. In this case, some people would say "yes". This means that, typically, losses have at least twice the impact of equivalent gains, a property called loss aversion (Tversky and Kahneman, 1992). Many laboratory and field studies have found evidence in monkeys for food rewards, and in humans for financial outcomes, features of consumer goods, food rewards, game show winnings, and apartment sales (Camerer and Loewenstein, 2004; Chen et al., 2006; Knutson et al., 2007). In prospect theory, this is modeled by a value function of losses that is steeper than that of gains (Fig. 3).

A fMRI study reported that the PFC and striatum are involved in loss aversion (Tom et al., 2007). Brain lesion studies have reported that amygdala lesion patients showed diminished loss aversion (De Martino et al., 2010). Sokol-Hessner et al. (2009) have shown that physiological arousal response (skin conductance response) to losses was greater than to equivalent gains on average. This means that losses are more emotionally laden and salient than equivalent gains. The study also reported that individuals with greater arousal response to losses versus gains tend to be more loss-aversive. More recently, the same research team, using fMRI, revealed that behavioral loss aversion was correlated with amygdala activation in response to losses relative to gains (Sokol-Hessner et al., 2012).

It is widely acknowledged that 5-HT plays a major role in emotional response or affective state, and enhancing central 5-HT transmission decrease amygdala activation in response to aversive stimuli (Takahashi et al., 2005). Although there have been no PET studies on the relationship between 5-HT transmission and loss aversion, circumstantial evidence suggests that central 5-HT tone might be associated with loss aversion. Enhancing 5-HT transmission by tryptophan load reduced the "reflection effect" (Murphy et al., 2009), which refers to the fact that decision-makers tend to prefer the guaranteed \$50 gain to a 50/50 gamble to win \$100 or no gain at all, showing risk-aversion. However, decision-makers tend to prefer a 50/50 gamble to lose \$100 or no loss at all to the guaranteed \$50 loss, showing risk-seeking. "Reflection effect" and "framing effect" can be partially explained using loss aversion. De Martino et al. (2006) reported that susceptibility to the framing effect was associated with amygdala activation. They also reported that genetic variation in the promoter region of the 5-HT transporter gene (5-HTTTLPR) predicted susceptibility to the framing effect. Homozygosity for s allele showed greater amygdala activation during decision-making and stronger framing effect than l carriers (Roiser et al., 2009). More recently, large-sample behavioral economics studies in a Chinese sample also showed that

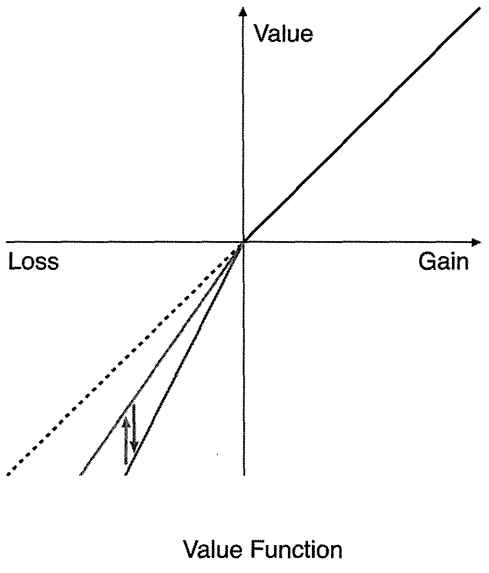

Fig. 3. Hypothesized model showing the contribution of central 5HT and NE tone to loss aversion. 5-HT and NE might contribute to shaping the slope of value function for loss. 5-HT might ease the slope of value function for loss (loss tolerance: green), and NE might intensify the slope (loss aversion: red). The value function is usually assumed to be a power function $v(x)=x^{\sigma}$, but we used common simplifying assumptions that σ is 1 for both value functions in gain and loss domains. The ratio (loss/gain) of the slope of linear functions was indicated as λ.

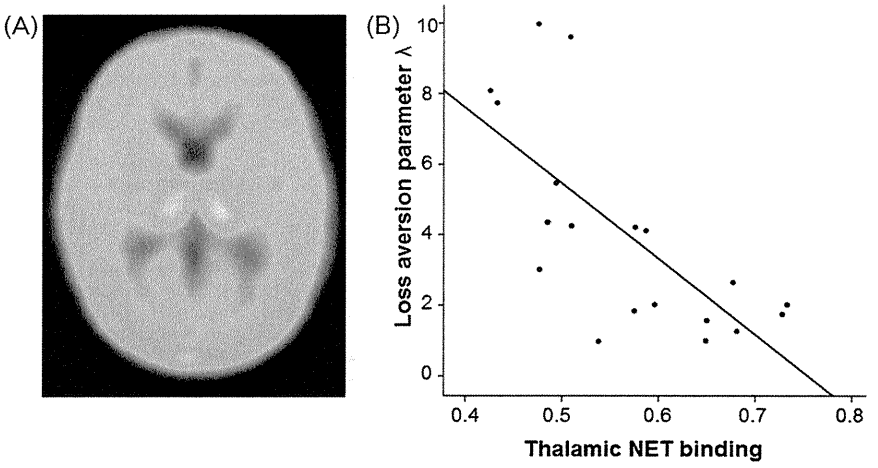

Fig. 4. Relationship between NET in the thalamus and loss aversion: (A) average of spatially normalized summed PET image of (S,S)-[^{18}F]FMeNER-D_2 is shown and (B) negative correlation between NET binding in the thalamus and loss aversion parameter λ is shown.

homozygosity for s allele showed higher loss aversion than l carriers (He et al., 2010). Although it is difficult to estimate pre-and post-synaptic (and net) 5-HT transmission by genetic variation in 5-HTTTLPR (Shioe et al., 2003), 5-HT neurotransmission seems to ease the aversive reaction to financial loss (Fig. 3).

In addition to 5-HT, a line of evidence suggests that norepinephrine (NE) might be involved in loss aversion. The role of NE in arousal is well established (Berridge and Waterhouse, 2003), and physiological arousal response was reported to be associated with behavioral loss aversion (Sokol-Hessner et al., 2009). Central NE blockade by propranolol attenuated the sensitivity to the magnitude of possible losses at gambles (Rogers et al., 2004). Lack of an appropriate PET radioligand has prevented us from investigating the role of central NE transmission in cognition, emotion and decision-making in vivo. However, (S,S)-18F-FMeNER-D2 has recently been developed as a radioligand for the measurement of norepinephrine transporter for PET (Arakawa et al., 2008; Schou et al., 2004). (S,S)-^{18}F-FMeNER-D_2 is a reboxetine analog and has high affinity and high selectivity for norepinephrine transporter (Fig. 4A). We utilized PET scans with (S,S)-[^{18}F]FMeNER-D_2 to investigate the relationship between central NET and loss aversion (Takahashi et al., 2013). Based on previous literatures, we were interested in the amygdala and PFC, but the relatively low expression of NET prevented reliable measurement of their NET binding with this radiologand. A NET-rich region available to PET imaging with this ligand is the thalamus. Therefore, we investigated the relationship between thalamic NET binding and loss aversion.

Loss aversion parameters were determined outside the PET scanner using a 50:50 mixed gamble (gain–loss). This parameter λ is similar to the parameter in prospect theory but makes the common simplifying assumptions of a linear rather than curvilinear value function (Fig. 3), and identical decision weights for a 0.5 probability of a gain or loss. The study revealed that there was a negative correlation between λ and NET binding in the thalamus (Fig. 4B). That is, individuals with low thalamic NET tend to show pronounced aversive reaction to financial losses. In other words, individuals with high thalamic NET tend to show more fearless decision-making. Although NE has been implicated in arousal, it was reported that NE also affects processing of salient information (Berridge and Waterhouse, 2003). Neurons of the locus coeruleus (LC), the major source of NE in the brain, are phasically evoked by salient or emotional stimuli (Aston-Jones et al., 1994), and phasic LC activation leads to NE release in target sites (Berridge and Waterhouse, 2003). Enhancing NE tone by NE re-uptake inhibitor improves detection of emotional stimuli (De Martino et al., 2008), and blockade of central NE by propranolol predominantly impairs processing of negatively emotional stimuli (Cahill et al., 1994). Thus, PET findings suggest that individuals with low NET in the thalamus might show exaggerated or prolonged effect of NE released by salient stimuli due to low reuptake, and consequently show pronounced emotional or arousal response to losses relative to gains. Thalamic NET might be an indirect mediator of the relationship between NE transmission and loss aversion. Similarly to 5-HT transmission, Rasch et al. (2009) reported that a genetic variation of ADRA2B, the gene encoding the α2b-adrenergic receptor, predicted amygdala responsivity to negative emotional stimuli. Future studies with a more appropriate radioligand for measuring NET in the amygdala and PFC, which are implicated in loss aversion, are recommended. For the present, it is not unreasonable to suppose that central NE transmission contributes to shaping the slope of the value function in the loss domain (Fig. 3).

In a clinical setting, NET blocker, atomoxetine, is used in the pharmacotherapy of Attention-Deficit Hyperactivity Disorder (ADHD). ADHD patients are known to show impulsive and reckless decision-making and have high comorbidity rates of drug addiction and gamble addiction (pathological gambling) (Breyer et al., 2009; Pattij and Vanderschuren, 2008). Our finding suggests that NET blockers might shift ADHD patients' decision-making from reckless (less loss-aversive) to more cautious (more loss-aversive) by reducing NET binding. Based on intuitive assumption that pathological gamblers show diminished aversive responses to financial losses, along with ADHD, one can make a prediction that NET inhibitors might be beneficial for pathological gambling. However, pathological gambling seems to be a heterogeneous disorder with various social and biological backgrounds. Diagnostic criteria of pathological gambling are similar to drug addiction, but one characteristic feature of pathological gambling is chasing (American Psychiatric Association, 1994). Pathological gamblers chase their losses and keep gambling in order to get even (but they end up piling up even more losses, and often debts, in reality). Chasing is phenomenon reflecting the unwillingness to accept losses and is similar to the disposition effect or reflection effect, which can be explained by loss aversion. Thus, contrary to intuitive prediction, some types of pathological gamblers might show exaggerated loss aversion. Compared to the DA system, the role of the NE system in reward processing has been less studied, and specifically, the research field that would elucidate the role of NE in decision-making in normal and pathological populations is worthy of further development.

3. Conclusion and future direction

The PET technique is a powerful tool for investigating the relationship between neurotransmitters and decision-making in vivo in human. However, standard PET studies tell us only the correlational relationship. Complementary pharmacological studies as well as animal studies are needed for a full understanding of the causal relationship. Another challenge is the translation of lab evidence into daily-life decision-making and behavior. Laboratory studies are typically conducted in a controlled and simplified environment. Just how well neurochemical information improves the predictability of decision-making model in a more naturalistic setting should be tested (Levallois et al., 2012). Mis-estimating risk could lead not only to drug/gamble addiction but also to other forms of neuropsychiatric disorders such as schizophrenia and depression. An interdisciplinary approach combining molecular imaging techniques, cognitive neuroscience, economics and clinical psychiatry will provide new perspectives for understanding the neurobiology of impaired decision-making in neuropsychiatric disorders as well as their drug development (Takahashi et al., 2012b; Takahashi, 2012a).

Conflict of interest

The author declares no conflict of interest.

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References

Adolphs, R., 2002. Neural systems for recognizing emotion. Curr. Opin. Neurobiol. 12, 169–177.

Arakawa, R., Okumura, M., Ito, H., Seki, C., Takahashi, H., Takano, H., Nakao, R., Suzuki, K., Okubo, Y., Halldin, C., Suhara, T., 2008. Quantitative analysis of norepinephrine transporter in the human brain using PET with (S,S)-^{18}F-FMeNER-D_2. J. Nucl. Med. 49, 1270–1276.

Association Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Aston-Jones, G., Rajkowski, J., Kubiak, P., Alexinsky, T., 1994. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J. Neurosci. 14, 4467–4480.

Berns, G.S., Capra, C.M., Chappelow, J., Moore, S., Noussair, C., 2008. Nonlinear neurobiological probability weighting functions for aversive outcomes. Neuroimage 39, 2047–2057.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84.

Breyer, J.L., Botzet, A.M., Winters, K.C., Stinchfield, R.D., August, G., Realmuto, G., 2009. Young adult gambling behaviors and their relationship with the persistence of ADHD. J. Gambl. Stud. 25, 227–238.

Cahill, L., Prins, B., Weber, M., McGaugh, J.L., 1994. Beta-adrenergic activation and memory for emotional events. Nature 371, 702–704.

Camerer, C.F., Loewenstein, G., 2004. Behavioral economics: past, present, future. In: Camerer, C.F., Loewenstein, G., Rabin, M. (Eds.), Advance in Behavioral Economics. Princeton University Press, Princeton, pp. 3–51.

Camerer, C.F., Fehr, E., 2006. When does "economic man" dominate social behavior? Science 311, 47–52.

Chen, M.K., Lakshminarayanan, V., Santos, L.R., 2006. How basic are behavioral biases? Evidence from capuchin monkey trading behavior. J. Polit. Econ. 114, 517–537.

Dagher, A., Robbins, T.W., 2009. Personality, addiction, dopamine: insights from Parkinson's disease. Neuron 61, 502–510.

De Martino, B., Camerer, C.F., Adolphs, R., 2010. Amygdala damage eliminates monetary loss aversion. Proc. Natl. Acad. Sci. U. S. A. 107, 3788–3792.

De Martino, B., Kumaran, D., Seymour, B., Dolan, R.J., 2006. Frames, biases, and rational decision-making in the human brain. Science 313, 684–687.

De Martino, B., Strange, B.A., Dolan, R.J., 2008. Noradrenergic neuromodulation of human attention for emotional and neutral stimuli. Psychopharmacology (Berl.) 197, 127–136.

Ekelund, J., Slifstein, M., Narendran, R., Guillin, O., Belani, H., Guo, N., Hwang, Y., Hwang, D., Abi-Dargham, A., Laruelle, M., 2007. In vivo DA D1 receptor selectivity of NNC 112 and SCH 23390. Mol. Imaging Biol. 9, 117–125.

Fehr, E., Camerer, C., 2007. Social neuroeconomics: the neural circuitry of social preferences. Trends Cogn. Sci. 11, 419–427.

Frith, U., Frith, C.D., 2003. Development and neurophysiology of mentalizing. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 358, 459–473.

Gallagher, D.A., O'Sullivan, S.S., Evans, A.H., Lees, A.J., Schrag, A., 2007. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. Mov. Disord. 22, 1757–1763.

Glimcher, P.W., Dorris, M.C., Bayer, H.M., 2005. Physiological utility theory and the neuroeconomics of choice. Games Econ. Behav. 52, 213–256.

He, Q., Xue, G., Chen, C., Lu, Z., Dong, Q., Lei, X., Ding, N., Li, J., Li, H., Chen, C., 2010. Serotonin transporter gene-linked polymorphic region (5-HTTLPR) influences decision making under ambiguity and risk in a large Chinese sample. Neuropharmacology 59, 518–526.

Hsu, M., Krajbich, I., Zhao, C., Camerer, C., 2009. Neural response to reward anticipation under risk is nonlinear in probabilities. J. Neurosci. 29, 2231–2237.

Knutson, B., Rick, S., Wimmer, G.E., Prelec, D., Loewenstein, G., 2007. Neural predictors of purchases. Neuron 53, 147–156.

Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage 54, 2492–2502.

Levallois, C., Clithero, J.A., Wouters, P., Smidts, A., Huettel, S.A., 2012. Translating upwards: linking the neural and social sciences via neuroeconomics. Nat. Rev. Neurosci. 13, 789–797.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., Dagher, A., 2002. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[^{11}C]raclopride study in healthy men. Neuropsychopharmacology 27, 1027–1035.

Ligneul, R., Sescousse, G., Barbalat, G., Domenech, P., Dreher, J., 2012. Shifted risk preferences in pathological gambling. Psychol. Med. (Epub ahead of print).

Martinez, D., Slifstein, M., Narendran, R., Foltin, R.W., Broft, A., Hwang, D.R., Perez, A., Abi-Dargham, A., Fischman, M.W., Kleber, H.D., Laruelle, M., 2009. Dopamine D1 receptors in cocaine dependence measured with PET and the choice to self-administer cocaine. Neuropsychopharmacology 34, 1774–1782.

Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, J., 2005. The neural basis of human moral cognition. Nat. Rev. Neurosci. 6, 799–809.

Moore, R., Vinsant, S., Nader, M., Porrino, L., Friedman, D., 1998. Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. Synapse 30, 88–96.

Murphy, S.E., Longhitano, C., Ayres, R.E., Cowen, P.J., Harmer, C.J., Rogers, R.D., 2009. The role of serotonin in nonnormative risky choice: the effects of tryptophan supplements on the "reflection effect" in healthy adult volunteers. J. Cogn. Neurosci. 21, 1709–1719.

Onur, O.A., Walter, H., Schlaepfer, T.E., Rehme, A.K., Schmidt, C., Keysers, C., Maier, W., Hurlemann, R., 2009. Noradrenergic enhancement of amygdala responses to fear. Soc. Cogn. Affect. Neurosci. 4, 119–126.

Pattij, T., Vanderschuren, L.J.M.J., 2008. The neuropharmacology of impulsive behaviour. Trends Pharmacol. Sci. 29, 192–199.

Paulus, M., Frank, L., 2006. Anterior cingulate activity modulates nonlinear decision weight function of uncertain prospects. Neuroimage 30, 668–677.

Prelec, D., 1998. The probability weighting function. Econometrica 66, 497–527.

Rangel, A., Camerer, C., Montague, P.R., 2008. A framework for studying the neurobiology of value-based decision making. Nat. Rev. Neurosci. 9, 545–556.

Rasch, B., Spalek, K., Buholzer, S., Luechinger, R., Boesiger, P., Papassotiropoulos, A., de Quervain, D.J., 2009. A genetic variation of the noradrenergic system is related to differential amygdala activation during encoding of emotional memories. Proc. Natl. Acad. Sci. U. S. A. 106, 19191–19196.

Rogers, R., Lancaster, M., Wakeley, J., Bhagwagar, Z., 2004. Effects of beta-adrenoceptor blockade on components of human decision-making. Psychopharmacology (Berl.) 172, 157–164.

Roiser, J.P., de Martino, B., Tan, G.C., Kumaran, D., Seymour, B., Wood, N.W., Dolan, R.J., 2009. A genetically mediated bias in decision making driven by failure of amygdala control. J. Neurosci. 29, 5985–5991.

Sanfey, A.G., Rilling, J.K., Aronson, J.A., Nystrom, L.E., Cohen, J.D., 2003. The neural basis of economic decision-making in the ultimatum game. Science 300, 1755–1758.

Schou, M., Halldin, C., Sóvágó, J., Pike, V.W., Hall, H., Gulyás, B., Mozley, P.D., Dobson, D., Shchukin, E., Innis, R.B., 2004. PET evaluation of novel radiofluorinated reboxetine analogs as norepinephrine transporter probes in the monkey brain. Synapse 53, 57–67.

Shioe, K., Ichimiya, T., Suhara, T., Takano, A., Sudo, Y., Yasuno, F., Hirano, M., Shinohara, M., Kagami, M., Okubo, Y., Nankai, M., Kanba, S., 2003. No association between genotype of the promoter region of serotonin transporter gene and serotonin transporter binding in human brain measured by PET. Synapse 48, 184–188.

Sokol-Hessner, P., Camerer, C.F., Phelps, E.A., 2012. Emotion regulation reduces loss aversion and decreases amygdala responses to losses. Soc. Cogn. Affect. Neurosci. (Epub ahead of print).
Sokol-Hessner, P., Hsu, M., Curley, N.G., Delgado, M.R., Camerer, C.F., Phelps, E.A., 2009. Thinking like a trader selectively reduces individuals' loss aversion. Proc. Natl. Acad. Sci. U. S. A. 106, 5035–5040.
Steeves, T.D., Miyasaki, J., Zurowski, M., Lang, A.E., Pellecchia, G., Van Eimeren, T., Rusjan, P., Houle, S., Strafella, A.P., 2009. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [^{11}C]raclopride PET study. Brain 132, 1376–1385.
St Onge, J.R., Floresco, S.B., 2009. Dopaminergic modulation of risk-based decision making. Neuropsychopharmacology 34, 681–697.
Takahashi, H., 2012a. Monoamines and assessment of risks. Curr. Opin. Neurobiol. 22, 1062–1067.
Takahashi, H., Fujie, S., Camerer, C., Arakawa, R., Takano, H., Kodaka, F., Matsui, H., Ideno, T., Okubo, S., Takemura, K., Yamada, M., Eguchi, Y., Murai, T., Okubo, Y., Kato, M., Ito, H., Suhara, T., 2013. Norepinephrine in the brain is associated with aversion to financial loss. Mol. Psychiatry 18, 3–4.
Takahashi, H., Kato, M., Matsuura, M., Mobbs, D., Suhara, T., Okubo, Y., 2009. When your gain is my pain and your pain is my gain: neural correlates of envy and schadenfreude. Science 323, 937–939.
Takahashi, H., Matsui, H., Camerer, C., Takano, H., Kodaka, F., Ideno, T., Okubo, S., Takemura, K., Arakawa, R., Eguchi, Y., Murai, T., Okubo, Y., Kato, M., Ito, H., Suhara, T., 2010a. Dopamine D receptors and nonlinear probability weighting in risky choice. J. Neurosci. 30, 16567–16572.
Takahashi, H., Takano, H., Kodaka, F., Arakawa, R., Yamada, M., Otsuka, T., Hirano, Y., Kikyo, H., Okubo, Y., Kato, M., Obata, T., Ito, H., Suhara, T., 2010b. Contribution of dopamine D1 and D2 receptors to amygdala activity in human. J. Neurosci. 30, 3043–3047.
Takahashi, H., Yahata, N., Koeda, M., Matsuda, T., Asai, K., Okubo, Y., 2004. Brain activation associated with evaluative processes of guilt and embarrassment: an fMRI study. Neuroimage 23, 967–974.
Takahashi, H., Yahata, N., Koeda, M., Takano, A., Asai, K., Suhara, T., Okubo, Y., 2005. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. Neuroimage 27, 991–1001.
Takahashi, H., Yamada, M., Suhara, T., 2012b. Functional significance of central D1 receptors in cognition: beyond working memory. J. Cereb. Blood Flow Metab. 32, 1248–1258.
Tobler, P.N., Christopoulos, G.I., O'Doherty, J.P., Dolan, R.J., Schultz, W., 2008. Neuronal distortions of reward probability without choice. J. Neurosci. 28, 11703–11711.
Tom, S., Fox, C., Trepel, C., Poldrack, R., 2007. The neural basis of loss aversion in decision-making under risk. Science 315, 515–518.
Trepel, C., Fox, C., Poldrack, R., 2005. Prospect theory on the brain? Toward a cognitive neuroscience of decision under risk. Cogn. Brain Res. 23, 34–50.
Tversky, A., Kahneman, D., 1992. Advances in prospect theory: cumulative representation of uncertainty. J. Risk Uncertain. 5, 297–323.
Yasuno, F., Ota, M., Ando, K., Ando, T., Maeda, J., Ichimiya, T., Takano, A., Doronbekov, T.K., Fujimura, Y., Nozaki, S., Suhara, T., 2007. Role of ventral striatal dopamine D1 receptor in cigarette craving. Biol. Psychiatry 61, 1252–1259.

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Psychiatry and Clinical Neurosciences

PCN Frontier Review

Cognitive neuroscience of social emotions and implications for psychopathology: Examining embarrassment, guilt, envy, and schadenfreude

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Social emotions are affective states elicited during social interactions and integral for promoting socially appropriate behaviors and discouraging socially inappropriate ones. Social emotion-processing deficits significantly impair interpersonal relationships, and play distinct roles in the manifestation and maintenance of clinical symptomatology. Elucidating the neural correlates of discrete social emotions can serve as a window to better understanding and treating neuropsychiatric disorders. Moral cognition and social emotion-processing broadly recruit a fronto–temporo–subcortical network, supporting empathy, perspective-taking, self-processing, and reward-processing. The present review specifically examines the neural correlates of embarrassment, guilt, envy, and schadenfreude. Embarrassment and guilt are self-conscious emotions, evoked during negative evaluation following norm violations and supported by a fronto–temporo–posterior network. Embarrassment is evoked by social transgressions and recruits greater anterior temporal regions, representing conceptual social knowledge. Guilt is evoked by moral transgressions and recruits greater prefrontal regions, representing perspective-taking and behavioral change demands. Envy and schadenfreude are fortune-of-other emotions, evoked during social comparison and supported by a prefronto–striatal network. Envy represents displeasure in others' fortunes, and recruits increased dorsal anterior cingulate cortex, representing cognitive dissonance, and decreased reward-related striatal regions. Schadenfreude represents pleasure in others' misfortunes, and recruits reduced empathy-related insular regions and increased reward-related striatal regions. Implications for psychopathology and treatment design are discussed.

Key words: embarrassment, envy, functional magnetic resonance imaging, guilt, schadenfreude.

SO FAR, ABOUT morals, I know only that what is moral is what you feel good after and what is immoral is what you feel bad after.

Ernest Hemingway, *Death in the Afternoon*

INTRODUCTION TO SOCIAL EMOTIONS

Social emotions are the driving force for maintaining interpersonal relationships, integral for motivating

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socially appropriate behaviors and seeking reparations for inappropriate ones. A large body of research has explored the neural correlates of social emotions, broadly examining moral cognition, empathy, and social decision-making, as well as investigating distinct emotions, such as guilt and envy. This literature not only informs the neural bases of prosocial and antisocial behaviors, such as altruistic giving, reciprocal cooperation, and social withdrawal, but also sheds light onto atypical cognitive processes underlying neuropsychiatric disorders, ranging from depression and anxiety to autism and frontotemporal dementia. This research is not only capable of elucidating the antecedents of clinical symptomatology, but also offers insight into future treatment avenues. Although a complete review of the neural bases of social emotions is beyond the scope of this paper, we summarize recent neuroimaging research – specifically examining embarrassment, guilt, envy, and schadenfreude – and discuss clinical implications.

Moral emotions

Social emotions are broadly defined as context-dependent affective states, evoked during social interactions.[1] These include moral and self-conscious emotions (SCE), associated with obedience or transgression of societal norms, and fortune-of-other emotions (FOE), evoked via social comparison. Moral emotions are related to the interests and welfare of specific individuals or society at large,[2] and are integral for promoting socially acceptable behaviors and inhibiting socially unacceptable actions.[3,4] This class of emotions represents the recognition and adoption of universally accepted rules and culturally defined conventions.[5] Moll *et al.* characterized moral emotions as the product of 'contextual social knowledge', integrating event knowledge, social semantic knowledge, and emotional/motivational states.[6]

Self-conscious emotions

SCE are a subset of moral emotions and the product of personal reflection and inferred evaluation. SCE are evoked by direct experience or in anticipation of others' evaluations. SCE are primarily supported by three cognitive processes: (i) self-awareness, underlying self-referential processing; (ii) other-awareness, underlying mental state attribution; and (iii) social norm-awareness, underlying the identification and adoption of societal standards.[7,8] Unlike basic emotions (e.g., happiness, sadness), which emerge within the first 9 months, SCE are more cognitively demanding and emerge after 36 months, coinciding with the acquisition and internalization of social rules, expectations, and values.[9] Similar to moral emotions, SCE promote social goals, such as social regulation.[7,10,11] Tangney *et al.* suggested that SCE serve as an 'emotional moral barometer,' providing feedback on the acceptability of one's behavior.[5] Consequently, these predicted or inferred evaluations guide moral behavior and social decision-making. Prototypical SCE include embarrassment, guilt, shame, and pride.

Fortune-of-other emotions

FOE are the product of social comparison and represent affective responses to others' attributes, possessions, or outcomes.[12–14] Similar to SCE, which arise from a discrepancy between one's ideal self and current self, FOE represent a discrepancy between one's current status and the status of another person. FOE are divided into four categories: 'happy for', 'sorry for', 'resentment', and 'gloating', and are modulated by four factors: (i) personal desirability of an outcome; (ii) inferred desirability of an outcome for a target; (iii) inferred target deservedness; and (iv) target likeability.[12]

A CLOSER LOOK AT EMBARRASSMENT, GUILT, ENVY, AND SCHADENFREUDE

Embarrassment

Embarrassment and guilt are SCE, representing inferred negative self-evaluations in response to moral or social norm violations. Embarrassment is generally evoked by less severe, but more personal, social transgressions.[5,15,16] Embarrassment has a strong public focus and commonly :represents 'normative public deficiencies,' such as acting clumsy or committing a faux pas. Embarrassment is typically short-lived and more likely to be found amusing and discussed with others.[5,15] Embarrassment is characterized by heightened physiological responding (e.g., blushing, increased heart rate) and universally recognized appeasement gestures, such as downward head tilt and eye gaze.[17–20] Accordingly, embarrassment serves self-regulatory functions, signaling the need to monitor, hide, or change one's behavior,[5,11] and promoting prosocial or reparative actions.[21,22]

Guilt

Guilt and shame are similar SCE, typically elicited by severe, moral violations, and are more painful and less fleeting than embarrassment. Guilt and shame are evoked by comparable situations that do not differ in severity, morality, or personal responsibility; however, they represent distinct attributions and promote different behaviors.[23] Guilt represents internal attributions of unstable, discrete behaviors, while shame represents internal attributions of stable, global self-evaluations.[24] Guilt is evoked by specific transgressions and motivates prosociality, other-oriented empathy, and reparation, while shame is evoked by perceived self-deficiencies and promotes self-defense, denial, and avoidance.[11,15] A person may feel guilt after offending a friend (action-focused), but feel shame when perceiving oneself as disloyal (global self-focused). While guilt encourages accountability and atonement, intended to restore relationships, shame motivates escape and withdrawal, intended to prevent further self-denigration. Thus, both embarrassment and guilt (but not shame) are psychologically adaptive emotions that serve social regulatory functions, including inhibiting transgressions and encouraging reparation.[11]

Envy

Envy is a 'resentment' FOE, representing displeasure evoked by another person's fortune, or negative affect resulting from upward social comparison.[12] A person may feel envy when a colleague receives a sought-after promotion or a coveted role in a play. Dispositional envy is associated with feelings of inferiority,[25] while episodic envy is modulated by domain self-relevance, perceived target likeability, and perceived target deservedness, such that greater envy is evoked during social comparison of self-relevant traits, particularly when a comparison target is disliked or perceived as undeserving.[12,26–28]

Schadenfreude

Schadenfreude is a 'gloating' FOE, representing pleasure evoked by another person's misfortune, or positive affect resulting from downward social comparison.[12] A person may feel schadenfreude when a rival athlete loses a competition or a bully experiences pain. A related concept, 'counterempathy', or anti-empathy, represents incongruent affective responding to others' fortunes and misfortunes, and strongly resembles envy and schadenfreude. Schadenfreude is modulated by target likeability and target deservedness.[28–31] Schadenfreude is strongly related to envy: episodic envy is a significant predictor of episodic schadenfreude and mediates the relationship between dispositional envy and episodic schadenfreude.[28,32]

WHAT CAN WE LEARN FROM SOCIAL COGNITIVE NEUROSCIENCE?

Clinical studies

Two broad bodies of literature, clinical behavioral studies and neuroimaging studies, have investigated the neural bases of social emotions. Clinical studies allow researchers to examine naturally occurring social cognitive impairments, resulting from atypical neural development or acquired neural damage. Studying clinical populations can help elucidate the neural mechanisms underlying distinct social cognitive processes and can offer causal explanations for the manifestation of specific deficits.

A primary limitation of clinical research is a reduced level of control and specificity, more readily afforded by experimental manipulations. Clinical populations demonstrate a wide range of social and cognitive deficits, making it difficult to determine, from behavioral studies alone, how neural impairments influence distinct abilities. In addition, clinical populations often reveal impairments extending across multiple neural regions or complex neural networks, making it difficult to ascertain which regions are distinctly responsible for diverse deficits.

Neuroimaging studies

Neuroimaging research complements and extends clinical studies by investigating the neural correlates of similar, but distinct, processes using fine-grain manipulations. Neuroimaging can shed light onto the unique functions of neural regions and the integrative roles of large-scale neural networks, while avoiding the confounds of comorbidity and extensive neural damage. Neuroimaging can also elucidate the separable cognitive and affective components underlying varying processes. For example, neuroimaging can help clarify if attenuated empathy is due to poor perspective-taking, emotion recognition, or interoception, by revealing activation patterns of dis-