mice compared with wild-type mice, suggesting hyperactivation of *Adcyap1*$^{-/-}$ prefrontal cortical neurons by amphetamine. Amphetamine-induced increase in the number of c-Fos-positive neurons in the dorsomedial striatum (Fig. 6) and other regions, including the cingulate cortex and nucleus accumbens (data not shown), was not significantly different between the two groups.

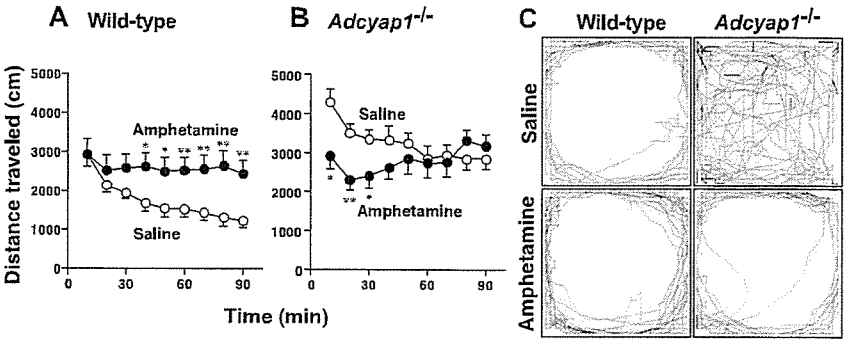

Figure 3. Locomotor activity in the open field test. *A*, *B*, Locomotor activity in wild-type (*A*) and *Adcyap1*$^{-/-}$ (*B*) mice that received 2 mg/kg amphetamine (closed circles) or saline (open circles). $n = 16$ per group. $^{*}p < 0.05$ and $^{**}p < 0.01$ versus saline. *C*, Representative locomotor patterns of saline-treated (top panels) or 2 mg/kg amphetamine-treated (bottom panels) wild-type (left panels) and *Adcyap1*$^{-/-}$ (right panels) mice during 25–30 min of a 90 min recording in an open field test. Data are expressed as means ± SEM.

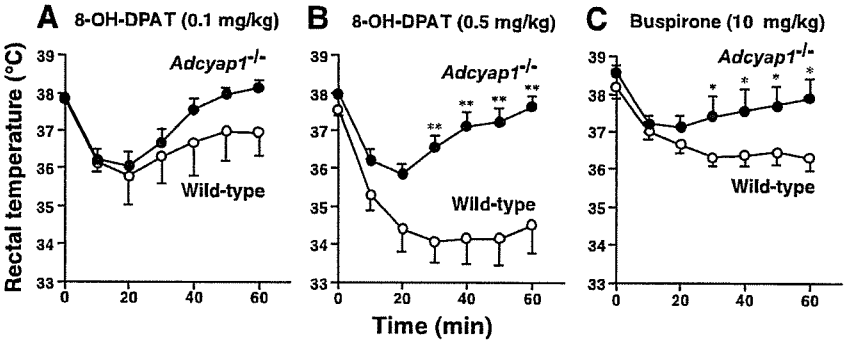

Figure 4. 5-HT$_{1A}$ agonist-induced hypothermia. Wild-type (open circles) and *Adcyap1*$^{-/-}$ (closed circles) mice were injected intraperitoneally with 0.1 mg/kg 8-OH-DPAT (*A*), 0.5 mg/kg 8-OH-DPAT (*B*), or 10 mg/kg buspirone (*C*). Rectal temperature was measured at the indicated times. $n = 7–8$ per group. $^{*}p < 0.05$ and $^{**}p < 0.01$ versus wild-type mice. Data are expressed as means ± SEM.

Discussion

Psychostimulants are controlled substances, because they have long-term sensitizing effects and a potential for abuse, and they may also be neurotoxic. However, psychostimulant treatment has long been recognized to attenuate hyperactivity, paradoxically, and often to improve cognitive performance (Castellanos and Tannock, 2002; Solanto, 2002; Garland and Kirkpatrick, 2004). Animal studies have demonstrated that psychostimulants have biphasic effects on motor activity and cognitive processes (Solanto, 1998), but underlying mechanisms remain mostly uncharacterized. We demonstrated that *Adcyap1*$^{-/-}$ mice showed psychopathological changes, including PPI deficits, and investigated the effects of psychostimulants on hyperactivity, PPI deficits, and excessive jumping activity, as well as the role of 5-HT$_{1A}$ signaling in the paradoxical actions of amphetamine on hyperactivity. These findings seem a long way from the clinical disorders of hyperkinesia and cognitive impairment, but we hope to provide models with some typical features of psychostimulant responses in these disorders.

There is considerable evidence for the involvement of dopaminergic systems in the control of PPI (Geyer et al., 2001). We demonstrated that, although hyperlocomotion (Hashimoto et al., 2001) and jumping behavior in *Adcyap1*$^{-/-}$ mice were effectively attenuated by haloperidol (a D_2 antagonist), PPI deficits were not reversed by haloperidol. Other than DA, glutamatergic systems are important for modulating PPI (Geyer et al., 2001). PPI is reduced in rodents and humans by noncompetitive NMDA antagonists, such as phencyclidine and dizocilpine [(+)-5-methyl-10,11-dihydro-5*H*-dibenzo [a,d] cyclohepten-5,10-imine maleate]. Several studies have shown that PACAP can potentiate NMDA receptor functions (Stella and Magistretti, 1996; Liu and Madsen, 1997; Pellegri et al., 1998). Recently, we showed that *Adcyap1*$^{-/-}$ mice do not exhibit inflammatory or neuropathic pain, and PACAP is required for functional coupling of neuronal nitric oxide synthase to NMDA receptors in the spinal cord for chronic pain to occur (Mabuchi et al., 2004). This raises the possibility that similar mechanisms might be involved in psychomotor changes in *Adcyap1*$^{-/-}$ mice. PPI deficits in *Adcyap1*$^{-/-}$ mice may therefore be ascribable in part to NMDA hypofunction.

One of the most striking findings in our study was that amphetamine completely reversed PPI deficits in *Adcyap1*$^{-/-}$ mice and, to our knowledge, this is the first animal model showing PPI deficits and paradoxical responses to psychostimulants. DA transporter knock-out mice were shown to exhibit PPI deficits, which were improved by the D_2 receptor antagonist raclopride (Ralph et al., 2001a) and the 5-HT$_{2A}$ receptor antagonist M100907 (Barr et al., 2004). Therefore, it will be interesting to investigate the effects of psychostimulants on PPI deficits in DA transporter knock-out mice.

Adcyap1$^{-/-}$ mice did not show a significant increase in PPI from 4 to 8 weeks of age, suggesting that the process of sensorimotor gating remains functionally immature. Developmental issues are considered to be particularly relevant to understanding PPI deficits in humans, because PPI appears to develop in children 5–8 years of age (Ornitz et al., 1990). In addition, *Adcyap1*$^{-/-}$ mice showed a slight decrease in 5-HT metabolite 5-hydroxyindoleacetic acid in their brain (Hashimoto et al., 2001), and this was manifested at 4 weeks of age (the earliest age tested) (our unpublished data). Several lines of evidence suggest that PACAP acts as a neurotrophic factor and plays diverse roles in mammalian neurogenesis (Arimura, 1998; Vaudry et al., 2000). Therefore, it is conceivable that developmental defects in 5-HT systems, or the relative balance of tone between 5-HT and other neurotransmitter systems, such as the glutamatergic system, may contribute to PPI deficits and hyperactivity in *Adcyap1*$^{-/-}$ mice. However, this does not exclude the possibility that PACAP is actively involved in psychological functions. Three

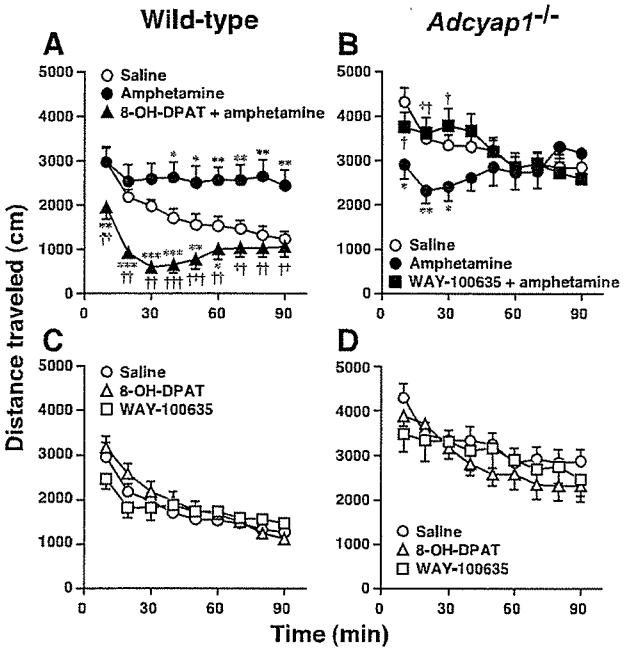

Figure 5. Locomotor activity in the open field test. ***A–D***, Locomotor activity in wild-type (***A***, ***C***) and *Adcyap1*$^{-/-}$ (***B***, ***D***) mice that received 0.05 mg/kg 8-OH-DPAT (triangles), 0.3 mg/kg WAY-100635 (squares), or saline (circles) either alone (open symbols) or in combination with 2 mg/kg amphetamine (closed symbols). The results of the experiment with amphetamine or saline alone are the same as those in Figure 3. $n = 15–16$ per group. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ versus saline alone; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, and $^{\dagger\dagger\dagger}p < 0.001$ versus amphetamine. Data are expressed as means ± SEM.

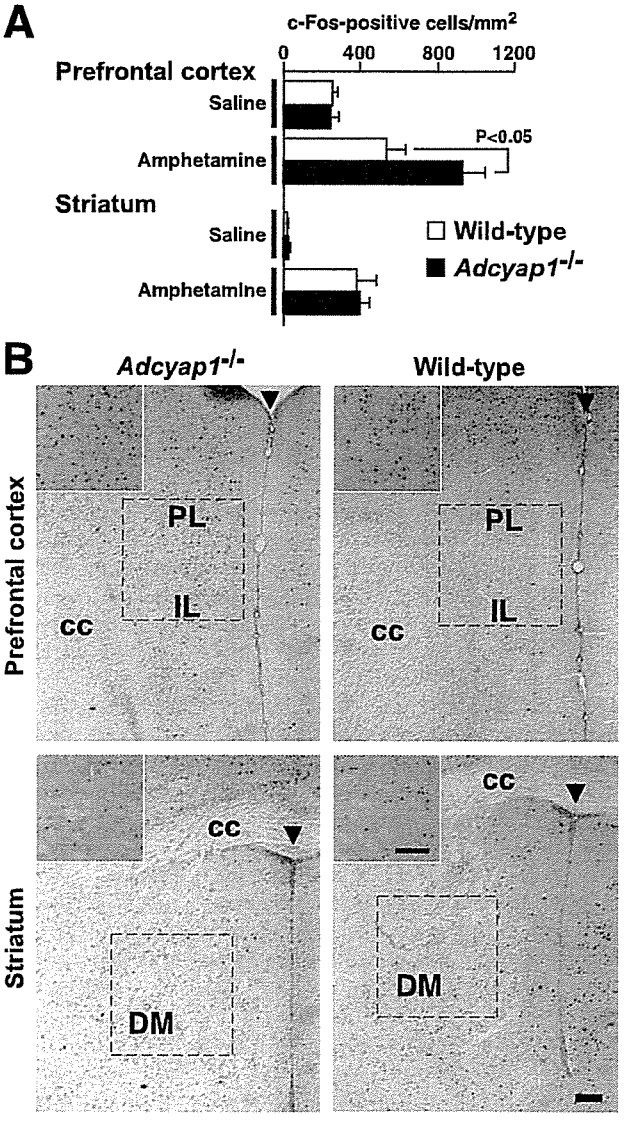

Figure 6. c-Fos-positive neurons in medial prefrontal cortex and dorsomedial striatum in amphetamine-treated *Adcyap1*$^{-/-}$ mice. ***A***, Number of c-Fos-positive neurons in the outlined regions in ***B*** in wild-type (open bars) and *Adcyap1*$^{-/-}$ (closed bars) mice that received 10 mg/ml amphetamine. $n = 6–7$ per group. ***B***, Photomicrographs showing representative c-Fos labeling in medial prefrontal cortex (top panels) and dorsomedial striatum (bottom panels) in amphetamine-treated *Adcyap1*$^{-/-}$ (left panels) and wild-type (right panels) mice. Insets, High magnifications of c-Fos staining. PL, Prelimbic cortex; IL, infralimbic cortex; DM, dorsomedial striatum; cc, corpus callosum; arrowheads, midline. Scale bars, 100 μm. Data are expressed as means ± SEM.

different PACAP knock-out lines (Gray et al., 2001; Hamelink et al., 2002; Colwell et al., 2004) developed separately from our colony have been reported to also show dysfunction of lipid and carbohydrate metabolism, cold hypersensitivity, impaired catecholamine regulation in the sympathoadrenal axis, and deficits in the circadian light response, suggesting putative developmental and/or neuroplastic abnormalities in these mutant mice.

It has been postulated that prefrontal cortex dysregulation may lead to disinhibition in targets of the prefrontal cortex projection, with a possible relevance to dysregulation of motor functions and PPI (Swerdlow and Geyer, 1998; Goldman-Rakic et al., 2000). *In vivo* microdialysis showed that basal and amphetamine-induced release of extracellular DA and 5-HT in the prefrontal cortex did not differ significantly between *Adcyap1*$^{-/-}$ and wild-type mice (DA, $F_{(20,180)} = 0.198$; not significant; 5-HT, $F_{(20,180)} = 1.069$; not significant). However, the number of c-Fos-positive neurons increased in the medial prefrontal cortex of *Adcyap1*$^{-/-}$ mice compared with wild-type mice after amphetamine administration. This result raises the possibility that hyperactivation of prefrontal cortical neurons by amphetamine might result in an increased inhibitory control by prefrontal neurons in *Adcyap1*$^{-/-}$ mice. It has been demonstrated that c-*fos* mRNA expression in the frontal cortex is increased by environmental novelty, but this effect is not further increased by amphetamine (Badiani et al., 1998). Likewise, when exposed to novelty (alone), the increase in c-Fos-positive neurons in the prefrontal cortex tended to be greater in *Adcyap1*$^{-/-}$ mice compared with wild-type mice, but the effect of novelty was similar to that of amphetamine in the respective groups of mice (data not shown). Additional studies to define and characterize these cell populations responsible for the effects of amphetamine and novelty will help to investigate the neuronal mechanisms for psychostimulant treatment.

Studies in DA transporter knock-out mice suggest the tantalizing possibility that hyperkinetic behavior might be controlled through precise targeting of 5-HT receptors, or even through enhanced availability of 5-HT precursors (Gainetdinov et al., 1999). The latter possibility is still controversial, because therapeutic efficacy of selective serotonergic drugs is not commonly recognized in treating hyperkinetic disorder (Gainetdinov and Caron, 2000; Popper, 2000; Davids et al., 2003). The reason for this may be simply a result of the large multiplicity of 5-HT receptor subtypes and existence of multiple 5-HT autoreceptors, having sometimes opposing or no effects on locomotion (Geyer,

1996; Lucki, 1998). Regarding the former possibility (precise targeting of 5-HT receptors), the present study showed that WAY-100635 blocked the amphetamine-elicited antihyperkinetic effect in *Adcyap1*$^{-/-}$ mice, and that amphetamine produced a paradoxical calming effect in 8-OH-DPAT-treated wild-type mice. Previous reports show that 8-OH-DPAT attenuates psychostimulant-induced behavioral sensitization and increment in locomotor activity, where both presynaptic and postsynaptic 5-HT_{1A} receptor-dependent mechanisms are suggested to be involved (Przegalinski and Filip, 1997; Przegalinski et al., 2000; Carey et al., 2005). However, the paradoxical calming effect of psychostimulant plus 5-HT_{1A} receptor agonist combination has hitherto not been addressed and may provide provocative clues into the mechanisms of the therapeutic effects of psychostimulants. Together with previous reports, the present data suggest that the targeting of 5-HT_{1A} receptors, adjunctive to psychostimulants, are promising for pharmaceutical intervention in hyperkinetic disorder.

Histochemical studies have shown that PACAP immunoreactivity is present in several brain regions involved in the DA and 5-HT systems, including the cerebral cortex, nucleus accumbens, amygdala, hypothalamus, substantia nigra, ventral tegmental area, and dorsal raphe nucleus (Masuo et al., 1993; Piggins et al., 1996). PAC_1 receptors are expressed broadly in both the target areas and nuclei of origin of these monoaminergic systems (Hashimoto et al., 1996). $VPAC_1$ and $VPAC_2$ receptors are also expressed in these systems (Usdin et al., 1994). These observations suggest a functional relationship between PACAP and monoaminergic neurons. Serotonergic cell bodies are located mainly in the raphe nuclei, whereas 5-HT-containing terminals are widely distributed in the brain. Among 5-HT receptor subtypes, 5-HT_{1A} receptors are expressed presynaptically as the primary somatodendritic autoreceptor on serotonergic raphe neurons and postsynaptically in a variety of other neurons (Barnes and Sharp, 1999). Although there is no report of colocalization analysis between PACAP/PACAP receptors and 5-HT-containing elements, it is plausible that PACAP modulates the serotonergic system both at the origin and innervation sites. The reduced hypothermic response to 5-HT_{1A} agonists in *Adcyap1*$^{-/-}$ mice supports the functional coupling between the two systems.

The supplemental figure (available at www.jneurosci.org as supplemental material) shows a schematic representation of possible relationships between locomotor activity and degree of stimulation of 5-HT_{1A} systems in amphetamine-treated *Adcyap1*$^{-/-}$ and wild-type mice. Neither WAY-100635 nor 8-OH-DPAT alone influenced locomotor activity in both groups, indicating that changes in 5-HT_{1A} systems per se do not influence locomotor activity. The observations that WAY-100635 blocked the amphetamine-elicited antihyperkinetic effect in *Adcyap1*$^{-/-}$ mice, and that amphetamine induced hypokinesia in 8-OH-DPAT-treated wild-type mice, indicate that the 5-HT_{1A} relative activity has a great influence on the effects of amphetamine. Psychostimulants have been hypothesized to exert rate-dependent effects that show a negative linear correlation with the baseline rate of activity (Solanto, 1998, 2002). The present results suggest that the stimulation level of 5-HT_{1A} systems, or the relative balance with other 5-HT receptor subtypes or neurotransmitter systems, might be involved in the rate-dependent effects elicited by psychostimulants.

Many psychiatric disorders are multifactorial, reflecting longitudinal and complex interactions of causative agents, including genetic and environmental factors. Pathogenesis remains poorly understood; therefore, animal models provide useful tools to investigate the mechanisms underlying human diseases and for the design of new treatments (Lipska and Weinberger, 2000). Although, *Adcyap1*$^{-/-}$ mice do not provide an animal model of some specific psychiatric disorder per se, the present study may provide insights into the pathophysiology and etiology of hyperkinetic disorder and other disorders including disrupted PPI.

References

Aguirre N, Ballaz S, Lasheras B, Del-Rio J (1998) MDMA ("Ecstasy") enhances 5-HT_{1A} receptor density and 8-OH-DPAT-induced hypothermia: blockade by drugs preventing 5-hydroxytryptamine depletion. Eur J Pharmacol 346:181–188.

Arimura A (1998) Perspectives on pituitary adenylate cyclase activating polypeptide (PACAP) in the neuroendocrine, endocrine, and nervous systems. J Physiol (Japan) 48:301–331.

Badiani A, Oates MM, Day HE, Watson SJ, Akil H, Robinson TE (1998) Amphetamine-induced behavior, dopamine release, and c-*fos* mRNA expression: modulation by environmental novelty. J Neurosci 18:10579–10593.

Barnes NM, Sharp T (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38:1083–1152.

Barr AM, Lehmann-Masten V, Paulus M, Gainetdinov RR, Caron MG, Geyer MA (2004) The selective serotonin-2A receptor antagonist M100907 reverses behavioral deficits in dopamine transporter knockout mice. Neuropsychopharmacology 29:221–228.

Carey RJ, DePalma G, Damianopoulos E, Shanahan A, Muller CP, Huston JP (2005) Evidence that the 5-HT_{1A} autoreceptor is an important pharmacological target for the modulation of cocaine behavioral stimulant effects. Brain Res 1034:162–171.

Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617–628.

Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M (1996) Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. Biol Psychiatry 39:33–41.

Colwell CS, Michel S, Itri J, Rodriguez W, Tam J, Lelievre V, Hu Z, Waschek JA (2004) Selective deficits in the circadian light response in mice lacking PACAP. Am J Physiol Regul Integr Comp Physiol 287:R1194–R1201.

Davids E, Zhang K, Tarazi FI, Baldessarini RJ (2003) Animal models of attention-deficit hyperactivity disorder. Brain Res Brain Res Rev 42:1–21.

Franklin KBJ, Paxinos G (1997) The mouse brain in stereotaxic coordinates. San Diego: Academic.

Gainetdinov RR, Caron MG (2000) An animal model of attention deficit hyperactivity disorder. Mol Med Today 6:43–44.

Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG (1999) Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science 283:397–401.

Garland M, Kirkpatrick P (2004) Atomoxetine hydrochloride. Nat Rev Drug Discov 3:385–386.

Geyer MA (1996) Serotonergic functions in arousal and motor activity. Behav Brain Res 73:31–35.

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156:117–154.

Goldman-Rakic PS, Muly III EC, Williams GV (2000) D_1 receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 31:295–301.

Gray SL, Cummings KJ, Jirik FR, Sherwood NM (2001) Targeted disruption of the pituitary adenylate cyclase-activating polypeptide gene results in early postnatal death associated with dysfunction of lipid and carbohydrate metabolism. Mol Endocrinol 15:1739–1747.

Hamelink C, Tjurmina O, Damadzic R, Young WS, Weihe E, Lee HW, Eiden LE (2002) Pituitary adenylate cyclase-activating polypeptide is a sympathoadrenal neurotransmitter involved in catecholamine regulation and glucohomeostasis. Proc Natl Acad Sci USA 99:461–466.

Hashimoto H, Nogi H, Mori K, Ohishi H, Shigemoto R, Yamamoto K, Matsuda T, Mizuno N, Nagata S, Baba A (1996) Distribution of the mRNA for a pituitary adenylate cyclase-activating polypeptide receptor in the rat brain: an in situ hybridization study. J Comp Neurol 371:567–577.

Hashimoto H, Shintani N, Tanaka K, Mori W, Hirose M, Matsuda T, Sakaue

M, Miyazaki J, Niwa H, Tashiro F, Yamamoto K, Koga K, Tomimoto S, Kunugi A, Suetake S, Baba A (2001) Altered psychomotor behaviors in mice lacking pituitary adenylate cyclase-activating polypeptide (PACAP). Proc Natl Acad Sci USA 98:13355–13360.

Hashimoto H, Shintani N, Baba A (2006) New insights into the central PACAPergic system from the phenotypes in PACAP- and PACAP receptor-knockout mice. Ann NY Acad Sci, in press.

Hawk Jr LW, Yartz AR, Pelham Jr WE, Lock TM (2003) The effects of methylphenidate on prepulse inhibition during attended and ignored prestimuli among boys with attention-deficit hyperactivity disorder. Psychopharmacology 165:118–127.

Kawaguchi C, Tanaka K, Isojima Y, Shintani N, Hashimoto H, Baba A, Nagai K (2003) Changes in light-induced phase shift of circadian rhythm in mice lacking PACAP. Biochem Biophys Res Commun 310:169–175.

Lipska BK, Weinberger DR (2000) To model a psychiatric disorder in animals: schizophrenia as a reality test. Neuropsychopharmacology 23:223–239.

Liu GJ, Madsen BW (1997) PACAP38 modulates activity of NMDA receptors in cultured chick cortical neurons. J Neurophysiol 78:2231–2234.

Lucki I (1998) The spectrum of behaviors influenced by serotonin. Biol Psychiatry 44:151–162.

Mabuchi T, Shintani N, Matsumura S, Okuda-Ashitaka E, Hashimoto H, Muratani T, Minami T, Baba A, Ito S (2004) Pituitary adenylate cyclase-activating polypeptide is required for the development of spinal sensitization and induction of neuropathic pain. J Neurosci 24:7283–7291.

Masuo Y, Suzuki N, Matsumoto H, Tokito F, Matsumoto Y, Tsuda M, Fujino M (1993) Regional distribution of pituitary adenylate cyclase activating polypeptide (PACAP) in the rat central nervous system as determined by sandwich-enzyme immunoassay. Brain Res 602:57–63.

Ornitz EM, Guthrie D, Lane SJ, Sugiyama T (1990) Maturation of startle facilitation by sustained prestimulation. Psychophysiology 27:298–308.

Pellegri G, Magistretti PJ, Martin JL (1998) VIP and PACAP potentiate the action of glutamate on BDNF expression in mouse cortical neurones. Eur J Neurosci 10:272–280.

Piggins HD, Stamp JA, Burns J, Rusak B, Semba K (1996) Distribution of pituitary adenylate cyclase activating polypeptide (PACAP) immunoreactivity in the hypothalamus and extended amygdala of the rat. J Comp Neurol 376:278–294.

Popper CW (2000) Pharmacologic alternatives to psychostimulants for the treatment of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 9:605–646.

Przegalinski E, Filip M (1997) Stimulation of serotonin $(5\text{-HT})_{1A}$ receptors attenuates the locomotor, but not the discriminative, effects of amphetamine and cocaine in rats. Behav Pharmacol 8:699–706.

Przegalinski E, Siwanowicz J, Baran L, Filip M (2000) Activation of serotonin $(5\text{-HT})_{1A}$ receptors inhibits amphetamine sensitization in mice. Life Sci 66:1011–1019.

Ralph RJ, Paulus MP, Fumagalli F, Caron MG, Geyer MA (2001a) Prepulse inhibition deficits and perseverative motor patterns in dopamine transporter knock-out mice: differential effects of D_1 and D_2 receptor antagonists. J Neurosci 21:305–313.

Ralph RJ, Paulus MP, Geyer MA (2001b) Strain-specific effects of amphetamine on prepulse inhibition and patterns of locomotor behavior in mice. J Pharmacol Exp Ther 298:148–155.

Sakaue M, Ago Y, Baba A, Matsuda T (2003) The 5-HT_{1A} receptor agonist MKC-242 reverses isolation rearing-induced deficits of prepulse inhibition in mice. Psychopharmacology 170:73–79.

Shintani N, Mori W, Hashimoto H, Imai M, Tanaka K, Tomimoto S, Hirose M, Kawaguchi C, Baba A (2002) Defects in reproductive functions in PACAP-deficient female mice. Regul Pept 109:45–48.

Solanto MV (1998) Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res 94:127–152.

Solanto MV (2002) Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res 130:65–71.

Stella N, Magistretti PJ (1996) Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) potentiate the glutamate-evoked release of arachidonic acid from mouse cortical neurons. Evidence for a cAMP-independent mechanism. J Biol Chem 271:23705–23710.

Swerdlow NR, Geyer MA (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schizophr Bull 24:285–301.

Tanaka K, Hashimoto H, Shintani N, Yamamoto A, Baba A (2004) Reduced hypothermic and hypnotic responses to ethanol in PACAP-deficient mice. Regul Pept 123:95–98.

Usdin TB, Bonner TI, Mezey E (1994) Two receptors for vasoactive intestinal polypeptide with similar specificity and complementary distributions. Endocrinology 135:2662–2680.

Vaudry D, Gonzalez BJ, Basille M, Yon L, Fournier A, Vaudry H (2000) Pituitary adenylate cyclase-activating polypeptide and its receptors: from structure to functions. Pharmacol Rev 52:269–324.

ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 32 (2006) 1472 – 1482

Impaired self-awareness and theory of mind: An fMRI study of mentalizing in alexithymia

Yoshiya Moriguchi,[a,b,c,1,2] Takashi Ohnishi,[b,*] Richard D. Lane,[d,3] Motonari Maeda,[e] Takeyuki Mori,[b,1] Kiyotaka Nemoto,[b,1] Hiroshi Matsuda,[b,c,1,2] and Gen Komaki[a,1]

[a] *Department of Psychosomatic Research, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1, Ogawa-Higashi Cho, Kodaira City, Tokyo 187-8553, Japan*
[b] *Department of Radiology, National Center Hospital for Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1, Ogawa-Higashi Cho, Kodaira City, Tokyo 187-8553, Japan*
[c] *Department of Nuclear Medicine, Saitama Medical School Hospital, 38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan*
[d] *Department of Psychiatry, Psychology and Neuroscience, General Clinical Research Center, Health Sciences Center, The University of Arizona, PO Box 245110, Tucson, Arizona 85724-5110, USA*
[e] *Graduate School of Art and Design, Joshibi University of Art and Design, 1900 Asamizodai, Sagamihara, Kanagawa 228-8538 Japan*

Received 13 February 2006; revised 5 April 2006; accepted 10 April 2006
Available online 23 June 2006

Alexithymic individuals have difficulty in recognizing and describing emotions in themselves. We investigated the neuronal basis of mentalizing in alexithymia to determine whether there is a common neuronal substrate associated with knowing the mental states of the self and others. Individuals high in alexithymia (n = 16) and low in alexithymia (n = 14) were selected from a pool of 310 college students using a combination of the Toronto Alexithymia Scale (TAS-20) and the Structured Interview version of the Beth Israel Questionnaire (SIBIQ). We compared the two groups on psychological measures, including ratings of mentalizing and the Interpersonal Reactivity Index (IRI), and regional brain activation using functional magnetic resonance imaging (fMRI) during a mentalizing animation task. The results for both groups showed activation in regions associated with mentalizing: medial prefrontal cortices (MPFC), temporo-parietal junctions (TPJ), and the temporal pole (TP). Alexithymics had lower mentalizing and IRI perspective-taking scores and less activation in the right MPFC. Activity in the MPFC was positively correlated with the mentalizing score and the IRI perspective-taking score. Although there were no group differences in cerebral activity in the TPJ and the TP, the activity in the right TP had a positive correlation with mentalizing and IRI personal distress scores. These results suggest that alexithymic individuals have an impairment in mentalizing associated with an inability to take the perspective of others. Thus, the skills involved in comprehending the self and others are inter-related and play an important role in emotion regulation.

Introduction

Alexithymia is a disturbance in both affective and cognitive functioning characterized by difficulty in describing or recognizing the emotions of the self. Alexithymia was originally described by Sifneos (1972) in patients with psychosomatic disorders. Subsequently, alexithymia was regarded as an impairment of emotion self-regulation that is found in a broad range of physical and psychiatric disorders (e.g., alcoholism, drug addiction, and post traumatic stress disorders; see Taylor et al., 1997). At the present time, alexithymia is not considered a discrete disorder but rather a personality characteristic that is expressed with variable intensity in the general population.

Although alexithymia refers to a deficit in emotional self-awareness, Bydlowski et al. (2005) reported that high alexithymic patients with eating disorders showed impairment in the ability to describe the emotional experiences of others in hypothetical situations. Thus, emotional self-awareness seems to be closely related to sensitivity to the emotions of others. Furthermore, the capacity to differentiate the emotions of the self from those of another person in a given context appears to be crucial for managing a variety of emotional states (Bydlowski et al., 2005). Lane and Schwartz (1987) noted that as the level of emotional awareness increases, the differentiation of self from other increases. In the absence of such differentiation, emotions remain global and undifferentiated, leading to a relative inability to use one's own emotions to guide the selection of adaptive behavior.

Understanding that others have beliefs, desires, and intentions different from the self is a cognitive skill known as "Theory of mind" (ToM) or 'mentalizing' (Frith and Frith, 2003). Autistic spectrum disorders, including Asperger's syndrome, are characterized by an impairment of ToM (Baron-Cohen et al., 1985, 1997).

* Corresponding author. Fax: +81 42 346 1944.
E-mail address: tohnishi@hotmail.com (T. Ohnishi).
[1] Fax: +81 42 346 1944.
[2] Fax: +81 49 276 1301.
[3] Fax: +1 520 626 2004.
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2006.04.186

Asperger's syndrome is associated with high alexithymia scores (Berthoz and Hill, 2005; Frith, 2004; Hill et al., 2004). This suggests that the ability to describe the mental states of self and other is related. Alexithymia was also associated with impairment in the ability to identify emotions from facial expressions (Pandey and Mandal, 1997; Parker et al., 2005; Lane et al., 1996). Alexithymia has been related to certain psychiatric disorders characterized by a deficit in the ability to know what others are thinking and feeling or a lack of empathy, for example, schizophrenia (Cedro et al., 2001; Maggini and Raballo, 2004a,b; Stanghellini and Ricca, 1995; Todarello et al., 2005; van 't Wout et al., 2004), and borderline (Guttman and Laporte, 2002) and psychopathic personality disorders (Haviland et al., 2004). Thus, disorders characterized by ToM impairment are also associated with alexithymia.

It would therefore appear likely that individuals with alexithymia have an impaired ability to know the minds of others, which might contribute to difficulties in emotion regulation and interpersonal relations. However, the relation between alexithymia and mentalizing has only been sparsely investigated (for example, see Wastell and Taylor, 2002), and its neural basis remains to be examined.

We therefore investigated neuronal activation in individuals with high and low alexithymia during a ToM task using functional magnetic resonance imaging (fMRI). We hypothesized that alexithymia would be associated with decreased neuronal activity in the medial prefrontal cortex (MPFC), the temporo-parietal junction (TPJ), and the temporal pole (TP), a neuronal activity pattern characteristic of subjects who are known to have a deficit in the capacity for mentalizing, such as patients with Asperger's syndrome (Castelli et al., 2002; Frith and Frith, 2003).

Materials and method

Subjects

We screened 310 college students (105 males and 205 females) for alexithymia using a self-administrated questionnaire, TAS-20 (Taylor et al., 2003; Komaki et al., 2003). Individuals with high or low TAS-20 total scores ($n = 20$, score > 60 and $n = 18$, score < 39, respectively) were selected to obtain two groups that were maximally divergent on alexithymia. This yielded 38 volunteers (30 females, 8 males; 19 to 22 years of age, mean age = 20.4 years, SD = 0.938). All subjects gave written informed consent. The study was approved by the local ethics committees and conducted in accordance with the Declaration of Helsinki.

All subjects were interviewed by two medical doctors (psychiatry and psychosomatic medicine) using The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Otsubo et al., 2005). All subjects were confirmed to have no major medical or neurological or psychiatric disorders and no history of psychiatric and psychosomatic disorders, including depression and anxiety disorders. Subjects were also administered the National Adult Reading Test (NART; Nelson and O'Connell, 1978; the Japanese version was developed by Matsuoka et al., 2002) to assess an intelligence quotient (IQ), which has been reported to correlate with alexithymia. All subjects were right-handed, confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971).

All 38 subjects completed the psychological assessment (described above), the structured interview for alexithymia (SIBIQ, see below; Arimura et al., 2002; Sriram et al., 1988) and the fMRI study. The TAS-20 and SIBIQ scores are shown in Table 1. The 38 subjects were included in the fMRI study for correlational analyses between regional brain activities in response to mentalizing stimuli and the scores on the psychological measurements.

Some of the subjects had TAS-20 and SIBIQ scores that were discrepant on the two measures of alexithymia. To maximize the likelihood that subjects were correctly classified with regard to alexithymia, four participants with high TAS-20 and low SIBIQ scores and 4 with low TAS-20 and high SIBIQ scores were discarded. This yielded an Alexithymia (ALEX) group {$n = 16$, 3 males, mean(SD) age = 20.2 (1.0)} and a Non-alexithymia (NonALEX) group {$n = 14$, 2 males, mean (SD) age = 20.8 (0.89)}, described in Table 1. These groups were used to examine group differences of the effects of the mentalizing stimuli on brain activity as measured by the fMRI and are to be distinguished from the sample of 38 subjects based on TAS-20 scores only.

Questionnaires

In the initial screening for high and low alexithymia, each subject had completed the 20-item Toronto Alexithymia Scale (TAS-20: Taylor et al., 2003; Komaki et al., 2003). The TAS-20 uses a five-point Likert response scale and has a three-factor structure consisting of 'difficulty identifying feelings', 'difficulty describing feelings', and 'externally oriented thinking'.

To confirm each subject's high or low level of alexithymia, we conducted a modified Structured Interview based on the Beth Israel Hospital Psychosomatic Questionnaire for alexithymia (SIBIQ; Arimura et al., 2002; Sriram et al., 1988). Originally, the SIBIQ was developed to ask about patients' feelings related to their physical or psychiatric symptoms. For interviewing our non-patient

Table 1
Features of TAS-20 and SIBIQ scores in each group

	min–max, mean (SD)			T
	One sample ($n = 38$)	NonALEX ($n = 14$)	ALEX ($n = 16$)	
TAS-20				
Total	26–74, 51.2 (16.5)	26–38, 34.1 (3.7)	61–74, 66.1 (4.5)	−21.28
Difficulty in identifying feeling	7–32, 18.0 (8.1)	7–19, 10.6 (3.7)	19–32, 24.7 (3.9)	−10.33
Difficulty in describing feeling	5–25, 15.4 (6.2)	5–18, 9.6 (3.9)	15–24, 20.1 (2.4)	−9.16
Externally oriented thinking	9–30, 17.9 (5.1)	9–21, 13.9 (3.3)	13–30, 21.4 (4.0)	−5.57
SIBIQ total	18–70, 42.2 (16.7)	18–56, 31.5 (11.8)	25–70, 52.2 (14.1)	−4.39

All T values are significant $P < 0.001$; TAS-20; 20-item Toronto Alexithymia Scale, SIBIQ; the modified Structured Interview based on Beth Israel hospital psychosomatic Questionnaire for alexithymia, ALEX; Alexithymia group, NonALEX; Non-alexithymia group.

subjects, we modified the interview by adding questions about their feelings and emotions in response to bad/sad/difficult (negative) or happy/good/satisfying (positive) events they had experienced. In case they replied that they had experienced no such life events, we asked subjects to imagine situations that typically evoke emotional responses, similar to the Alexithymia Provoked Response Questionnaire (APRQ; Krystal et al., 1986) and asked that they describe their own emotions. Subjects' answers were scored by two medical doctors who were acquainted clinically with alexithymic people, and their two scores were averaged for each subject. There are no standard cutoffs on the SIBIQ. We set the thresholds at the top quartile of the SIBIQ scores (equivalent to >47) as 'high' alexithymia and at the lowest quartile (<25) as 'low' alexithymia.

The Interpersonal Reactivity Index (IRI; Davis, 1996; Aketa, 1999) was used to evaluate empathic ability. The IRI evaluates four domains related to empathy and representation of other's mental states: 'Empathic Concern' consisting of feeling emotional concern for others; 'Perspective Taking' which refers to cognitively taking the perspective of another; 'Fantasy', consisting of emotional identification with characters in books, films etc.; and 'Personal Distress' which refers to having negative feelings in response to the distress of others.

Stimuli for fMRI measurements

We conducted one fMRI session with each subject to assess the neural network associated with mentalizing, using eight silent visual animations for ToM (Abell et al., 2000; Castelli et al., 2000, 2002; Ohnishi et al., 2004; http://www.icn.ucl.ac.uk/dev_group/research.htm). We used two types of animations (4 ToM animations with two triangles acting like humans and 4 control animations with two triangles moving randomly), which were modified to be matched in length (20 s) without diminishing the meaning of the originals. The basic visual characteristics in terms of shape, overall speed, and orientation changes were as similar as possible in all the conditions.

Scanning method and procedure

All MRI measurements were performed with a 1.5 T Magnetom Vision plus MRI scanner (Siemens, Erlangen, Germany) using a standard head coil. Cerebral activation was measured with fMRI using blood–oxygen-level-dependent (BOLD) contrast. After automatic shimming, a time series of 125 volumes was obtained using single-shot gradient-refocused echo-planar imaging (TR 4000 ms; TE 60 ms; flip angle 90°; inter-scan interval 4 s; in-plane resolution 3.44 × 3.44 mm; FOV 22 cm; contiguous 4 mm slices to cover the entire brain). For structural imaging, a three-dimensional volumetric MRI was acquired using a T1-weighted gradient echo sequence that produced a gapless series of thin sagittal sections using an MPRage sequence (TE/TR, 4.4/11.4 ms; flip angle, 15°; acquisition matrix, 256 × 256; 1NEX field of view, 31.5 cm; slice thickness, 1.23 mm).

The fMRI protocol was a block design with two kinds of epochs: a ToM task condition and a control random-movement condition. Each epoch lasted 20 s, equivalent to five whole-brain fMRI volume acquisitions. The first five volumes of each fMRI sequence were discarded because of non-steady magnetization, and the remaining 120 volumes were used for the analyses. The subjects viewed the stimuli projected onto a screen, ~50 cm from the subject's head, through a mirror attached to the head coil.

Before each fMRI experiment, subjects were told to watch the animations and think about what the triangles were doing and thinking. After each scan, the subjects again watched the same stimuli on a computer screen outside the scanner and were asked to recall what they had thought, during the fMRI scan, that the triangles had been doing. Then the subjects were asked to tell the experimenter what they had thought, in response to the experimenter's neutral question: "What was happening in this animation?" Their verbal descriptions were coded on two different dimensions (based on the criteria of Castelli et al., 2000, 2002): 'Intentionality' (the degree of appreciation of mental states), and 'Appropriateness' (how well and correctly the underlying script was captured). The Intentionality score reflected the use of mental state terms, with scores ranging from 0 (non-deliberate action) to 5 (deliberate action aimed at affecting another's mental state). The Appropriateness score measured the understanding of the event depicted in the animations, as intended by the designers (0 to 3). Detailed scoring procedures are given in the report by Castelli et al. (2000).

Data analyses

We used Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, London) to realign EPI images and co-register them to the subjects' T1-weighted MR images. Then the T1 images were transformed to the anatomical space of a template brain whose space is based on the MNI (Montreal Neurological Institute) stereotactic space. The parameters for the transformation were applied to the co-registered EPI images. The normalized images were smoothed using an 8-mm FWHM Gaussian kernel. A first fixed level of analysis was computed subject-wise using the general linear model with the hemodynamic response function modeled as a boxcar function whose length covered one animation of a particular type. To test the hypotheses about regionally specific effects of the mentalizing animation condition, the estimates were compared by means of linear contrasts for each epoch. The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM$\{t\}$. Anatomic localization is presented using the Talairach coordinate system (Talairach and Tournoux, 1988). First-level contrasts were then introduced in a second-level random-effect analysis (Friston et al., 1999) to allow for population inferences.

Main effects of mentalizing stimuli were computed using a conjunction analysis for the one-sample t tests for the alexithymia and the non-alexithymia group, which yielded SPM$\{t\}$, subsequently transformed to the unit normal distribution SPM$\{z\}$. A voxel-level and a cluster-level spatial extent threshold of $P < 0.05$ corrected for multiple comparisons (False discovery rate, $t > 2.76$) were used to identify mentalizing-related brain areas.

To compare the alexithymic group ($n = 16$) and the non-alexithymic group ($n = 14$) within the regions activated in the present conjunction analysis, a two-sample t test was used. To avoid type-II errors, we conducted a hypothesis-driven approach for the regions that had been identified as important components associated with the mentalizing-related tasks {i.e., medial prefrontal cortex (MPFC), temporo-parietal junction in superior temporal sulcus (TPJ), and temporal pole and neighbor peri-

amygdaloid cortex (TP/Amy) (Frith and Frith, 2003)}. We examined the group differences with a height threshold (Z = 3.09, $P < 0.001$ uncorrected) and an extent threshold $k = 20$, and a small volume correction (10 mm radius sphere) implemented in SPM2, centered on the peak coordinates revealed in the conjunction analysis of the mentalizing conditions, with the height and extent thresholds set at $P < 0.05$ corrected (family-wise error). By adding SVC, we could confirm that the region with group effects is near the coordinates with an a priori hypothesis (within 10 mm radius). Furthermore, to examine mentalizing-related activity, we created regions of interest (ROI: 10 mm radius sphere) centered on each peak coordinate in the present one-sample t test and calculated individual mean contrast values of each ROI using MarsBaR software (http://marsbar.sourceforge.net/). Correlation coefficients between these individual mean values and psychological variables were calculated.

Results

Behavioral measures

There was no difference between the groups in the ratio of male to female subjects (13 alexithymia females to 3 alexithymia males and 12 non-alexithymia females to 2 non-alexithymia males; χ^2 = 0.168, Fisher's Exact probability = 1.00, two tailed), so scores for men and women were combined (see Table 2). The alexithymia group scored significantly lower than the non-alexithymia group on ToM intentionality, appropriateness, IRI perspective taking and empathic concern, and scored significantly higher on IRI personal distress. Scores on the reading test (JART; reflecting IQ) revealed no group differences.

fMRI measurement

The results of neural activations during the ToM task compared to the control random task by conjunction analysis between the two groups are shown in Table 3 and Fig. 1. We found no remarkable change in the analyses of neural activation after analyzing the data only for the female subjects (analyses not shown). Activations in the right MPFC, bilateral TPJs, and the right TP/Amy were observed. Additionally activations were observed in the following areas: occipital visual cortices, cerebellum, middle temporal gyri, inferior/middle frontal gyri, thalamus, parietal precuneus, and supplementary motor cortices.

In the group comparisons, there were no significant group differences using a conservative statistical threshold (family-wise error $P < 0.05$). However, significantly decreased activations during the ToM task in the alexithymic group were noted in the right medial prefrontal cortex (MPFC; BA10 (x, y, z) mm = (12, 65, 19), Z = 3.69, k = 25) and the right superior temporal area (BA22 (x, y, z)mm = (46, −35, 2), Z = 4.16, k = 44) using a more lenient statistical threshold {$Z < 3.09$ ($P < 0.001$), $k > 20$}. On the other hand, there were no statistically significant increased activations during the ToM task in the alexithymic group even using a more lenient statistical threshold (uncorrected $P < 0.005$). We extracted 4 clusters and selected 4 peak coordinates in individual clusters based on a priori hypotheses (i.e., MPFC, TPJ, and TP) and from the peaks of the clusters generated in the conjunction analysis {right MPFC (x, y, z) mm = (14, 65, 19); right TPJ (53, −48, 13); left TPJ (−57, −50, 17); right TP (50, 9, −24)}. The two regions found in the group comparison were tested by means of the SVC (10 mm sphere) centered on those coordinates from the conjunction analysis, and the only region within a 10 mm radius centered on each coordinate that had been specified by an a priori hypothesis was a decrease in the right MPFC in the alexithymia group (height and extent, P = 0.010, 0.015 corrected with SVC, respectively; Fig. 2).

Correlations between BOLD activity during the ToM task in each ROI and psychological measurements (Table 4) revealed positive correlations between appropriateness of understanding of ToM scripts and BOLD activity in the right MPFC, left TPJ, and right TP. BOLD activity in the right MPFC was significantly correlated with ToM appropriateness and IRI perspective taking and negatively correlated with SIBIQ score. The highest correlation among these was with perspective taking (see Fig. 3). BOLD activity in the right TP was positively correlated with mentalizing and IRI personal distress scores.

Discussion

Our study demonstrates differences between individuals in behavioral and neural responses to a mentalizing task as a function of alexithymia. Alexithymia, a disturbance in self-awareness, was associated with impairment in mentalizing and the related empathic ability of perspective taking, the ability to see things from the point of view of another person. Neural activity in the medial prefrontal cortex was decreased in alexithymics, and activity in the same region was closely related to perspective-taking scores. To our

Table 2
Comparison of ToM, empathy-related, and IQ scores in the alexithymia and the non-alexithymia group

	Mean (SD)		T	P
	NonALEX (n = 14)	ALEX (n = 16)		
ToM scoring				
Intentionality	17.2 (1.9)	>14.9 (3.5)	2.31	0.030*
Appropriateness	9.5 (1.7)	>7.9 (1.9)	2.34	0.026*
Interpersonal Reactivity Index (IRI)				
Fantasy	19.5 (6.7)	18.0 (5.6)	0.66	0.516 ns
Perspective taking	18.5 (4.7)	>14.6 (3.5)	2.64	0.014*
Empathic concern	20.2 (3.7)	>16.1 (5.0)	2.59	0.015*
Personal distress	12.2 (3.8)	< 15.6 (4.1)	−2.37	0.025*
Expected IQ (JART)	109.5 (6.4)	111.7 (8.3)	−0.82	0.419 ns

NonALEX; non alexithymia group, ALEX; alexithymia group. Statistical significance; *$P < 0.05$. ns; not significant.

Table 3
The coordinates and *T* and *Z* scores for the brain areas activated with main effects of ToM animated stimuli; Conjunction analysis demonstrating overlap of the alexithymia and non-alexithymia group

	Brodmann area	Talairach coordinates *x*, *y*, *z* {mm}			Voxel *P* (FDR corrected)	*T*	*Z*	Cluster *k*
Rt middle temporal gyrus	21	50	−31	0	0.000	10.79	6.73	11,894
Rt fusiform gyrus	37	42	−61	−9	0.000	10.42	6.61	
Rt temporo-parietal junction	22	53	−48	13	0.000	9.16	6.18	
Rt middle temporal gyrus/temporal pole	38	50	9	−24	0.000	8.03	5.74	
		40	4	−34	0.000	6.41	4.99	
Rt parahippocampal gyrus/amygdala	*	24	−5	−17	0.014	3.43	3.11	
Lt occipital lingual gyrus	18	−24	−91	−2	0.000	10.25	6.56	7769
Lt cerebellum posterior pyramis	*	−14	−79	−30	0.000	8.05	5.75	
Lt temporo-parietal junction	22	−57	−52	16	0.000	5.50	4.51	
		−65	−48	17	0.000	5.90	4.72	
Rt cerebellum posterior pyramis	*	16	−81	−31	0.000	6.70	5.13	563
Lt inferior frontal gyrus	45	−53	24	14	0.001	4.90	4.13	425
Rt thalamus	*	8	−11	4	0.001	4.61	3.95	55
Rt parietal precuneus	7	6	−52	43	0.002	4.31	3.75	196
Lt parietal precuneus	7	−6	−50	41	0.011	3.55	3.19	
Lt inferior frontal gyrus	9	−42	9	31	0.003	4.24	3.69	313
Lt middle frontal gyrus	6	−44	4	44	0.005	3.89	3.45	
Rt medial prefrontal cortex	10	12	63	17	0.009	3.66	3.28	199
	9	10	62	30	0.003	4.20	3.67	
Rt supplementary motor area	8	6	49	44	0.005	3.96	3.5	63
Lt middle temporal gyrus	21	−57	−6	−11	0.011	3.55	3.2	26
Lt postcentral gyrus	2	−49	−28	60	0.013	3.45	3.12	19
Rt brainstem midbrain	*	6	−23	−2	0.015	3.41	3.09	6
Rt superior frontal gyrus	6	10	13	62	0.016	3.35	3.05	45
Lt fusiform gyrus	20	−42	−21	−24	0.017	3.34	3.04	29
Rt postcentral gyrus	2	69	−20	30	0.019	3.27	2.98	9
Lt frontal lobe/rectal gyrus	11	−4	30	−22	0.020	3.25	2.97	27
Lt uncus	20	−34	−7	−30	0.020	3.25	2.97	14
Lt thalamus	*	−10	−15	4	0.048	2.78	2.59	1

Rt; right, Lt; left, FDR; False discovery rate, *k*; cluster extent.

knowledge, this is the first study to investigate and demonstrate the neural substrates of ToM in alexithymia.

Previous imaging studies concerning alexithymia (Berthoz et al., 2002a,b; Kano et al., 2003; Mantani et al., 2005) have classified subjects as alexithymic or non-alexithymic solely based on the TAS-20. Self-administered questionnaires ask respondents to describe or estimate how they think, imagine, and feel about their own emotional states. However, the concept of alexithymia includes a core difficulty in identifying and describing the emotional state of the self. This may result in some inaccuracy in their ability to evaluate and rate themselves on their ability to identify or describe their feelings appropriately. In addition to using a self-administered questionnaire (TAS-20) as a screening instrument, we used a structured interview (SIBIQ) to select the sample. Together with the large sample obtained in the present study, this strategy enabled us to overcome a limitation of the TAS-20 and confidently classify subjects as alexithymic or non-alexithymic.

Behavioral measures

Our alexithymic group showed poorer ToM ability than the non-alexithymic group, based on the scoring of their verbal descriptions of the ToM animations. This is contrary to the findings of a study that used the False Beliefs subset of the Picture Sequencing Task (Wastell and Taylor, 2002). This discrepancy may be partly explained by the more rigorous selection criteria for the alexithymic sample in the present study, as discussed above. Another explanation is that the picture sequencing task is so simple that it may not have been able to detect subtleties in the evaluation of the mental states of others such as teasing, humor, joking, and *faux pas* (Nakamura et al., 2000). The performance in the Wastell and Taylor (2002) study may have been subject to ceiling effects, since only implicit but not explicit mentalizing was impaired. The movie stimuli in the present study included complex mental states such as persuading, bluffing, mocking, and surprising the other. The results of our behavioral measures suggest that alexithymia, impaired self-awareness, is associated with decreased mentalizing ability.

Fitzgerald and Molyneux (2004) proposed an overlap between alexithymia and Asperger's syndrome, which is an autistic spectrum disorder characterized by an impairment in mentalizing. Autistic spectrum disorders have been reported to be associated with alexithymia (e.g., Hill et al., 2004). Although alexithymia occurs in individuals who do not have autistic spectrum disorders, our findings suggest that even in these alexithymic individuals a deficit in mentalizing may be present. It is possible that the nature of the mentalizing deficit may differ in the two groups, with the deficit in the autistic spectrum disorders being more pervasive or severe.

Furthermore, we found that perspective-taking ability and empathic concern were decreased in the alexithymic group, while the tendency for experiencing personal distress was increased. Guttman and Laporte (2002) also reported that alexithymic individuals had higher levels of IRI personal distress and lower levels of perspective taking and fantasy. The factors of perspective taking and empathic concern reflect mature empathy, whereas personal distress may reflect a more immature

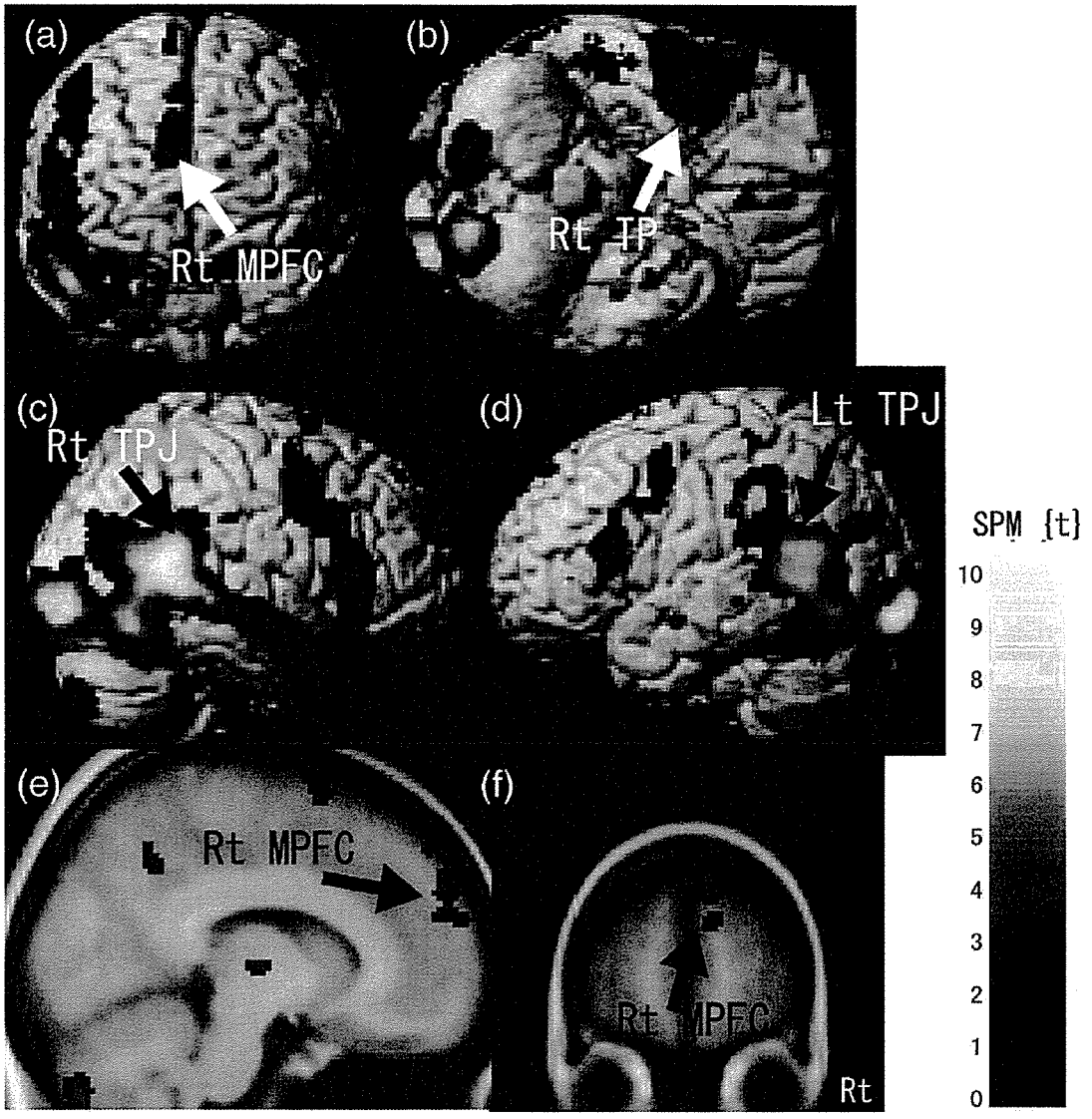

Fig. 1. Brain images showing main effects of ToM (mentalizing)-related stimuli on cerebral activity in a conjunction analysis of the alexithymia (n = 16) and non-alexithymia (n = 14) groups. The subjects were selected from 310 healthy subjects on the basis of high or low scores on the 20-item Toronto Alexithymia Scale (TAS-20). The figure illustrates the cerebral activations in response to ToM animations depicting two triangles moving like humans compared to control animations in a one-sample t test correcting for multiple comparisons throughout the whole brain (height and extent threshold; corrected False discovery rate $P < 0.05$). Activation was observed in the three regions predicted a priori to be associated with the ToM task (MPFC; medial prefrontal cortex, TPJ; temporo-parietal junction, and TP; temporal pole). (a) frontal view (b) bottom view, (c) right side, (d) left side, (e) sagittal section slice, (f) axial section slice.

tendency to identify with the other (Guttman and Laporte, 2000, 2002). The personal distress scale is associated with social dysfunction, fearfulness, uncertainty, emotional vulnerability, shyness, and anxiety. High personal distress was characterized by concern about evaluation by others and with lowered concern for others (Davis, 1983). Hence, alexithymics with high personal distress scores might not have mature empathetic ability but rather could easily be affected by others' mental state. This notion is consistent with the fact that, unlike the other subscales of the IRI, personal distress has been shown to correlate positively with measures of antisocial behavior and aggression (Beven et al., 2004; Davis, 1996), and that antisocial personality disorder is associated with alexithymia (high TAS score; Sayar et al., 2001). Note that a potential weakness of the present study is the absence of information regarding depressive and anxiety states, which have been reported to correlate with alexithymia (Honkalampi et al., 2001; Kojima et al., 2003; Muller et al., 2003; Saarijarvi et al., 2001). However, we confirmed by using the structured interview that none of the subjects were diagnosed with either depression or an anxiety disorder.

Brain activations

In the fMRI study, we replicated the loci (TPJ, TP adjacent to amygdala, and MPFC) that have been reported in previous studies of mentalizing (Castelli et al., 2000, 2002; Frith and Frith, 2003). TPJ activity reflects representation of goal-directed action states and is involved in the processing of detecting agency through biological-motion (Frith and Frith, 2003). Samson et al. (2004) showed that TPJ sustains not only low-level social perception but also higher-level social

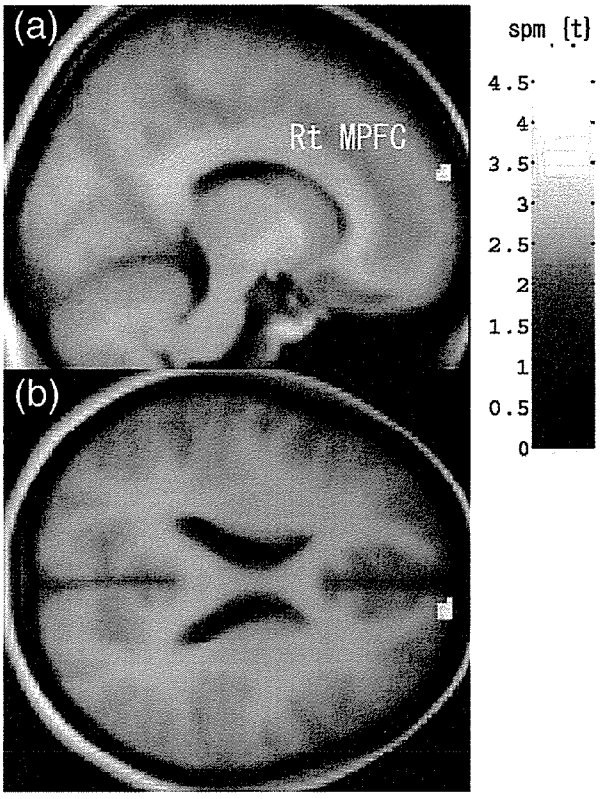

Fig. 2. Brain images of the comparisons showing less regional cerebral activation in individuals with alexithymia (n = 16) in response to the ToM task than those without alexithymia (n = 14). The sagittal (a) and axial (b) orthogonal views of the brain are shown for the cluster with less activation in the alexithymic group compared to the non-alexithymic group in the right medial prefrontal cortex (MPFC) (BA10, Talairach coordinates (x, y, z) mm = (12, 65, 19), peak Z = 3.69, cluster k = 25). The bars on the right show the range of t scores for statistical parametric mapping.

inference of someone else's belief, such as false-belief reasoning. Saxe and Kanwisher (2003) showed that the role of the TPJ in understanding other people is specific to reasoning about the content of mental states, and thinking about beliefs is also subserved by the TPJ (Saxe, 2005). These functions in the TPJ are supposed to support ToM abilities. The TP is concerned with generating the semantic and emotional context for the material currently being processed (Frith and Frith, 2003). The amygdala can process social information of various kinds, not just judgments of others' emotional states, and may underlie or partially overlap with ToM functions (Stone et al., 2003).

MPFC activity in the context of a mentalizing task has been studied by many researchers (e.g., Berthoz et al., 2002a,b; Brunet et al., 2000; Castelli et al., 2000, 2002; Ferstl and von Cramon, 2002; Fletcher et al., 1995; Goel et al., 1995; Gallagher et al., 2000; Macrae et al., 2004; Ochsner et al., 2004; Schultz et al., 2003; Vogeley et al., 2001). Frith and Frith (2003) proposed that the MPFC adjacent to the paracingulate region (anterior to posterior portion of rostral ACC) associated with mentalizing tasks is activated whenever people are attending to certain states of the self or others. This area is concerned with the representation of the mental states of the self and others decoupled from physical state representations. The correlation that we observed between perspective-taking ability and the degree of neural activity in the MPFC region in response to mentalizing tasks in the present study

Table 4
Correlation coefficients between activities related to ToM in each ROI and scores of psychological measurements

	Rt MPFC	Rt TPJ	Lt TPJ	Rt TP
ToM scoring				
Intentionality	0.26	0.09	0.16	**0.29***
Appropriateness	**0.35***	0.16	**0.32***	**0.52****
Structured Interview for BIQ (SIBIQ)				
Total	**−0.36***	−0.15	−0.10	−0.16
Interpersonal Reactivity Index (IRI)				
Fantasy	0.25	0.17	0.09	0.07
Perspective taking	**0.38****	0.24	0.22	−0.09
Empathic concern	0.25	0.01	−0.02	−0.04
Personal distress	0.27	0.23	0.11	**0.40****
Expected IQ (JART)	−0.08	0.16	0.06	0.14

Rt; right, Lt; left, MPFC; medial prefrontal cortex, TPJ; temporo-parietal junction, TP; temporal pole.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.005$.

is consistent with the Friths' proposal. Furthermore, Mitchell et al. (2005) showed that greater MPFC activation accompanied judgments specifically about targets' psychological states, compared to body parts, regardless of whether the target was a person or not (e.g., a dog). That report is consistent with our results that only triangles-moving-like-humans evoked MPFC activation in the subjects. Decety and Jackson (2004) pointed out that studies that investigated other-perspective versus self-perspective consistently involved the areas including the frontopolar cortex and medial prefrontal cortex when the participants adopted the perspective of another person. These neuroimaging studies about the functions in the MPFC together suggest that the area of the MPFC activated in

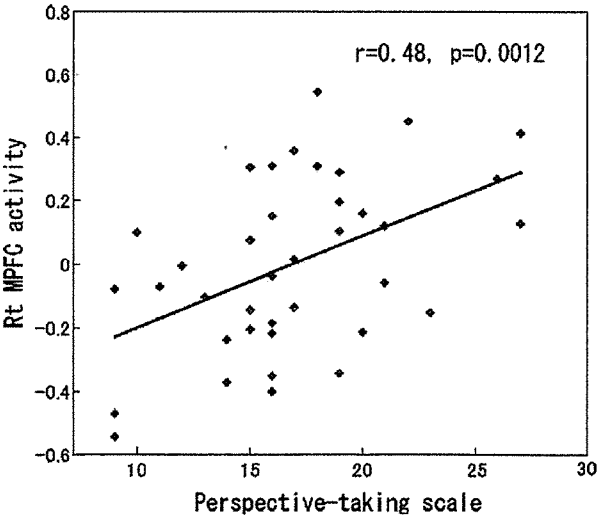

Fig. 3. The correlation between IRI perspective-taking scores and the activities in the right medial prefrontal cortex (MPFC) in one-sample (n = 38). The figure illustrates a significant positive correlation between the perspective-taking scores of the Interpersonal Reactivity Index (IRI) and right MPFC activity in response to the ToM task vs. control stimuli in one-sample (n = 38). The correlation coefficient (r) at the voxel (x = 14, y = 65, z = 21) = 0.48, P = 0.0012, R^2 = 0.229.

mentalizing tasks is indicative of the representation of the mental states of both the self and others decoupled from outward reality and from each other (i.e., meta-representation). This meta-representation process is a key to the higher cognitive ability of comprehending the minds of others; e.g., adopting the perspective of others as separable and distinct from one's own perspective.

We found relative inactivity in the right MPFC in alexithymic individuals. Neuroimaging studies in which alexithymics processed emotion-laden stimuli (Berthoz et al., 2002a,b; Kano et al., 2003; Lane et al., 1998), including another study of Japanese subjects (Kano et al., 2003), demonstrated hypofunction in the medial frontal area in neighboring dorsal anterior cingulate cortex.

Our finding that alexithymia is associated with compromised comprehension of others' mental states suggests that comprehension of the self and the other are closely related. Indeed, Ochsner et al. (2004) have demonstrated that evaluation of the emotional states of self and others relies on a network of common mechanisms centered on the MPFC. Jackson et al. (2005) reported that medial prefrontal activity was related to taking both self and others' perspective when viewing hands and feet in painful situations. Furthermore, individuals with autistic spectrum disorders have showed less activation in the MPFC in response to the same mentalizing task as that used in the present study (Castelli et al., 2002), and the MPFC has been reported to be associated with the impaired mentalizing in autism (Goel et al., 1995; Happe et al., 1996; Juhasz et al., 2001). In our study, individuals with high alexithymia, compared to those with low alexithymia, showed less activation in the MPFC in response to the mentalizing task. Thus, there could be a common neural component for both normal individuals with high alexithymia and autistic people with impaired mentalizing ability, which also indicates a common component of understanding the self and others.

To identify and describe one's own feelings as distinct from those of another person, one needs a third-person perspective different from the self per se which is full of emotion (i.e., enabling the self to be viewed as an object). To comprehend the mind of another, one should adopt the perspective of the other person. Therefore, the ability to generate perspectives that are different from the self (i.e., decoupling or meta-representation) is a crucial common component for understanding the mental states of self and others. A deficit in this mechanism should result in both alexithymia and impaired mentalizing and should be associated with a tendency to take on the other's distress contagiously and personally as one's own. This may be why alexithymia is associated with deficits in empathic ability (Guttman and Laporte, 2000, 2002; Rastam et al., 1997) and in reading emotion from posed facial expressions (Lane et al., 1996; Mann et al., 1994; Pandey and Mandal, 1997; Parker et al., 1993, 2005). Furthermore, some psychiatric disorders associated with alexithymia {e.g., autistic spectrum (Berthoz and Hill, 2005; Hill et al., 2004; Frith, 2004), schizophrenia (Cedro et al., 2001; Maggini and Raballo, 2004a,b; Stanghellini and Ricca, 1995; Todarello et al., 2005; van 't Wout et al., 2004), borderline personality (Guttman and Laporte, 2002), and psychopathy (Haviland et al., 2004)} have one common component: an ambiguous boundary between the self and others, including proneness to take on the emotional states of others with poor decoupling. That is why individuals with these disorders cannot take a third-person perspective outside the self, which is critical for regulating emotions. Indeed, Fonagy (2000) has asserted that a deficit in the capacity for reflection is the fundamental deficit in borderline personality disorder.

From a developmental viewpoint, Frith and Happé (1999) noted that there is little evidence from the developmental literature to suggest that mental states are attributed to the self before they are attributed to others (e.g., children do not pass the self's belief question in the Smarties test before passing the other's belief question). They emphasized a common representational mechanism for attributing mental states to self and others. Leslie (1987) also proposed that meta-representation is necessary for attribution of any mental state, including a false belief, and is necessary equally for self and other attribution. In infancy, before clear mental representation of the self emerges, the perception of emotional signals arising externally (i.e., the earliest ToM task) and the subjective experience of internal emotion are undifferentiated. Gradually the child comes to know his or her own emotional experience by virtue of feedback from the mother or other caregivers (Lane, 2000; Stern, 1985; Taylor et al., 1997). On the other hand, Frith and Frith (1999); Frith (1996) proposed that preexisting abilities that are relevant to mentalizing include the ability to distinguish between actions of the self and actions of others, so that skills that contribute to mentalizing ability also advance self-awareness. Nevertheless, the development of representations of the self and others are inseparable and parallel to each other. The results of the present study raise the possibility that some individuals experience a fundamental developmental deficit in this domain resulting in an impairment in knowing and communicating how one feels, which is labeled alexithymia.

The temporal pole (TP) has been reported to code for mnemonic and contextual information (Nakamura and Kubota, 1995), discrimination of familiar faces and scenes (Nakamura et al., 2000), personal and famous names (Sugiura et al., 2006), conditions evoking sadness (e.g., Beauregard et al., 2001; Eugene et al., 2003; Gillath et al., 2005; Levesque et al., 2003), and the retrieval of emotional memories (Dolan et al., 2000; Shin et al., 1999). Our study showed that TP activity was associated with mentalizing scores, indicating that the TP is associated with some aspect of the mentalizing function, as a semantic and mnemonic process (not perspective taking), given the previous studies and the Friths' hypothesis (2003). On the other hand, TP activity was correlated with personal distress scores as a potentially immature empathizing tendency (taking on another's emotional state without decoupling). The meta-representation process that produces the self's and the other's perspectives separately might not be included in the function of the TP area, but instead included in the MPFC. Given the reports that have shown the role of the TP for processing and referencing mnemonic information familiar to oneself, the present association between TP activities, mentalizing, and personal distress scores suggests that the TP serves as an important neural component of ToM function by utilizing personal experiences of one's own to comprehend the state of mind of others. If the ability to differentiate between the emotions of self and other is impaired, as in alexithymia, then personal distress in conjunction with impaired perspective taking may lead to inaccuracies in the attribution of mental states in the other.

Conclusion

Our findings demonstrate that alexithymia, a deficit in the ability to identify and describe the feeling states of the self, is related to impaired mentalizing (comprehending the mind of others), which in turn is associated with hypoactivity in the

MPFC. The deficit in mentalizing that we observed is associated with impairment in the higher cognitive ability to take a perspective different from the self, a skill that may be essential for the comprehension of the mental states of both self and others. The results also suggest that there is a common component, such as perspective taking, involved in both self-awareness and mentalizing. Impairment of this component may help to explain the impairment in emotional regulation characteristic of alexithymia. Additional research is needed to examine the extent to which these findings contribute to a more complete understanding of those psychiatric disorders that have been linked to alexithymia, including autistic spectrum disorders, schizophrenia, and borderline and psychopathic personality disorders.

Acknowledgments

This study was supported by the Research Grant (17A-3) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan.

We thank Dr. Uta Frith for her generous donation of the animation to the project.

References

Abell, F., Happé, F., Frith, U., 2000. Do triangles play tricks? Attribution of mental states to animated shapes in normal and abnormal development. J. Cogn. Dev. 15, 1–20.

Aketa, H., 1999. Structure and measurement of empathy: Japanese version of Davis's Interpersonal Reactivity Index (IRI-J). Psychol. Rep. Sophia Univ. 23, 19–31.

Arimura, T., Komaki, G., Murakami, S., Tamagawa, K., Nishikata, H., Kawai, K., Nozaki, T., Takii, M., Kubo, C., 2002. Development of the Structured Interview by the Modified Edition of Beth Israel Hospital Psychosomatic Questionnaire (SIBIQ) in Japanese edition to evaluate alexithymia. Jpn. J. Psychosom. Med. 42, 259–269.

Baron-Cohen, S., Leslie, A.M., Frith, U., 1985. Does the autistic child have a "theory of mind"? Cognition 21, 37–46.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., Robertson, M., 1997. Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger syndrome. J. Child Psychol. Psychiatry 38, 813–822.

Beauregard, M., Levesque, J., Bourgouin, P., 2001. Neural correlates of conscious self-regulation of emotion. J. Neurosci. 21, RC165.

Berthoz, S., Hill, E.L., 2005. The validity of using self-reports to assess emotion regulation abilities in adults with autism spectrum disorder. Eur. Psychiatry 20, 291–298.

Berthoz, S., Armony, J.L., Blair, R.J., Dolan, R.J., 2002a. An fMRI study of intentional and unintentional (embarrassing) violations of social norms. Brain 125, 1696–1708.

Berthoz, S., Artiges, E., Van De Moortele, P.F., Poline, J.B., Rouquette, S., Consoli, S.M., Martinot, J.L., 2002b. Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia. Am. J. Psychiatry 159, 961–967.

Beven, J.P., O'Brien-Malone, A., Hall, G., 2004. Using the interpersonal reactivity index to assess empathy in violent offenders. Int. J. Forensic Psychol. Issue 2, 33–41 (Sep).

Brunet, E., Sarfati, Y., Hardy-Bayle, M.C., Decety, J., 2000. A PET investigation of the attribution of intentions with a nonverbal task. NeuroImage 11, 157–166.

Bydlowski, S., Corcos, M., Jeammet, P., Paterniti, S., Berthoz, S., Laurier, C., Chambry, J., Consoli, S.M., 2005. Emotion-processing deficits in eating disorders. Int. J. Eat. Disord. 37, 321–329.

Castelli, F., Happe, F., Frith, U., Frith, C., 2000. Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. NeuroImage 12, 314–325.

Castelli, F., Frith, C., Happe, F., Frith, U., 2002. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain 125, 1839–1849.

Cedro, A., Kokoszka, A., Popiel, A., Narkiewicz-Jodko, W., 2001. Alexithymia in schizophrenia: an exploratory study. Psychol. Rep. 89, 95–98.

Davis, M.H., 1983. Measuring individual differences in empathy: evidence for a multidimensional approach. J. Pers. Soc. Psychol. 44, 113–126.

Davis, M.H., 1996. Empathy: A Social Psychological Approach. Westview Press, Boulder CO US.

Decety, J., Jackson, P.L., 2004. The functional architecture of human empathy. Behav. Cogn. Neurosci. Rev. 3, 71–100.

Dolan, R.J., Lane, R., Chua, P., Fletcher, P., 2000. Dissociable temporal lobe activations during emotional episodic memory retrieval. NeuroImage 11, 203–209.

Eugene, F., Levesque, J., Mensour, B., Leroux, J.M., Beaudoin, G., Bourgouin, P., Beauregard, M., 2003. The impact of individual differences on the neural circuitry underlying sadness. NeuroImage 19, 354–364.

Ferstl, E.C., von Cramon, D.Y., 2002. What does the frontomedian cortex contribute to language processing: coherence or theory of mind? NeuroImage 17, 1599–1612.

Fitzgerald, M., Molyneux, G., 2004. Overlap between alexithymia and Asperger's syndrome. Am. J. Psychiatry 161, 2134–2135.

Fletcher, P.C., Happe, F., Frith, U., Baker, S.C., Dolan, R.J., Frackowiak, R.S., Frith, C.D., 1995. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 57, 109–128.

Fonagy, P., 2000. Attachment and borderline personality disorder. J. Am. Psychoanal. Assoc. 48, 1129–1146.

Friston, K.J., Holmes, A.P., Worsley, K.J., 1999. How many subjects constitute a study? NeuroImage 10, 1–5.

Frith, C., 1996. The role of the prefrontal cortex in self-consciousness: the case of auditory hallucinations. Philos. Trans. R. Soc. London, Ser. B Biol. Sci. 351, 1505–1512.

Frith, U., 2004. Emanuel Miller lecture: confusions and controversies about Asperger syndrome. J. Child Psychol. Psychiatry 45, 672–686.

Frith, C.D., Frith, U., 1999. Interacting minds—A biological basis. Science 286, 1692–1695.

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

Frith, U., Happé, F., 1999. Theory of mind and self consciousness: what is it like to be autistic? Mind Lang. 14, 1–22.

Gallagher, H.L., Happe, F., Brunswick, N., Fletcher, P.C., Frith, U., Frith, C.D., 2000. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia 38, 11–21.

Gillath, O., Bunge, S.A., Shaver, P.R., Wendelken, C., Mikulincer, M., 2005. Attachment-style differences in the ability to suppress negative thoughts: exploring the neural correlates. NeuroImage 28, 835–847.

Goel, V., Grafman, J., Sadato, N., Hallett, M., 1995. Modeling other minds. NeuroReport 6, 1741–1746.

Guttman, H.A., Laporte, L., 2000. Empathy in families of women with borderline personality disorder, anorexia nervosa, and a control group. Fam. Process 39, 345–358.

Guttman, H., Laporte, L., 2002. Alexithymia, empathy, and psychological symptoms in a family context. Compr. Psychiatry 43, 448–455.

Happe, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., Dolan, R., Frackowiak, R., Frith, C., 1996. 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. NeuroReport 8, 197–201.

Haviland, M.G., Sonne, J.L., Kowert, P.A., 2004. Alexithymia and

psychopathy: comparison and application of California Q-set Prototypes. J. Pers. Assess. 82, 306–316.
Hill, E., Berthoz, S., Frith, U., 2004. Brief report: cognitive processing of own emotions in individuals with autistic spectrum disorder and in their relatives. J. Autism Dev. Disord. 34, 229–235.
Honkalampi, K., Koivumaa-Honkanen, H., Tanskanen, A., Hintikka, J., Lehtonen, J., Viinamaki, H., 2001. Why do alexithymic features appear to be stable? A 12-month follow-up study of a general population. Psychother. Psychosom. 70, 247–253.
Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2005. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44 (5), 752–761.
Juhasz, C., Behen, M.E., Muzik, O., Chugani, D.C., Chugani, H.T., 2001. Bilateral medial prefrontal and temporal neocortical hypometabolism in children with epilepsy and aggression. Epilepsia 42, 991–1001.
Kano, M., Fukudo, S., Gyoba, J., Kamachi, M., Tagawa, M., Mochizuki, H., Itoh, M., Hongo, M., Yanai, K., 2003. Specific brain processing of facial expressions in people with alexithymia: an H2 15O-PET study. Brain 126, 1474–1484.
Kojima, M., Senda, Y., Nagaya, T., Tokudome, S., Furukawa, T.A., 2003. Alexithymia, depression and social support among Japanese workers. Psychother. Psychosom. 72, 307–314.
Komaki, G., Maeda, M., Arimura, T., Nakata, A., Shinoda, H., Ogata, I., Shimura, M., Kawamura, N., Kubo, C., 2003 Aug.. The reliability and factorial validity of the Japanese version of the 20-item Toronto Alexithymia Scale. J. Psychosom. Res. 552, 143.
Krystal, J.H., Giller Jr., E.L., Cicchetti, D.V., 1986. Assessment of alexithymia in posttraumatic stress disorder and somatic illness: introduction of a reliable measure. Psychosom. Med. 48, 84–94.
Lane, R.D., Schwartz, G.E., 1987. Levels of emotional awareness: a cognitive-developmental theory and its application to psychopathology. Am. J. Psychiatry 144, 133–143.
Lane, R.D., 2000. Levels of emotional awareness: neurological, psychological and social perspectives. In: Parker, J., Bar-On, R. (Eds.), Handbook of Emotional Intelligence. Jossey Bass, San Francisco, pp. 171–191.
Lane, R.D., Sechrest, L., Reidel, R., Weldon, V., Kaszniak, A., Schwartz, G.E., 1996. Impaired verbal and nonverbal emotion recognition in alexithymia. Psychosom. Med. 58, 203–210.
Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.S., Holmes, A., Schwartz, G.E., 1998. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. J. Cogn. Neurosci. 10, 525–535.
Leslie, A.M., 1987. Pretence and representation: the origins of "theory of mind". Psychol. Rev. 94, 412–426.
Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.M., Bourgouin, P., Beauregard, M., 2003. Neural circuitry underlying voluntary suppression of sadness. Biol. Psychiatry 53, 502–510.
Macrae, C.N., Moran, J.M., Heatherton, T.F., Banfield, J.F., Kelley, W.M., 2004. Medial prefrontal activity predicts memory for self. Cereb. Cortex 14, 647–654.
Maggini, C., Raballo, A., 2004a. Alexithymia and schizophrenic psychopathology. Acta Biomed. Ateneo Parmense 75, 40–49.
Maggini, C., Raballo, A., 2004b. Self-centrality, basic symptoms model and psychopathology in schizophrenia. Psychopathology 37, 69–75.
Mann, L.S., Wise, T.N., Trinidad, A., Kohanski, R., 1994. Alexithymia, affect recognition, and the five-factor model of personality in normal subjects. Psychol. Rep. 74, 563–567.
Mantani, T., Okamoto, Y., Shirao, N., Okada, G., Yamawaki, S., 2005. Reduced activation of posterior cingulate cortex during imagery in subjects with high degrees of alexithymia: a functional magnetic resonance imaging study. Biol. Psychiatry 57, 982–990.
Matsuoka, K., Kim, Y., Hiro, H., Miyamoto, Y., Fujita, K., Tanaka, K., Koyama, K., Kazuki, N., 2002. Development of Japanese Adult Reading Test (JART) for Predicting Premorbid IQ in Mild Dementia. Seishinigaku 44, 503–511.
Mitchell, J.P., Banaji, M.R., Macrae, C.N., 2005. General and specific contributions of the medial prefrontal cortex to knowledge about mental states. NeuroImage 28, 757–762.
Muller, J., Buhner, M., Ellgring, H., 2003. Relationship and differential validity of alexithymia and depression: a comparison of the Toronto Alexithymia and Self-Rating Depression Scales. Psychopathology 36, 71–77.
Nakamura, K., Kubota, K., 1995. Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. J. Neurophysiol. 74, 162–178.
Nakamura, K., Kawashima, R., Sato, N., Nakamura, A., Sugiura, M., Kato, T., Hatano, K., Ito, K., Fukuda, H., Schormann, T., Zilles, K., 2000. Functional delineation of the human occipito-temporal areas related to face and scene processing. A PET study. Brain 123 (Pt. 9), 1903–1912.
Nelson, H.E., O'Connell, A., 1978. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 14, 234–244.
Ochsner, K.N., Knierim, K., Ludlow, D.H., Hanelin, J., Ramachandran, T., Glover, G., Mackey, S.C., 2004. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J. Cogn. Neurosci. 16, 1746–1772.
Ohnishi, T., Moriguchi, Y., Matsuda, H., Mori, T., Hirakata, M., Imabayashi, E., Hirao, K., Nemoto, K., Kaga, M., Inagaki, M., Yamada, M., Uno, A., 2004. The neural network for the mirror system and mentalizing in normally developed children: an fMRI study. NeuroReport 15, 1483–1487.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Otsubo, T., Tanaka, K., Koda, R., Shinoda, J., Sano, N., Tanaka, S., Aoyama, H., Mimura, M., Kamijima, K., 2005. Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. Psychiatry Clin. Neurosci. 59, 517–526.
Pandey, R., Mandal, M.K., 1997. Processing of facial expressions of emotion and alexithymia. Br. J. Clin. Psychol. 36 (Pt. 4), 631–633.
Parker, J.D., Taylor, G.J., Bagby, R.M., 1993. Alexithymia and the recognition of facial expressions of emotion. Psychother. Psychosom. 59, 197–202.
Parker, P.D., Prkachin, K.M., Prkachin, G.C., 2005. Processing of facial expressions of negative emotion in alexithymia: the influence of temporal constraint. J. Pers. 73, 1087–1107.
Rastam, M., Gillberg, C., Gillberg, I.C., Johansson, M., 1997. Alexithymia in anorexia nervosa: a controlled study using the 20-item Toronto Alexithymia Scale. Acta Psychiatr. Scand. 95, 385–388.
Saarijarvi, S., Salminen, J.K., Toikka, T.B., 2001. Alexithymia and depression: a 1-year follow-up study in outpatients with major depression. J. Psychosom. Res. 51, 729–733.
Samson, D., Apperly, I.A., Chiavarino, C., Humphreys, G.W., 2004. Left temporoparietal junction is necessary for representing someone else's belief. Nat. Neurosci. 7, 499–500.
Saxe, R., 2005. Against simulation: the argument from error. Trends Cogn. Sci. 9, 174–179.
Saxe, R., Kanwisher, N., 2003. People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind". NeuroImage 19, 1835–1842.
Sayar, K., Ebrinc, S., Ak, I., 2001. Alexithymia in patients with antisocial personality disorder in a military hospital setting. Isr. J. Psychiatry Relat. Sci. 38, 81–87.
Schultz, R.T., Grelotti, D.J., Klin, A., Kleinman, J., Van der Gaag, C., Marois, R., Skudlarski, P., 2003. The role of the fusiform face area in social cognition: implications for the pathobiology of autism. Philos. Trans. R. Soc. London, Ser. B Biol. Sci. 358, 415–427.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development

and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33.

Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.M., Metzger, L.J., Lasko, N.B., Orr, S.P., Pitman, R.K., 1999. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. Am. J. Psychiatry 156, 575–584.

Sifneos, P.E., 1972. Short-term Psychotherapy and Emotional Crisis. Harvard Univ. Press, Cambridge, MA.

Sriram, T.G., Pratap, L., Shanmugham, V., 1988. Towards enhancing the utility of Beth Israel Hospital Psychosomatic Questionnaire. Psychother. Psychosom. 49, 205–211.

Stanghellini, G., Ricca, V., 1995. Alexithymia and schizophrenias. Psychopathology 28, 263–272.

Stern, D.N., 1985. The Interpersonal World of the Infant: A View of Psychoanalysis and Developmental Psychology. Basic Books Inc., New York.

Stone, V.E., Baron-Cohen, S., Calder, A., Keane, J., Young, A., 2003. Acquired theory of mind impairments in individuals with bilateral amygdala lesions. Neuropsychologia 41, 209–220.

Sugiura, M., Sassa, Y., Watanabe, J., Akitsuki, Y., Maeda, Y., Matsue, Y., Fukuda, H., Kawashima, R., 2006. Cortical mechanisms of person representation: recognition of famous and personally familiar names. NeuroImage 12 (Feb., Electronic publication ahead of print).

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, New York.

Taylor, G.J., Bagby, R.M., Parker, J.D.A., 1997. Disorders of Affect Regulation: Alexithymia in Medical and Psychiatric Illness. Cambridge University Press Cambridge, Cambridge.

Taylor, G.J., Bagby, R.M., Parker, J.D., 2003. The 20-Item Toronto Alexithymia Scale: IV. Reliability and factorial validity in different languages and cultures. J. Psychosom. Res. 55, 277–283.

Todarello, O., Porcelli, P., Grilletti, F., Bellomo, A., 2005. Is alexithymia related to negative symptoms of schizophrenia? Psychopathology 38, 310–314.

van 't Wout, M., Aleman, A., Kessels, R.P., Laroi, F., Kahn, R.S., 2004. Emotional processing in a non-clinical psychosis-prone sample. Schizophr. Res. 68, 271–281.

Vogeley, K., Bussfeld, P., Newen, A., Herrmann, S., Happe, F., Falkai, P., Maier, W., Shah, N.J., Fink, G.R., Zilles, K., 2001. Mind reading: neural mechanisms of theory of mind and self-perspective. NeuroImage 14, 170–181.

Wastell, C.A., Taylor, A.J., 2002. Alexithymic mentalising: theory of mind and social adaptation. Soc. Behav. Pers. 30 (2), 141–148.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience Research
ELSEVIER
Neuroscience Research xxx (2006) xxx–xxx
www.elsevier.com/locate/neures

Navigation ability dependent neural activation in the human brain: An fMRI study

Takashi Ohnishi [a,*], Hiroshi Matsuda [a], Makiko Hirakata [a], Yoshikazu Ugawa [b]

[a] *Department of Radiology, National Center Hospital of Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1 Ogawa Higashi, Kodaira City, Tokyo 187-8551, Japan*
[b] *Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*

Received 30 December 2005; accepted 7 April 2006

Abstract

Visual-spatial navigation in familiar and unfamiliar environments is an essential requirement of daily life. Animal studies indicated the importance of the hippocampus for navigation. Neuroimaging studies demonstrated gender difference or strategies dependent difference of neural substrates for navigation. Using functional magnetic resonance imaging, we measured brain activity related to navigation in four groups of normal volunteers: good navigators (males and females) and poor navigators (males and females). In a whole group analysis, task related activity was noted in the hippocampus, parahippocampal gyrus, posterior cingulate cortex, precuneus, parietal association areas, and the visual association areas. In group comparisons, good navigators showed a stronger activation in the medial temporal area and precuneus than poor navigators. There was neither sex effect nor interaction effect between sex and navigation ability. The activity in the left medial temporal areas was positively correlated with task performance, whereas activity in the right parietal area was negatively correlated with task performance. Furthermore, the activity in the bilateral medial temporal areas was positively correlated with scores reflecting preferred navigation strategies, whereas activity in the bilateral superior parietal lobules was negatively correlated with them. Our data suggest that different brain activities related to navigation should reflect navigation skill and strategies.

Keywords: Functional magnetic resonance imaging; Visual-spatial navigation; Gender difference; Hippocampus; Parietal cortex

1. Introduction

Visual-spatial navigation in familiar and unfamiliar environments is an essential requirement of daily life. Several animal studies indicated the importance of the medial temporal lobe, including the hippocampus (place cell) for navigation (O'Keefe and Nadel, 1978; Muller et al., 1987; Eichenbaum et al., 1999). The cognitive-mapping hypothesis suggested a single allocentric (world-centered) representation of the environment residing mainly in the hippocampus proper (O'Keefe and Nadel, 1978), whereas the parietal association areas have been considered to be involved in the egocentric (body-centered) representation in the environment (Colby, 1999). Visual-spatial navigation is a cognitive function in which a reliable sex-specific difference is well known (Galea and Kimura, 1993; Astur et al., 1998; Moffat et al., 1998). A previous functional magnetic resonance imaging human study demonstrated a similar gender-different brain activity associated with a maze navigation task, distinct activation of the left hippocampus in males, whereas females recruited right parietal and right prefrontal cortex (Gron et al., 2000). The results indicated that behavioral gender differences in navigation performance could be accounted for within the framework of different neural substrates for navigation (Gron et al., 2000). However, it has been still unclear whether such a different activation pattern still present even when behavioral performance was controlled. As indicated by psychological studies, there are sex differences in preferred strategies (the route strategy or the orientation strategy) on navigation and acquisition of environmental knowledge (Lawton, 1994, 1996). It would be possible that the different brain activity for navigation may reflect different performance and/or strategies on navigation. In fact, a previous

* Corresponding author. Tel.: +81 42 341 2711; fax: +81 42 346 1790.
E-mail address: tohnishi@hotmail.com (T. Ohnishi).

0168-0102/$ – see front matter © 2006 Published by Elsevier Ireland Ltd and the Japan Neuroscience Society.
doi:10.1016/j.neures.2006.04.009

fMRI study demonstrated that human subjects spontaneously adopted different strategies to solve a navigation task and these strategies lead to differential activity in the brain (Iaria et al., 2003; Jordan et al., 2004).

To clarify whether distinct functional anatomy of visual-spatial navigation is possibly related to navigation ability, we performed fMRI studies with virtual maze navigation task in four groups of normal subjects consisting of men with a poor navigation ability, men with a good navigation ability, women with a poor navigation ability, and women with a good s navigation ability, and compared brain activities related to a navigation task.

2. Methods

2.1. Subjects

First as a screening, we asked 246 subjects (133 males: mean age (S.D.) = 30.2 (9.6); 113 females: mean age (S.D.) = 29.8 (13.5)) to fill out a self-administrated questionnaire, the sense of direction questionnaire-short form (SDQ-S) (Takeuchi, 1992). This consists of the following 17 questions pertaining to the sense of direction and comprising two scales, awareness of orientation (nine items) and memory for spatial behavior (eight items). (1) I can make correct choices as to cardinal directions in an unfamiliar place. (2) I have become confused, as to cardinal directions, when I am in an unfamiliar place. (3) I have difficulties in identifying the moving direction of the train with regard to cardinal direction. (4) When I get route information, I can make use of "left or right" information, but I cannot use cardinal directions. (5) I cannot make out which direction my room in a hotel faces. (6) I can tell where I am on a map. (7) I can visualize the route as a map-like image. (8) I feel anxious about my walking direction in an unfamiliar area. (9) I have poor memory for landmarks. (10) I cannot remember landmarks found in an area where I have often been. (11) I cannot use landmarks in finding my way. (12) I cannot remember the different aspects of scenery. (13) I often cannot find the way even if given detailed verbal information regarding the route. (14) I have a lot of difficulties reaching an unknown place even after consulting a map. (15) I often (or easily) forget which direction I turned. (16) I become totally confused as to the correct sequence of the return way as a consequence of a number of left–right turns in the route. (17) I cannot verify landmarks in a turn of the route. The SDQ-S is a five-point scale, ranging from "strongly agree (one point)" to "strongly disagree (five points)". Questions 1, 6 and 7, are scored in reverse order. Therefore, the higher score on the SDQ-S indicates higher navigation ability in daily life. The mean score of the SDQ-S in 246 individuals was 56.2 (S.D. = 15.27, range: 19–85). The females demonstrated a significantly lower score of SDQ-S (mean: 53.2; S.D.: 14.4) than males did (mean: 58.6; S.D.: 15.56) (two-sample t-test, $p = 0.01$).

Individuals with preferably high and low SDQ-S score ($n = 28$, score > 60 and $n = 28$, score < 39, respectively) among the applicants were selected in order to obtain a sample with as large a variance on the navigation ability as possible, and then 56 healthy right-handed normal subjects consisting of four groups, 14 male good navigators (mean age and S.D.: 28.6 and 8.8), 14 male poor navigators (26.78 and 6.43), 14 female good navigators (26.7 and 2.98), and 14 female poor navigators (27.85 and 5.32) were selected (no significant difference of age amongst groups). After description of the study, written informed consent was obtained from every subject. The study protocol was approved by the ethics committee of the National Center of Neurology and Psychiatry, Tokyo, Japan and was conducted by the principles of the Declaration of Helsinki. None had a history of neurological or psychiatric disorders or any sign of color blindness, visual field defects or visual-spatial problems. The mean scores (S.D.) of SDQ-S in each group were 34 (7.4) in male poor navigators, 30.6 (6.43) in female poor navigators, 75.33 (7.44) in male good navigators, and 73.5 (8.32) in female good navigators, respectively. The ANOVA, navigation ability (good and poor) by sex, with the score of SDQ-S, revealed only a significant main effects of navigation ability ($F(1, 54) = 52.98$, $p < 0.001$). There is no main effect of sex or interaction effect. The main effect of navigation ability showed that good navigators showed higher scores of SDQ-S than poor navigators did ($p < 0.001$). Five items (questions 1, 2, 4, 6, and 7) of the SDQ-S were considered to be associated with preferred navigation strategy in the daily life; i.e., individuals with higher scores tend to prefer the allocentric orientation strategy, whereas individuals with lower scores tend to have a difficulty in allocentric orientation strategy. We also analyzed the data of five items of of the SDQ-S.

2.2. fMRI procedure

Cerebral activation was measured with fMRI using blood oxygen level-dependent contrast. After automatic shimming, a time course series of 140 volumes was obtained using single-shot gradient-refocused echo-planar imaging (TR = 4000 ms, TE = 60 ms, flip angle = 90°, inter-scan interval 4 s, in-plane resolution 3.44 mm × 3.44 mm, FOV = 22 cm, contiguous 4-mm oblique slices to cover the entire brain, slice angle was selected to avoid susceptibility artifact from sphenoid sinus) with a 1.5 T MAGNETOM Vision plus MR scanner (Siemens, Erlangen, Germany) using the standard head coil. The first five volumes of each fMRI scan were discarded because of non-steady magnetization, with the remaining 135 volumes used for the analysis. Before the collection of fMRI data for each subject, we acquired a reference EPI scan and visually inspected it for artifacts (i.e., ghosting) as well as for good signal across the entire volume of acquisition, particularly the medial temporal lobes. Head motion was minimized by placing tight but comfortable foam padding around the subject's head. The fMRI protocol was a block design with nine blocks of virtual maze task, nine blocks of control task and nine blocks resting conditions. Each block lasted 20 s (equivalent to five whole-brain fMRI volume acquisitions).

2.3. Navigation tasks

We applied a passive-watching task, watching movies of exploration in mazes, as a navigation task to minimize explicit motor outputs and commands. Nine different simple three-dimensional mazes for task epochs were programmed with a commercially available software program for building design on a PC. The program has a function showing someone walking around a building presented from a first person's view, which is recorded as a movie file. During the task condition, the subjects were asked to watch a 15 s movie of exploration in a maze from the first person point of view, in a three-dimensional, fully textured environment. Fig. 1(left) displays a typical view experienced by subjects within the task condition. Immediately after the movie finished, two maps of the maze from a bird's eye view were presented for 5 s (Fig. 1, right). The one was correct map and another was wrong one. Subjects were asked to judge which map was correct. They used a two-button response box under their right hand to select the answer. To give a correct answer, the subjects have to construct an allocentric 'cognitive map' from egocentric spatial information during watching the movie. The stimuli were presented using Media player running on a PC and backprojected onto a screen, approximately 50-cm from the subject's head, using a 65,536-color liquid crystal display and an overhead projector. The subjects viewed the screen through a mirror attached to the head coil. During the control condition, subjects were asked to watch a movie of walking in a straight passage, which has the same texture as the maze presented during the task epoch. The movement speed was made the same with all task and control epochs. Prior to the fMRI measurement, all subjects were trained on a maze to familiarize with the task.

2.4. Data analysis

Data were analyzed with Statistical Parametric Mapping software (SPM2). Scans were realigned and spatially normalized to the standard stereotactic space of Talairach using EPI template. The parameter for affine and quadratic transformation to the EPI template that was already fit for Talairach space was estimated by least-squares means. Data were then smoothed in a spatial domain (full width at half-maxim = 8 mm × 8 mm × 8 mm) to improve the signal to noise ratio. After specifying the appropriate design matrix, delayed box-car function as a reference waveform, the condition, slow hemodynamic fluctuation unrelated to the task, and subject effects were estimated according to

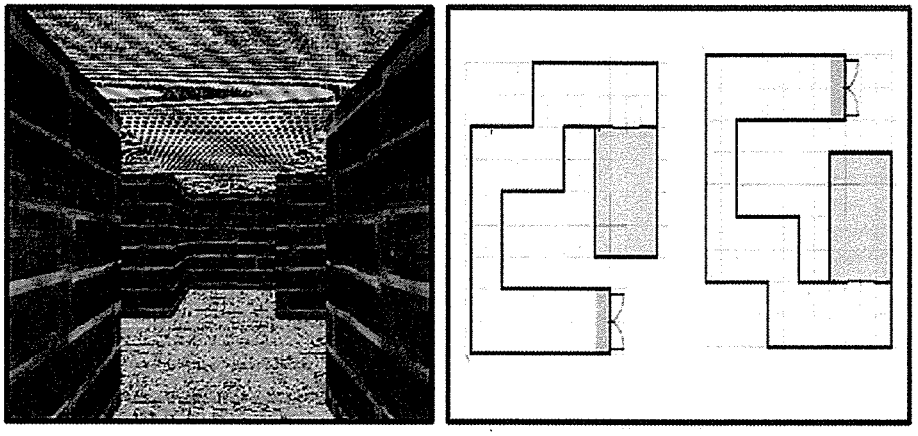

Fig. 1. An example of stimuli for fMRI. Left: typical view from inside the virtual maze. During the task condition, subjects were asked to watch a 15 s movie showing exploration in a maze from a first person point of view, three-dimensional, fully textured environment. Right: immediately after the movie was finished, two maps of the maze were presented for 5 s. During this period, subjects have to choose the correct map.

a general linear model taking temporal smoothness into account. To test hypotheses about regionally specific condition effects, the estimates were compared by means of linear contrasts of each control and task period. The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM $\{t\}$. To account for inter-individual variance, all group analyses were computed using a random-effects model (Friston et al., 1999). Group analysis across groups involved a one-sample t-test on the images generated by pooling over the session the individual contrasts of task condition versus control condition for each subject. Between groups, regionally specific main effects (navigation ability and sex) and interaction effects were analyzed by analysis of variance design matrix. Furthermore, we performed correlational analyses to find where activation responded to task performance (number of correct answers of the maze task during fMRI measurements, full score was nine points) and scores of five items of the SDQ-S. All the analyses, we used $p < 0.001$, corrected for multiple comparisons with false discovery rate (FDR) <0.05 as a statistical threshold. Since a recent human study demonstrated that hippocampus and parahippocampal gyrus differently contributed to spatial navigation (Ekstrom et al., 2003), we additionally performed regression analyses with region of interest analysis (ROI) to clarify whether activation response to task performance and scores of five items of the SDQ-S differ between hippocampus and parahippocampal gyrus. For this hypothesis-driven analysis, we used the Wake Forest University PickAtlas (Maldjian et al., 2003) to make ROIs for hippocampus and parahippocampal gyrus separately and used to marsbar (http://marsbar.sourceforge.net/) to extract values within ROIs. Using the extracted value of each ROI, we performed linear correlational analysis between task performance, scores of five items of the SDQ-S and magnitude of the activation within the ROIs in each region (hippocampus and parahippocampal gyrus), and examined if there were any region by task

Table 1
Brain activity related to maze task in the whole group

Anatomical region	Broadman area	Talairach coordinate			t-Value
		X	Y	Z	
Left					
Parahippocampal gyrus	30/35/36	−26	−30	−25	9.85
Hippocampus		−20	−35	−4	5.17
Posterior cingulate gyrus	30	−14	−58	7	6
Precuneus	7,19	−16	−65	51	15.68
Cuneus	17	−8	−91	3	9.36
Superior parietal lobule	7	−14	−61	53	13
Inferior parietal lobule	40	−36	−39	41	9.3
Fusiform gyrus	19/37	−44	−63	−22	10.15
Middle occipital gyrus	18/19	−44	−81	10	13.38
Superior colliculus		−3	−35	−3	5.98
Right					
Parahippocampal gyrus	30/35/36	34	−38	−27	10
Hippocampus		21	−37	−5	5.22
Posterior cingulate gyrus	29/30/31	20	−57	19	8.32
Precuneus	7,19	16	−65	53	16.85
Cuneus	17	16	−97	3	14.55
Superior parietal lobule	7	30	−56	53	11.1
Inferior parietal lobule	40	36	−45	41	8.34
Fusiform gyrus	19/37	32	−59	−17	11.3
Middle occipital gyrus	18/19	50	−68	−5	12.28
Lingual gyrus	17/18	12	−80	−8	12.98
Superior colliculus		3	−22	−4	5.96
Middle frontal gyrus	9	51	16	26	11.86

Table 2
Results of group comparison and correlational analysis

Anatomical regions	Broadman area	Talairach coordinate			*t*-Value
		X	*Y*	*Z*	
Post hoc *t*-test					
(1) Main effect (navigation ability)					
Good navigators > poor navigators (Fig. 3, left)					
L: hippocampus, parahippocampal gyrus	35	−16	−29	−5	5.6
R: hippocampus, parahippocampal gyrus	30	16	−35	−3	5.4
L: precuneus	7	−8	−54	52	4.27
R: precuneus	7	10	−52	49	4.9
Poor navigators > Good navigators (Fig. 3, right)					
R: inferior parietal lobule	40	59	−48	45	4.4
(2) Main effect (sex)					
Not significant					
(3) Interaction effect					
Not significant					
The correlation between task performance and brain activity					
(1) Positive correlation (Fig. 4)					
L: parahippocampal gyrus	35	−16	−30	−9	6.14
L: hippocampus		−20	−29	−4	5.98
(2) Negative correlation (Fig. 5)					
R: superior parietal lobule	7	44	−58	53	5.28
(3) Interaction effect					
Not significant					
The correlation between scores of 5 items of the SDQ-S					
(1) Positive correlation with SDQ-S					
L: parahippocampal gyrus	35	−17	−33	−6	7.87
L: hippocampus		−26	−32	−2	7.43
R: parahippocampal gyrus	35	20	−31	−5	6.53
R: hippocampus		28	−32	−3	6.34
(2) Negative correlation with SDQ-S					
L: superior Parietal Lobule	7	−40	−69	50	4.38
R: superior Parietal Lobule	7	41	−50	48	4.11

211

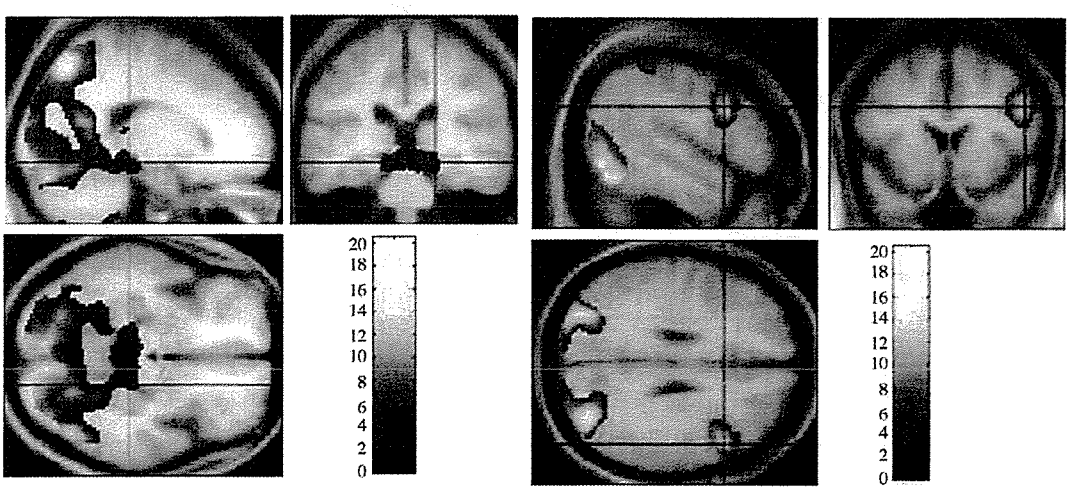

Fig. 2. Brain activity associate with maze task in the whole group. Left: activity in the bilateral middle occipital gyri, lingual gyri, fusiform gyri, parahippocampal gyri, hippocampi, posterior cingulate gyri, precuneus, cuneus and the superior colliculus is superimposed on T1 weighted MR images. Right: activity in the bilateral inferior parietal lobules, superior parietal lobules and right dorsolateral prefrontal cortex is superimposed on T1 weighted MR images.

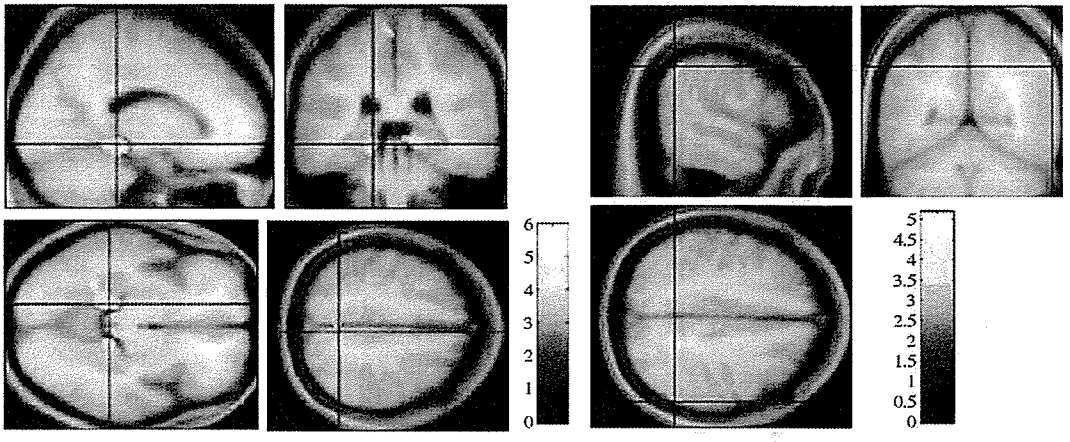

Fig. 3. Results of group comparisons. Left: in comparison with poor navigators, good navigators demonstrated a significantly stronger activation in the bilateral hippocampi, parahippocampal gyri and precunei. Right: in comparison with good navigators, poor navigators showed a significantly stronger activity in the right inferior parietal lobule.

performance or scores of five items of the SDQ-S interaction effects. The interaction effects of regions by task performance or scores of five items of the SDQ-S were estimated by a test of parallelism for an analysis of covariate. The statistical analysis for ROI analysis was performed using Statistical Package for the Social Sciences (SPSS, Japan Co., Tokyo, Japan).

3. Results

3.1. Behavioral data

Mean correct answers (S.D.) of the maze task during fMRI measurements were 7.93 (0.85) in male good navigators, 8.07 (0.83) in female good navigators, 5.57 (0.85) in male poor navigators, 5.64 (0.93) in female poor navigators, respectively. The ANOVA, navigation ability (good and poor) by sex, with the number correct answers of the maze task during fMRI measurements, revealed only a significant main effects of navigation ability demonstrated by SDQ-S ($F = 36.17$, $p < 0.001$). There was neither main effect of sex nor interaction effect between sex and navigation ability. The main effect of navigation ability showed that good navigators made more correct answers than poor navigators did ($p < 0.001$). Although, our subjects were selected by using self-administrated questionnaire (SDQ-S), task performance was well concordant with self-rating of navigation ability in daily life.

Regardless of sex, the SDQ-S showed that poor navigators relied on the egocentric route strategy whereas good navigators relied on the allocentric orientation strategy. For example, all poor navigators strongly agreed with question 4 (when I get route information, I can make use of "left or right" information, but I cannot use cardinal directions), whereas all good navigators disagreed with this question. Other questions also revealed that poor navigators have difficulty in using cardinal directions and a polar system for spatial

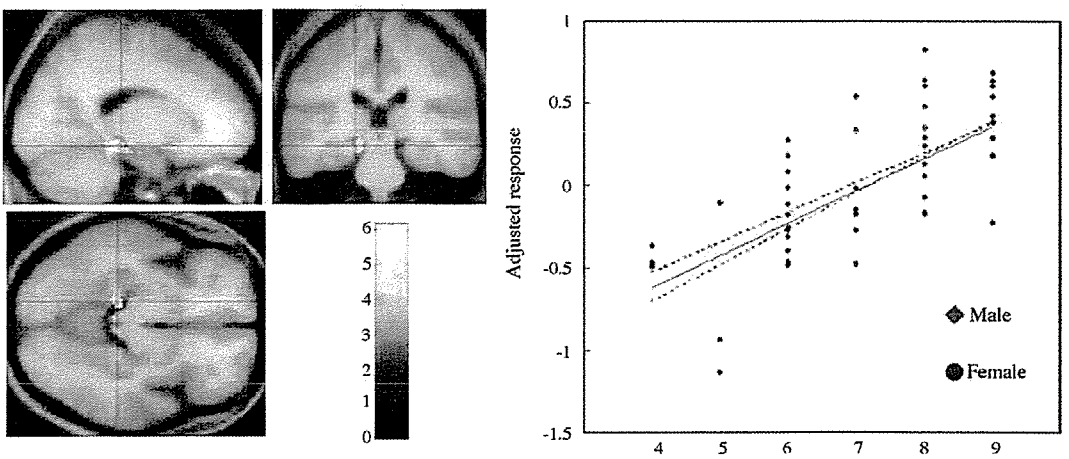

Fig. 4. Results of correlational analysis (positive correlation). Left: the area where activation responds linearly to the task performance. There was a significantly positive linear correlation between task performance and the degree of activation in the left hippocampus and parahippocampal gyrus. Right: the correlation between the task performance and the degree of activation at the voxel of peak activation in the left parahippocampus. A positive correlation was noted (whole subjects: $y = 0.195X - 1.4$, $r = 0.72$, $p < 0.001$; men: $y = 0.1793X - 1.239$, $r = 0.723$, $p < 0.001$; women: $y = 0.218X - 1.572$, $r = 0.719$, $p < 0.001$). Blue diamonds: male subjects; red circles: female subjects; black solid line: the regression line for all subjects; blue dashed line: regression line for male subjects; red dashed line: female subjects.