Fig. 1. Regions of interest drawn on all anatomically standardized images (1: cerebellum, 2: substantia nigra, 3: thalamus, 4: anterior nuclei, 5: dorsomedial nucleus, 6: pulvinar, 7: caudate head, 8: nucleus accumbens, 9: putamen, 10: globus pallidus, 11: hippocampus, 12: parahippocampal gyrus, 13: uncus, 14: anterior part of the cingulate gyrus, 15: posterior part of the cingulate gyrus, 16: base side of frontal cortex, 17: convexity side of frontal cortex, 18: lateral side of temporal cortex, 19: parietal cortex, 20: cuneus of occipital cortex). All images are transaxial sections parallel to the anterior-posterior commissure (AC–PC) line. The slice positions are −42, −34, −22, −14, −8, 0, 4, 20, 36 and 52 mm from the AC–PC line.

irreversible binding. The occipital cortex was used as a region with no irreversible binding, as this region is known to have the lowest dopamine concentration (Brown et al., 1979) and lowest aromatic L-amino acid decarboxylase activity (Lloyd and Hornykiewicz, 1972). Integration intervals (t_1 to t_2) of 29 to 89 min, representing late portions of the time–activity curves, were used (Ito et al., 2006b).

Data analysis

All MR images were coregistered to the PET images with the statistical parametric mapping (SPM2) system (Friston et al., 1990). MR images were transformed into the standard brain size and shape by linear and nonlinear parameters by SPM2 (anatomic standardization). The brain templates used in SPM2 for anatomic standardization were T1 templates for MR images, i.e., Montreal Neurological Institute (MNI)/International Consortium for Brain Mapping (ICBM) 152 T1 templates as supplied with SPM2. All PET images were also transformed into the standard brain size and shape by using the same parameters as the MR images. Thus, brain images of all subjects had the same anatomic format. Gray matter, white matter, and cerebrospinal fluid images were segmented and extracted from all anatomically standardized MR images by applying voxel-based morphometry methods with the SPM2 system (Ashburner and Friston, 2000). These segmented MR images indicate the tissue fraction of gray or white matter per voxel (mL/mL). All anatomically standardized PET, gray matter and white matter images were smoothed with an 8-mm FWHM isotropic Gaussian kernel, because final spatial resolution of PET camera was approximately 8 mm FWHM.

Regions of interest (ROIs) were drawn on all anatomically standardized PET, gray matter and white matter images with reference to the T1-weighted MR image (Fig. 1). ROIs were defined for the cerebellar cortex, substantia nigra with ventral tegmental

area, thalamus and its subregions (anterior nuclei, dorsomedial nucleus, and pulvinar) (Okubo et al., 1999; Yasuno et al., 2004), caudate head, nucleus accumbens, putamen, globus pallidus, hippocampus, posterior part of parahippocampal gyrus, uncus including amygdala, anterior and posterior parts of the cingulate gyrus, base and convexity sides of frontal cortex, lateral side of temporal cortex, parietal cortex, and cuneus of occipital cortex,

Table 2
Representative MNI coordinates in ROIs drawn on anatomically standardized images

Region	Right			Left		
	X	Y	Z	X	Y	Z
Cerebellum	30	−74	−42	−30	−74	−42
Substantia nigra	6	−20	−14	−6	−20	−42
Thalamus	11	−18	4	−11	−18	4
AN	5	−12	4	−5	−12	4
DMN	8	−22	4	−8	−22	4
PUL	14	−29	4	−14	−29	4
Caudate head	12	16	4	−12	16	4
Nucleus accumbens	17	13	−8	−18	12	−8
Putamen	24	9	0	−24	7	0
Globus pallidus	19	0	0	−18	−2	0
Hippocampus	31	−12	−22	−30	−13	−22
Parahippocampal gyrus	28	−21	−22	−28	−23	−22
Uncus	21	−3	−22	−22	−2	−22
Anterior cingulate	7	44	4	−7	45	4
Posterior cingulate	8	−47	36	−8	−47	36
Frontal base	35	56	0	−34	56	0
Frontal convexity	35	31	36	−36	27	36
Lateral temporal cortex	59	−11	−22	−58	−13	−22
Parietal cortex	45	−62	36	−45	−65	36
Occipital cuneus	10	−81	4	−8	−81	4

AN: anterior nuclei, DMN: dorsomedial nucleus, PUL: pulvinar in the thalamus.
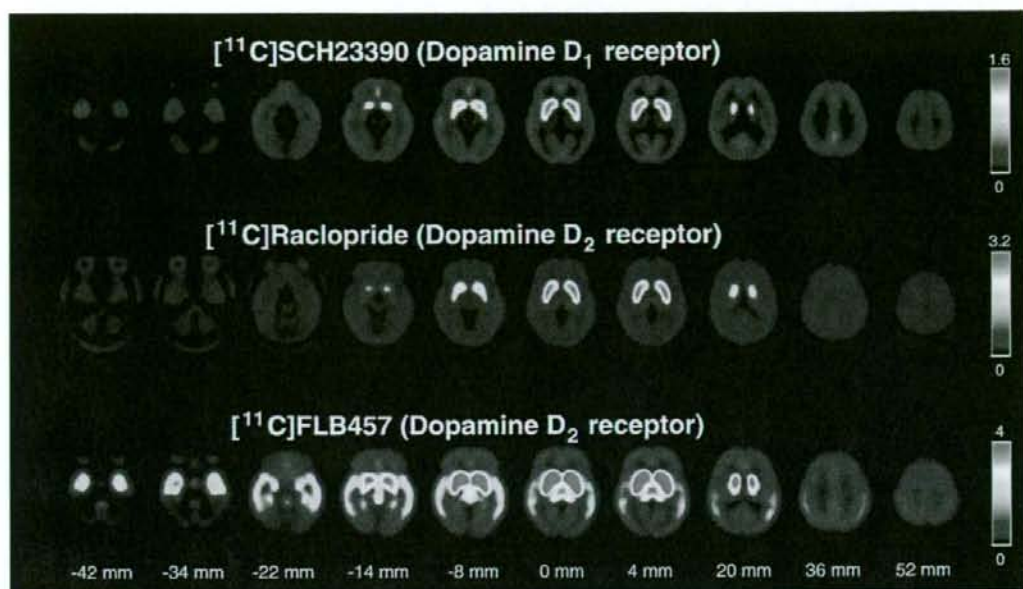
Fig. 2. Anatomically standardized averaged PET images obtained with [¹¹C]SCH23390, [¹¹C]raclopride, and [¹¹C]FLB457. All images are transaxial sections parallel to the AC–PC line. The slice positions are −42, −34, −22, −14, −8, 0, 4, 20, 36, and 52 mm from the AC–PC line. The anterior is at the top of the image and the subjects' right is at the left. Scale maximum and minimum values are 1.6 and 0 of BP for [¹¹C]SCH23390, 3.2 and 0 of BP for [¹¹C]raclopride, and 4 and 0 of BP for [¹¹C]FLB457, respectively.
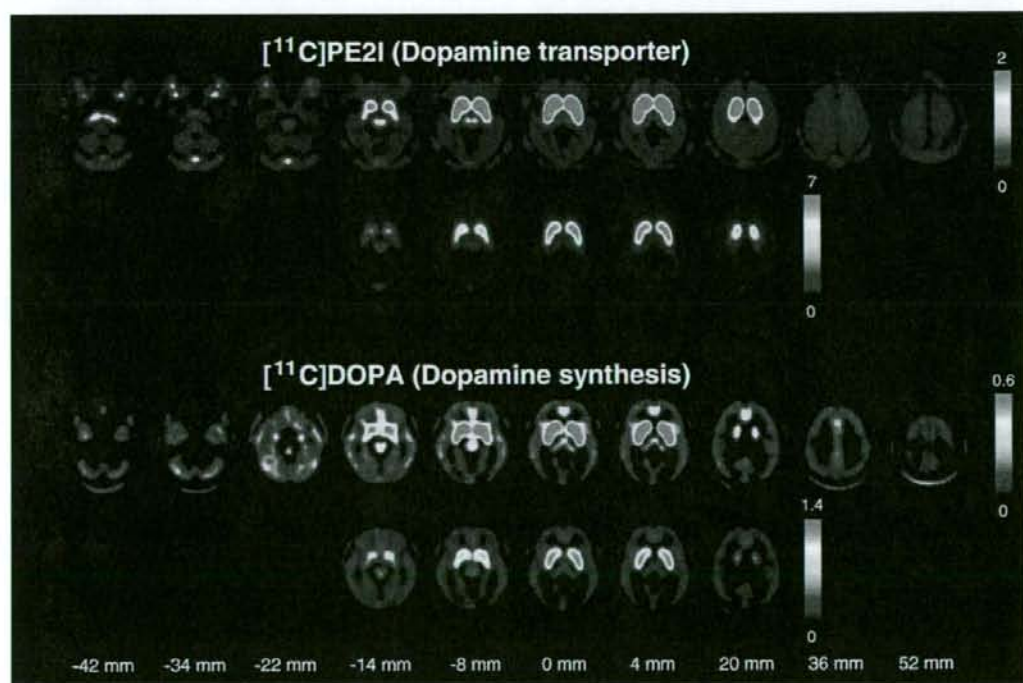

Fig. 3. Anatomically standardized averaged PET images obtained with [¹¹C]PE2I and L-[β-¹¹C]DOPA. All images are transaxial sections parallel to the AC-PC line. The slice positions are −42, −34, −22, −14, −8, 0, 4, 20, 36, and 52 mm from the AC–PC line. The anterior is at the top of the image and the subjects' right is at the left. Scale maximum and minimum values are 7 or 2 and 0 of BP for [¹¹C]PE2I, and 1.4 or 0.6 and 0 of *I* for L-[β-¹¹C]DOPA, respectively.

considering regional distribution of dopaminergic neurotransmission system. Representative MNI coordinates in ROIs (approximations of the arithmetic center of ROIs) are given in Table 2.

To compare BP and I values between tracers for each ROI, percentages of the putamen of BP or I were calculated for [^{11}C]SCH23390, [^{11}C]PE2I, and L-[β-^{11}C]DOPA, because the putamen showed highest BP and I values among all brain regions for all tracers. Since [^{11}C]FLB457 is not favorable for estimating striatal BP values, the percentage of BP of the putamen in the extrastriatal regions was calculated as the percentage of the putaminal BP values for [^{11}C]raclopride mediated with thalamic BP values:

% of putamen in extrastriatal regions

$$= \frac{\text{Extrastriatum(FLB)}}{\text{Putamen(Racl.)}} \cdot \frac{\text{Thalamus(Racl.)}}{\text{Thalamus(FLB)}}$$

where Extrastriatum(FLB) is BP in the extrastriatal regions for [^{11}C]FLB457, Putamen(Racl.) is BP in the putamen for [^{11}C]raclopride, and Thalamus(Racl.) and Thalamus(FLB) are BP in the thalamus for [^{11}C]raclopride and [^{11}C]FLB457 studies, respectively. Although [^{11}C]raclopride binding in the extrastriatal regions is low (Farde et al., 1988), it has been reported that the specific binding of [^{11}C]raclopride in the thalamus was low but detectable (Ito et al., 1999). In these calculation, values without the partial volume correction (see below) were used.

Partial volume correction

BP and I values are affected by the regional gray matter fraction because of the limited spatial resolution of the PET scanner. The BP and I values per gray matter fraction in an ROI for cerebellar and cerebral cortical regions can be calculated as BP or I divided by the gray matter fraction obtained from segmented MR images for each ROI (Ito et al., 2006a).

Results

Anatomically standardized averaged images of BP and I are shown in Figs. 2 and 3, respectively. The BP and I values of each ROI for [^{11}C]SCH23390, [^{11}C]raclopride, [^{11}C]FLB457, [^{11}C]PE2I, and L-[β-^{11}C]DOPA are given in Table 3. Percentages of the putamen for BP or I values of [^{11}C]SCH23390, [^{11}C]FLB457, [^{11}C]PE2I, and L-[β-^{11}C]DOPA are shown in Fig. 4. In the substantia nigra with ventral tegmental area, binding to dopamine D_2 receptors, but very low binding to D_1 receptors, was observed. In the striatum, greatest bindings to dopamine D_1, D_2 receptors and transporters as well as the highest dopamine synthesis were observed. For the limbic regions, relatively high bindings of dopamine D_2 receptors were observed in the uncus. Relatively high dopamine synthesis was observed in the uncus and anterior part of the cingulate gyrus. For the other neocortical regions, the highest binding to dopamine D_2 receptors was observed in the temporal cortex. D_1 receptor binding among the neocortical regions was uniformly observed. Binding to dopamine transporter was very low in the neocortical regions. In the thalamus, relatively high binding to dopamine D_2 receptors was observed, but binding to D_1 receptors was very low.

Anatomically standardized averaged T1-weighted MR images and averaged images of gray and white matter fractions are shown in Fig. 5. The tissue fraction values of gray and white matter per voxel in cerebellar and cerebral cortices are given in Table 4, and the BP and I values with correction for the gray matter fraction in an ROI are shown in Table 5. Almost the same order of BP and I values among cerebral cortical regions was observed between before and after the correction for the gray matter fraction.

Discussion

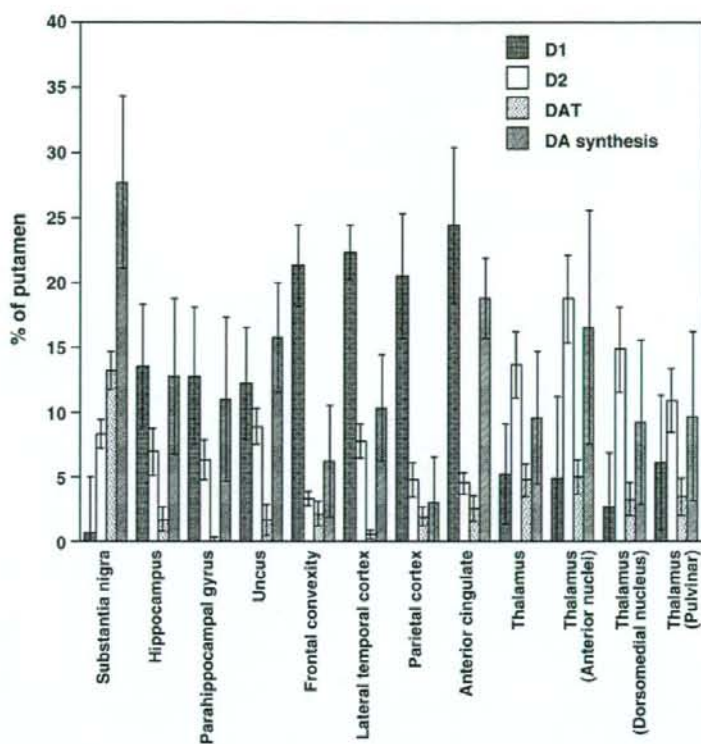A normal database for pre and postsynaptic dopaminergic neurotransmission components, including the striatal and extra-

Table 3
Average binding potential (BP) and dopamine synthesis index (I) values

Region	BP				I
	[^{11}C]SCH23390	[^{11}C]raclopride	[^{11}C]FLB457	[^{11}C]PE2I	L-[β-^{11}C]DOPA
Cerebellum	–	–	–	–	0.09±0.05
Substantia nigra	0.01±0.06	0.20±0.07	1.72±0.26	0.82±0.12	0.33±0.08
Thalamus	0.08±0.06	0.38±0.05	2.80±0.40	0.29±0.08	0.12±0.07
AN	0.07±0.08	0.42±0.10	3.84±0.51	0.30±0.08	0.20±0.13
DMN	0.04±0.06	0.32±0.07	3.04±0.52	0.20±0.09	0.11±0.08
PUL	0.09±0.07	0.38±0.06	2.24±0.41	0.21±0.09	0.12±0.09
Caudate head	1.13±0.24	2.21±0.22	6.69±0.94	5.84±1.00	0.79±0.17
Nucleus accumbens	1.20±0.23	2.19±0.38	6.73±1.11	4.75±0.70	0.94±0.14
Putamen	1.39±0.24	2.84±0.30	7.97±1.15	6.22±0.90	1.20±0.16
Globus pallidus	0.83±0.23	1.80±0.25	5.57±0.91	3.38±0.72	0.74±0.13
Hippocampus	0.20±0.09	0.27±0.06	1.42±0.24	0.10±0.05	0.16±0.09
Parahippocampal gyrus	0.18±0.10	0.25±0.05	1.30±0.22	−0.01±0.03	0.14±0.09
Uncus	0.17±0.07	0.26±0.05	1.84±0.26	0.09±0.06	0.19±0.07
Anterior cingulate	0.34±0.11	0.31±0.07	0.93±0.16	0.16±0.05	0.22±0.05
Posterior cingulate	0.41±0.11	0.36±0.05	1.01±0.36	0.14±0.07	0.12±0.04
Frontal base	0.25±0.08	0.25±0.04	0.75±0.20	0.09±0.03	0.07±0.06
Frontal convexity	0.30±0.08	0.27±0.04	0.70±0.18	0.13±0.05	0.07±0.05
Lateral temporal cortex	0.31±0.07	0.32±0.04	1.61±0.30	0.03±0.02	0.12±0.05
Parietal cortex	0.29±0.10	0.29±0.02	1.02±0.35	0.11±0.04	0.04±0.04
Occipital cuneus	0.37±0.10	0.29±0.05	0.50±0.27	0.12±0.04	–

Values are shown as mean±SD.
AN: anterior nuclei, DMN: dorsomedial nucleus, PUL: pulvinar in the thalamus.

Fig. 4. Percentage of the putamen for BP or *I* values of [^{11}C]SCH23390 (dopamine D$_1$ receptor), [^{11}C]FLB457 (dopamine D$_2$ receptor), [^{11}C]PE2I (dopamine transporter (DAT)), and L-[β-^{11}C]DOPA (dopamine (DA) synthesis) for the substantia nigra, hippocampus, parahippocampal gyrus, uncus, frontal convexity, lateral temporal cortex, parietal cortex, anterior cingulate, thalamus and its subregions (anterior nuclei, dorsomedial nucleus, and pulvinar). Values are mean ± SD.

striatal dopamine D$_1$ and D$_2$ receptor bindings, dopamine transporter binding, and endogenous dopamine synthesis in the living human brain could be constructed by making use of the anatomic standardization technique. Although the subjects all differed in terms of the database (dopamine D$_1$, D$_2$ receptor, transporter, and synthesis), the anatomic standardization technique allowed us to compare between regional distributions of each dopaminergic neurotransmission component in vivo. While partial volume effects cause systemic underestimations of BP and *I* values, the partial volume correction did not change the order of BP and *I* values among cerebral cortical regions. This database is expected to be useful for various researches to understand the physiology of dopaminergic functions in the living human brain; however, regional differences in test-retest reliability in PET measurements should be considered (Hirvonen et al., 2001; Sudo et al., 2001). In addition, it has been reported that the reference tissue model method with the basis function method might cause overestimation and underestimation of BP in regions with low and high BP, respectively (Cselenyi et al., 2006; Gunn et al., 1997). Since BP values calculated from measured data may show some bias depending on kinetic models and calculation methods, it is not obvious if calculated BP values linearly reflect the biological pre- and postsynaptic functions. Thus, there might be some limitations in comparison of regional distributions between tracers using percentages of the putamen. This database can also be used in the investigation of regional abnormalities of dopaminergic neurotransmission in neuropsychia-

tric disorders, if database will be constructed from a large number of subjects. It might be difficult to use our database in other PET center due to between-center differences in data acquisition protocols, image reconstruction process, quantification methods, etc. (Ito et al., 2004). To solve these differences, further studies were required.

Nigrostriatal dopaminergic system

Midbrain

The ascending projections from the dopaminergic neurons in the substantia nigra to the striatum compose the nigrostriatal dopaminergic system (Bentivoglio and Morelli, 2005). Binding to dopamine D$_2$ receptors in the midbrain including the substantia nigra and ventral tegmental area was observed to be the same in the living human brain as in human postmortem studies (Hall et al., 1996; Joyce et al., 1991), suggesting the existence of receptors in dopaminergic neurons. On the other hand, no binding to dopamine D$_1$ receptors was observed in this region. These observations support the finding that dopaminergic autoreceptors in the midbrain are mainly of D$_2$ type (Meador-Woodruff et al., 1994; Morelli et al., 1987). In the living human brain, dopamine synthesis in the midbrain was greater than in the cerebral neocortical regions, although the aromatic L-amino acid decarboxylase activity in the substantia nigra was almost the same as in the parietal and occipital cortices in the human postmortem brain (Lloyd and Hornykiewicz, 1972). A medium amount of dopamine transporter was also found in the
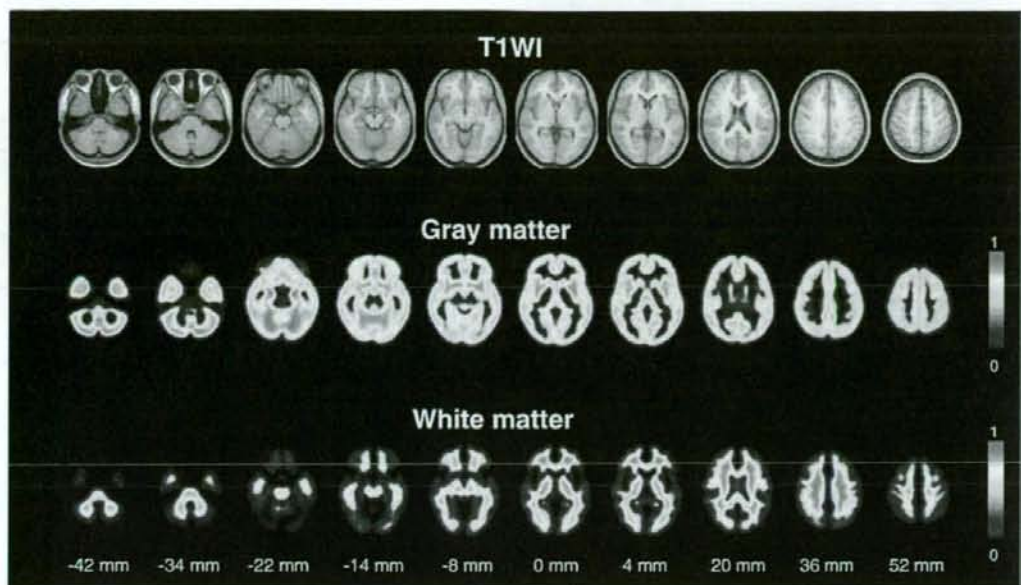
Fig. 5. Anatomically standardized averaged T1-weighted MR images and averaged images of gray and white matter fractions. All images are transaxial sections parallel to the AC–PC line. The slice positions are −42, −34, −22, −14, −8, 0, 4, 20, 36, and 52 mm from the AC–PC line. The anterior is at the top of the image and the subjects' right is at the left. Scale maximum and minimum values for gray and white matter images are 1 and 0 of gray and white matter fractions (mL/mL), respectively. T1WI, T1-weighted image.

midbrain, similar to a human postmortem study (Hall et al., 1999) and animal studies (Boja et al., 1994; Ciliax et al., 1995).

Striatum

The highest bindings to dopamine D_1 and D_2 receptors were observed in the striatum among the all brain regions, indicating the highest density of receptors, the same as reported in human postmortem studies (Hall et al., 1994). The highest binding to dopamine transporter in the striatum was also observed, indicating the highest transporter density (Boja et al., 1994; Ciliax et al., 1995; Hall et al., 1999). These findings indicate that this region is rich in dopaminergic synapses. Although the microdistribution of dopamine D_2 receptors in the striatum is differential with D_2 predominating in the striosomes and D_1 in the matrix (Joyce et al., 1986), the distributions of dopamine D_1 and D_2 receptor bindings appeared almost uniform in the striatum on account of the limited spatial resolution of the PET scanner. The highest dopamine synthesis was also observed in the striatum. This finding is in good agreement with previous studies showing the highest aromatic L-amino acid decarboxylase activity (Lloyd and Hornykiewicz, 1972) and the highest dopamine concentration in the striatum (Brown et al., 1979). These findings, in total, reflect the dense dopamine innervation of this region from the substantia nigra (Moore et al., 2003).

Globus pallidus

In the globus pallidus, higher bindings to dopamine D_1 and D_2 receptors as compared with other extrastriatal regions were observed, much the same as in human postmortem studies (Hall et al., 1996, 1994). These findings support the concept of the dopaminergic pallidal projections from neurons in the substantia nigra

and ventral tegmental area (Bentivoglio and Morelli, 2005; Parent et al., 1990). In addition, it has been reported that binding to dopamine D_2 receptors in the external segment of the pallidum was higher than that in the internal segment in the human postmortem brain (Hall et al., 1996; Joyce et al., 1991). However, spillover from striatal radioactivity owing to the limited spatial resolution of the PET scanner might hamper an accurate estimation of pallidal binding. BP values of [^{11}C]raclopride in the globus pallidus and nucleus accumbens were different from previous study of the living human brain (Ito et al., 1999). These differences might be caused by differences in anatomic standardization techniques, methods of calculation of BP, image reconstruction process, PET cameras, etc.

Mesocorticolimbic dopaminergic system

Limbic system

The ascending projections from dopaminergic neurons in the ventral tegmental area to the cerebral cortices and limbic system compose the mesocorticolimbic dopaminergic system (Bentivoglio and Morelli, 2005). The ventral striatum, the so-called limbic striatum, including the nucleus accumbens is also innervated by the ventral tegmental area (Bentivoglio and Morelli, 2005; Joel and Weiner, 2000).

Relatively high bindings of dopamine D_2 receptors were observed in the uncus including the amygdala, parahippocampal gyrus, and hippocampus as compared with cerebral neocortical regions. These distributions are in good agreement with those found in human postmortem studies (Hall et al., 1996, 1994; Joyce et al., 1991). It has been reported that densities of dopamine D_2 receptors in the hippocampus are lower than in the amygdala and parahippocampal gyrus (Hall et al., 1996, 1994). The present study also

Table 4
Average tissue fractions of gray and white matter per voxel in cerebellar and cerebral cortices (mL/mL)

Region	Tissue fraction	
	Gray matter	White matter
Cerebellum	0.75 ± 0.04	0.16 ± 0.03
Hippocampus	0.80 ± 0.04	0.14 ± 0.03
Parahippocampal gyrus	0.74 ± 0.03	0.19 ± 0.03
Uncus	0.83 ± 0.03	0.03 ± 0.01
Anterior cingulate	0.65 ± 0.04	0.20 ± 0.03
Posterior cingulate	0.72 ± 0.04	0.18 ± 0.05
Frontal base	0.55 ± 0.02	0.29 ± 0.02
Frontal convexity	0.57 ± 0.04	0.29 ± 0.04
Lateral temporal cortex	0.66 ± 0.02	0.25 ± 0.02
Parietal cortex	0.55 ± 0.03	0.35 ± 0.03
Occipital cuneus	0.64 ± 0.04	0.27 ± 0.04

Values are shown as mean ± SD.

showed lower binding of dopamine D_2 receptors in the hippocampus than in the uncus. A human postmortem study showed aromatic L-amino acid decarboxylase activity in the amygdala but not in the hippocampus (Lloyd and Hornykiewicz, 1972). In the present study, dopamine synthesis was observed in the hippocampus in addition to the uncus including amygdala and parahippocampal gyrus although the spatial resolution of the PET scanner was limited. The present results might indicate the dopaminergic innervation to the hippocampus in addition to the amygdala and the parahippocampal gyrus (Joyce and Murray, 1994). As for the other extrastriatal regions, bindings to dopamine transporter were very low (Hall et al., 1999).

The anterior part of the cingulate gyrus representing the limbic system has projections from the dopaminergic neurons in the ventral tegmental area, and connections with hippocampal regions. In this region, bindings to dopamine D_1 and D_2 receptors similar to those in neocortical regions were observed. Binding to dopamine transporter was very low in this region, as in neocortical regions. It should be noted that dopamine synthesis was relatively higher in the anterior cingulate than in neocortical regions.

Neocortex

In the cerebral neocortical regions, binding to dopamine D_2 receptors was found to be low comparing with the other brain regions as previous studies of the living human brain (Okubo et al.,

1999) and postmortem brain (Hall et al., 1996, 1994; Joyce et al., 1991; Lidow et al., 1989) have also reported. Regional differences in D_2 receptor binding among the neocortical regions were observed in the living human brain as in the human postmortem brain (Hall et al., 1996, 1994; Joyce et al., 1991), i.e., highest binding in the temporal cortex and lowest binding in the occipital cortex. Binding to dopamine D_2 receptors was higher in the parietal cortex than in the frontal and occipital cortices. Binding to dopamine D_1 receptors in the cerebral neocortical regions as compared with the striatum was higher than that to D_2 receptors as shown in a previous human postmortem study (Hall et al., 1994). Using the present database of dopamine D_1 and D_2 receptors, it could be observed that regional distribution of D_1 receptor binding among the neocortical regions was more uniform as compared with that to D_2 receptors. Percentages of the putamen for BP of dopamine D_2 receptors in the cerebral neocortical regions were around 5–10% in the present study, whereas those were reported to be about 1% in a previous human postmortem study with [^{125}I]epidepride (Hall et al., 1996). This discrepancy might be caused by the difference in used radioligands. The difference between in vivo and in vitro conditions might also cause such discrepancy.

In the present study, the binding to dopamine transporter was almost negligible level in the cerebral neocortical regions, as also reported in a human postmortem study (Hall et al., 1999), although both dopamine D_1 and D_2 receptors exist in these regions. These data indicate that released dopamine in the dopaminergic synapse might be inactivated by enzymatic degradation rather than by reuptake to the transporter (Hall et al., 1999). In addition, dopamine reuptake through the norepinephrine transporter in cerebral cortical regions with low levels of the dopamine transporter was observed in mice (Moron et al., 2002). Dopamine synthesis was observed in the cerebral neocortical regions except the occipital cortex. Among these regions, highest and lowest dopamine synthesis was observed in the temporal and frontal cortex, respectively. This regional difference in dopamine synthesis was in good agreement with that in aromatic L-amino acid decarboxylase activity (Lloyd and Hornykiewicz, 1972). In the temporal cortex, highest dopamine synthesis and highest dopamine D_2 receptor binding were observed among the neocortical regions. On the other hand, it should be noted that the parietal cortex showed relatively low dopamine synthesis and relatively high dopamine D_2 receptor binding as compared with the frontal cortex.

In the present study, database were constructed from male subjects. However, it has been reported that a gender difference in

Table 5
Average binding potential (BP) and dopamine synthesis index (I) values with correction for gray matter fraction in an ROI

Region	BP				I
	[^{11}C]SCH23390	[^{11}C]raclopride	[^{11}C]FLB457	[^{11}C]PE2I	L-[β-^{11}C]DOPA
Cerebellum	–	–	–	–	0.12 ± 0.06
Hippocampus	0.24 ± 0.11	0.34 ± 0.07	1.77 ± 0.33	0.12 ± 0.06	0.20 ± 0.12
Parahippocampal gyrus	0.25 ± 0.13	0.33 ± 0.07	1.75 ± 0.30	-0.01 ± 0.04	0.18 ± 0.12
Uncus	0.21 ± 0.08	0.31 ± 0.06	2.22 ± 0.31	0.11 ± 0.07	0.23 ± 0.08
Anterior cingulate	0.53 ± 0.16	0.47 ± 0.10	1.41 ± 0.24	0.24 ± 0.08	0.34 ± 0.06
Posterior cingulate	0.57 ± 0.11	0.50 ± 0.06	1.38 ± 0.47	0.20 ± 0.10	0.17 ± 0.05
Frontal base	0.45 ± 0.13	0.46 ± 0.07	1.35 ± 0.37	0.16 ± 0.05	0.13 ± 0.11
Frontal convexity	0.52 ± 0.13	0.46 ± 0.07	1.18 ± 0.29	0.24 ± 0.10	0.12 ± 0.08
Lateral temporal cortex	0.47 ± 0.11	0.47 ± 0.06	2.39 ± 0.40	0.05 ± 0.03	0.18 ± 0.08
Parietal cortex	0.53 ± 0.16	0.52 ± 0.05	1.80 ± 0.60	0.21 ± 0.06	0.06 ± 0.08
Occipital cuneus	0.58 ± 0.15	0.45 ± 0.07	0.78 ± 0.40	0.18 ± 0.06	–

Values are shown as mean ± SD.

dopamine D_2 receptor binding was observed in the frontal cortex (Kaasinen et al., 2001). Further studies to investigate gender differences in pre- and postsynaptic dopaminergic neurotransmission components using database would be required.

Thalamic dopaminergic system

The dopaminergic projections to the thalamus from neurons in the hypothalamus, periaqueductal gray matter, ventral mesencephalon, and the lateral parabrachial nucleus were reported (Sanchez-Gonzalez et al., 2005). Therefore, a dopaminergic system targeting the thalamus, which might be independent from the nigrostriatal dopaminergic system and the mesocorticolimbic dopaminergic system, has been proposed (Sanchez-Gonzalez et al., 2005). In the present study, relatively high binding to dopamine D_2 receptors was observed in the thalamus. In particular, anterior nuclei and dorsomedial nucleus showed higher binding in the present study, the same as reported by previous studies of the living human brain (Okubo et al., 1999) and human postmortem brain (Hall et al., 1996; Rieck et al., 2004). On the other hand, binding to dopamine D_1 receptors was very low (Hall et al., 1994). Binding to dopamine transporter was very low in the thalamus, the same as in the postmortem study (Hall et al., 1999), although dopamine D_2 receptors exist in this region. This means that released dopamine in the thalamic dopaminergic synapse might be inactivated by enzymatic degradation, the same as reported in other extrastriatal regions (Hall et al., 1999). Although aromatic L-amino acid decarboxylase activity in the thalamus has been reported to be very low (Lloyd and Hornykiewicz, 1972), dopamine synthesis in this region was observed in the living human brain, supporting the existence of dopaminergic innervation in the thalamus.

In conclusion, we have built a normal database of pre- and postsynaptic dopaminergic neurotransmission components in the living human brain using PET and the anatomic standardization technique. This database enables us to compare regional distributions of striatal and extrastriatal dopamine D_1 and D_2 receptor bindings, dopamine transporter binding, and endogenous dopamine synthesis. This database is expected to be useful for various researches to understand the physiology of dopaminergic functions in the living human brain. This database can also be used in the investigation of regional abnormalities of dopaminergic neurotransmission in neuropsychiatric disorders.

Acknowledgments

References

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. NeuroImage 11, 805–821.

Bentivoglio, M., Morelli, M., 2005. The organization and circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. In: Dunnett, S.B., Bentivoglio, M., Bjorklund, A., Hokfelt, T. (Eds.), Handbook of Chemical Neuroanatomy. Dopamine, vol. 21. Elsevier, Amsterdam, pp. 1–107.

Boja, J.W., Vaughan, R., Patel, A., Shaya, E.K., Kuhar, M.J., 1994. The dopamine transporter. In: Niznik, H.B. (Ed.), Dopamine Receptors and Transporters. Marcel Dekker, Inc., New York, pp. 611–644.

Brix, G., Zaers, J., Adam, L.E., Bellemann, M.E., Ostertag, H., Trojan, H., Haberkorn, U., Doll, J., Oberdorfer, F., Lorenz, W.J., 1997. Performance evaluation of a whole-body PET scanner using the NEMA protocol. J. Nucl. Med. 38, 1614–1623.

Brown, R.M., Crane, A.M., Goldman, P.S., 1979. Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: concentrations and in vivo synthesis rates. Brain Res. 168, 133–150.

Ciliax, B.J., Heilman, C., Demchyshyn, L.L., Pristupa, Z.B., Ince, E., Hersch, S.M., Niznik, H.B., Levey, A.I., 1995. The dopamine transporter: immunochemical characterization and localization in brain. J. Neurosci. 15, 1714–1723.

Cselenyi, Z., Olsson, H., Halldin, C., Gulyas, B., Farde, L., 2006. A comparison of recent parametric neuroreceptor mapping approaches based on measurements with the high affinity PET radioligands [¹¹C] FLB 457 and [¹¹C]WAY 100635. NeuroImage 32, 1690–1708.

Dhawan, V., Ma, Y., Pillai, V., Spetsieris, P., Chaly, T., Belakhlef, A., Margouleff, C., Eidelberg, D., 2002. Comparative analysis of striatal FDOPA uptake in Parkinson's disease: ratio method versus graphical approach. J. Nucl. Med. 43, 1324–1330.

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

Farde, L., Ehrin, E., Eriksson, L., Greitz, T., Hall, H., Hedstrom, C.G., Litton, J.E., Sedvall, G., 1985. Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. Proc. Natl. Acad. Sci. U. S. A. 82, 3863–3867.

Farde, L., Halldin, C., Stone-Elander, S., Sedvall, G., 1987a. PET analysis of human dopamine receptor subtypes using ¹¹C-SCH 23390 and ¹¹C-raclopride. Psychopharmacology 92, 278–284.

Farde, L., Wiesel, F.A., Hall, H., Halldin, C., Stone-Elander, S., Sedvall, G., 1987b. No D_2 receptor increase in PET study of schizophrenia. Arch. Gen. Psychiatry 44, 671–672.

Farde, L., Pauli, S., Hall, H., Eriksson, L., Halldin, C., Hogberg, T., Nilsson, L., Sjogren, I., Stone-Elander, S., 1988. Stereoselective binding of ¹¹C-raclopride in living human brain—a search for extrastriatal central D2-dopamine receptors by PET. Psychopharmacology 94, 471–478.

Farde, L., Wiesel, F.A., Stone-Elander, S., Halldin, C., Nordstrom, A.L., Hall, H., Sedvall, G., 1990. D_2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [¹¹C]raclopride. Arch. Gen. Psychiatry 47, 213–219.

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

Fox, P.T., Mintun, M.A., Reiman, E.M., Raichle, M.E., 1988. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. J. Cereb. Blood Flow Metab. 8, 642–653.

Friston, K.J., Frith, C.D., Liddle, P.F., Dolan, R.J., Lammertsma, A.A., Frackowiak, R.S., 1990. The relationship between global and local changes in PET scans. J. Cereb. Blood Flow Metab. 10, 458–466.

Gjedde, A., 1988. Exchange diffusion of large neutral amino acids between blood and brain. In: Rakic, L., Begley, D.J., Davson, H., Zlokovic, B.V. (Eds.), Peptide and Amino Acid Transport Mechanisms in the Cerebral Nervous System. Stockton Press, New York, pp. 209–217.

Gjedde, A., Reith, J., Dyve, S., Leger, G., Guttman, M., Diksic, M., Evans, A., Kuwabara, H., 1991. Dopa decarboxylase activity of the living human brain. Proc. Natl. Acad. Sci. U. S. A. 88, 2721–2725.

Gunn, R.N., Lammertsma, A.A., Hume, S.P., Cunningham, V.J., 1997. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. NeuroImage 6, 279–287.

Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., Farde, L., 1994. Distribution of D$_1$- and D$_2$-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology 11, 245–256.

Hall, H., Farde, L., Halldin, C., Hurd, Y.L., Pauli, S., Sedvall, G., 1996. Autoradiographic localization of extrastriatal D$_2$-dopamine receptors in the human brain using [^{125}I]epidepride. Synapse 23, 115–123.

Hall, H., Halldin, C., Guilloteau, D., Chalon, S., Emond, P., Besnard, J., Farde, L., Sedvall, G., 1999. Visualization of the dopamine transporter in the human brain postmortem with the new selective ligand [^{125}I]PE2I. NeuroImage 9, 108–116.

Halldin, C., Stone-Elander, S., Farde, L., Ehrin, E., Fasth, K.J., Langstrom, B., Sedvall, G., 1986. Preparation of ^{11}C-labelled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography. International Journal of Radiation Applications and Instrumentation—Part A. Appl. Radiat. Isotopes 37, 1039–1043.

Halldin, C., Farde, L., Hogberg, T., Mohell, N., Hall, H., Suhara, T., Karlsson, P., Nakashima, Y., Swahn, C.G., 1995. Carbon-11-FLB 457: a radioligand for extrastriatal D$_2$ dopamine receptors. J. Nucl. Med. 36, 1275–1281.

Halldin, C., Foged, C., Chou, Y.H., Karlsson, P., Swahn, C.G., Sandell, J., Sedvall, G., Farde, L., 1998. Carbon-11-NNC 112: a radioligand for PET examination of striatal and neocortical D1-dopamine receptors. J. Nucl. Med. 39, 2061–2068.

Hartvig, P., Agren, H., Reibring, L., Tedroff, J., Bjurling, P., Kihlberg, T., Langstrom, B., 1991. Brain kinetics of L-[β-^{11}C]dopa in humans studied by positron emission tomography. J. Neural Transm. Gen. Sect. 86, 25–41.

Hietala, J., Syvalahti, E., Vuorio, K., Rakkolainen, V., Bergman, J., Haaparanta, M., Solin, O., Kuoppamaki, M., Kirvela, O., Ruotsalainen, U., Salokangas, R.K.R., 1995. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346, 1130–1131.

Hirvonen, J., Nagren, K., Kajander, J., Hietala, J., 2001. Measurement of cortical dopamine D$_1$ receptor binding with [^{11}C]SCH23390: a test-retest analysis. J. Cereb. Blood Flow Metab. 21, 1146–1150.

Hoshi, H., Kuwabara, H., Leger, G., Cumming, P., Guttman, M., Gjedde, A., 1993. 6-[^{18}F]fluoro-L-DOPA metabolism in living human brain: a comparison of six analytical methods. J. Cereb. Blood Flow Metab. 13, 57–69.

Huang, S.C., Yu, D.C., Barrio, J.R., Grafton, S., Melega, W.P., Hoffman, J.M., Satyamurthy, N., Mazziotta, J.C., Phelps, M.E., 1991. Kinetics and modeling of L-6-[^{18}F]fluoro-dopa in human positron emission tomographic studies. J. Cereb. Blood Flow Metab. 11, 898–913.

Ito, H., Hietala, J., Blomqvist, G., Halldin, C., Farde, L., 1998. Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [^{11}C]raclopride binding. J. Cereb. Blood Flow Metab. 18, 941–950.

Ito, H., Okubo, Y., Halldin, C., Farde, L., 1999. Mapping of central D$_2$ dopamine receptors in man using [^{11}C]raclopride: PET with anatomic standardization technique. NeuroImage 9, 235–242.

Ito, H., Sudo, Y., Suhara, T., Okubo, Y., Halldin, C., Farde, L., 2001. Error analysis for quantification of [^{11}C]FLB 457 binding to extrastriatal D$_2$ dopamine receptors in the human brain. NeuroImage 13, 531–539.

Ito, H., Kanno, I., Kato, C., Sasaki, T., Ishii, K., Ouchi, Y., Iida, A., Okazawa, H., Hayashida, K., Tsuyuguchi, N., Kuwabara, Y., Senda, M., 2004. Database of normal human cerebral blood flow, cerebral blood volume, cerebral oxygen extraction fraction and cerebral metabolic rate of oxygen measured by positron emission tomography with ^{15}O-labelled carbon dioxide or water, carbon monoxide and oxygen: a multicentre study in Japan. Eur. J. Nucl. Med. Mol. Imaging 31, 635–643.

Ito, H., Inoue, K., Goto, R., Kinomura, S., Taki, Y., Okada, K., Sato, K., Sato, T., Kanno, I., Fukuda, H., 2006a. Database of normal human cerebral blood flow measured by SPECT: I. Comparison between I-123-IMP, Tc-99m-HMPAO, and Tc-99m-ECD as referred with O-15 labeled water PET and voxel-based morphometry. Ann. Nucl. Med. 20, 131–138.

Ito, H., Ota, M., Ikoma, Y., Seki, C., Yasuno, F., Takano, A., Maeda, J., Nakao, R., Suzuki, K., Suhara, T., 2006b. Quantitative analysis of dopamine synthesis in human brain using positron emission tomography with L-[β-^{11}C]DOPA. Nucl. Med. Commun. 27, 723–731.

Ito, H., Shidahara, M., Takano, H., Takahashi, H., Nozaki, S., Suhara, T., 2007. Mapping of central dopamine synthesis in man using positron emission tomography with L-[β-^{11}C]DOPA. Ann. Nucl. Med. 21, 355–360.

Joel, D., Weiner, I., 2000. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 96, 451–474.

Joyce, J.N., Murray, A., 1994. Distribution of D$_1$- and D$_2$-like dopamine receptors in human brain. In: Niznik, H.B. (Ed.), Dopamine Receptors and Transporters. Marcel Dekker, Inc., New York, pp. 345–381.

Joyce, J.N., Sapp, D.W., Marshall, J.F., 1986. Human striatal dopamine receptors are organized in compartments. Proc. Natl. Acad. Sci. U. S. A. 83, 8002–8006.

Joyce, J.N., Janowsky, A., Neve, K.A., 1991. Characterization and distribution of [^{125}I]epidepride binding to dopamine D$_2$ receptors in basal ganglia and cortex of human brain. J. Pharmacol. Exp. Ther. 257, 1253–1263.

Kaasinen, V., Nagren, K., Hietala, J., Farde, L., Rinne, J.O., 2001. Sex differences in extrastriatal dopamine D$_2$-like receptors in the human brain. Am. J. Psychiatry 158, 308–311.

Kohler, C., Hall, H., Ogren, S.O., Gawell, L., 1985. Specific in vitro and in vivo binding of ^{3}H-raclopride. A potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. Biochem. Pharmacol. 34, 2251–2259.

Laakso, A., Vilkman, H., Alakare, B., Haaparanta, M., Bergman, J., Solin, O., Peurasaari, J., Rakkolainen, V., Syvalahti, E., Hietala, J., 2000. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. Am. J. Psychiatry 157, 269–271.

Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. NeuroImage 4, 153–158.

Lammertsma, A.A., Bench, C.J., Hume, S.P., Osman, S., Gunn, K., Brooks, D.J., Frackowiak, R.S., 1996. Comparison of methods for analysis of clinical [^{11}C]raclopride studies. J. Cereb. Blood Flow Metab. 16, 42–52.

Laruelle, M., 1998. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. Q. J. Nucl. Med. 42, 211–221.

Laruelle, M., Abi-Dargham, A., van Dyck, C., Gil, R., D'Souza, D.C., Krystal, J., Seibyl, J., Baldwin, R., Innis, R., 2000. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [^{123}I]b-CIT. Biol. Psychiatry 47, 371–379.

Lidow, M.S., Goldman-Rakic, P.S., Rakic, P., Innis, R.B., 1989. Dopamine D$_2$ receptors in the cerebral cortex: distribution and pharmacological characterization with [^{3}H]raclopride. Proc. Natl. Acad. Sci. U. S. A. 86, 6412–6416.

Lindstrom, L.H., Gefvert, O., Hagberg, G., Lundberg, T., Bergstrom, M., Hartvig, P., Langstrom, B., 1999. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(β-^{11}C) DOPA and PET. Biol. Psychiatry 46, 681–688.

Lloyd, K.G., Hornykiewicz, O., 1972. Occurrence and distribution of aromatic L-amino acid (L-DOPA) decarboxylase in the human brain. J. Neurochem. 19, 1549–1559.

Meador-Woodruff, J.H., Damask, S.P., Watson Jr., S.J., 1994. Differential expression of autoreceptors in the ascending dopamine systems of the human brain. Proc. Natl. Acad. Sci. U. S. A. 91, 8297–8301.

Moore, R.Y., Whone, A.L., McGowan, S., Brooks, D.J., 2003. Monoamine

neuron innervation of the normal human brain: an ^{18}F-DOPA PET study. Brain Res. 982, 137–145.

Morelli, M., Carboni, E., Devoto, S., Di Chiara, G., 1987. 6-Hydroxydopamine lesions reduce specific [3H]sulpiride binding in the rat substantia nigra: direct evidence for the existence of nigral D-2 autoreceptors. Eur. J. Pharmacol. 140, 99–104.

Moron, J.A., Brockington, A., Wise, R.A., Rocha, B.A., Hope, B.T., 2002. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J. Neurosci. 22, 389–395.

Muller, L., Halldin, C., Farde, L., Karlsson, P., Hall, H., Swahn, C.G., Neumeyer, J., Gao, Y., Milius, R., 1993. [11C] β-CIT, a cocaine analogue. Preparation, autoradiography and preliminary PET investigations. Nucl. Med. Biol. 20, 249–255.

Nagano, A.S., Ito, K., Kato, T., Arahata, Y., Kachi, T., Hatano, K., Kawasumi, Y., Nakamura, A., Yamada, T., Abe, Y., Ishigaki, T., 2000. Extrastriatal mean regional uptake of fluorine-18-FDOPA in the normal aged brain-an approach using MRI-aided spatial normalization. NeuroImage 11, 760–766.

Nordstrom, A.L., Farde, L., Eriksson, L., Halldin, C., 1995. No elevated D$_2$ dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [11C]N-methylspiperone. Psychiatry Res. 61, 67–83.

Okubo, Y., Olsson, H., Ito, H., Lofti, M., Suhara, T., Halldin, C., Farde, L., 1999. PET mapping of extrastriatal D$_2$-like dopamine receptors in the human brain using an anatomic standardization technique and [11C]FLB 457. NeuroImage 10, 666–674.

Parent, A., Lavoie, B., Smith, Y., Bedard, P., 1990. The dopaminergic nigropallidal projection in primates: distinct cellular origin and relative sparing in MPTP-treated monkeys. Adv. Neurol. 53, 111–116.

Reith, J., Benkelfat, C., Sherwin, A., Yasuhara, Y., Kuwabara, H., Andermann, F., Bachneff, S., Cumming, P., Diksic, M., Dyve, S.E., Etienne, P., Evans, A.C., Lal, S., Shevell, M., Savard, G., Wong, D.F., Chouinard, G., Gjedde, A., 1994. Elevated dopa decarboxylase activity

in living brain of patients with psychosis. Proc. Natl. Acad. Sci. U. S. A. 91, 11651–11654.

Rieck, R.W., Ansari, M.S., Whetsell Jr., W.O., Deutch, A.Y., Kessler, R.M., 2004. Distribution of dopamine D$_2$-like receptors in the human thalamus: autoradiographic and PET studies. Neuropsychopharmacology 29, 362–372.

Sanchez-Gonzalez, M.A., Garcia-Cabezas, M.A., Rico, B., Cavada, C., 2005. The primate thalamus is a key target for brain dopamine. J. Neurosci. 25, 6076–6083.

Sudo, Y., Suhara, T., Inoue, M., Ito, H., Suzuki, K., Saijo, T., Halldin, C., Farde, L., 2001. Reproducibility of [11C]FLB 457 binding in extrastriatal regions. Nucl. Med. Commun. 22, 1215–1221.

Suhara, T., Sudo, Y., Okauchi, T., Maeda, J., Kawabe, K., Suzuki, K., Okubo, Y., Nakashima, Y., Ito, H., Tanada, S., Halldin, C., Farde, L., 1999. Extrastriatal dopamine D$_2$ receptor density and affinity in the human brain measured by 3D PET. Int. J. Neuropsychopharmacol. 2, 73–82.

Suhara, T., Okubo, Y., Yasuno, F., Sudo, Y., Inoue, M., Ichimiya, T., Nakashima, Y., Nakayama, K., Tanada, S., Suzuki, K., Halldin, C., Farde, L., 2002. Decreased dopamine D$_2$ receptor binding in the anterior cingulate cortex in schizophrenia. Arch. Gen. Psychiatry 59, 25–30.

Tedroff, J., Aquilonius, S.M., Hartvig, P., Lundqvist, H., Bjurling, P., Langstrom, B., 1992. Estimation of regional cerebral utilization of [11C]-L-3,4-dihydroxy-phenylalanine (DOPA) in the primate by positron emission tomography. Acta Neurol. Scand. 85, 166–173.

Watson, C.C., Newport, D., Casey, M.E., 1996. A single scatter simulation technique for scatter correction in 3D PET. In: Grangeat, P., Amans, J.L. (Eds.), Three-Dimensional Image Reconstruction in Radiology and Nuclear Medicine. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 255–268.

Yasuno, F., Suhara, T., Okubo, Y., Sudo, Y., Inoue, M., Ichimiya, T., Takano, A., Nakayama, K., Halldin, C., Farde, L., 2004. Low dopamine D$_2$ receptor binding in subregions of the thalamus in schizophrenia. Am. J. Psychiatry 161, 1016–1022.

Difference in age of onset of psychosis between epilepsy and schizophrenia

Naoto Adachi [a,b,*], Tsunekatsu Hara [c], Yasunori Oana [d], Masato Matsuura [e], Yoshiro Okubo [f], Nozomi Akanuma [b], Masumi Ito [b], Masaaki Kato [b], Teiichi Onuma [b]

[a] Adachi Mental Clinic, Kitano 7-5-12, Kiyota, Sapporo 004-0867, Japan
[b] National Center Hospital for Mental, Nervous, and Muscular Disorder, NCNP, Tokyo, Japan
[c] Komagino Hospital, Tokyo, Japan
[d] Department of Neuropsychiatry, Tokyo Medical University Hospital, Tokyo, Japan
[e] Department of Neuropsychiatry, Nihon University Hospital, Tokyo, Japan
[f] Department of Neuropsychiatry, Tokyo Medical and Dental University Hospital, Tokyo, Japan

Summary   To clarify the nature of psychosis development in epilepsy patients, we studied differences in age of onset of psychosis between epilepsy patients with psychosis (epilepsy-psychosis) and schizophrenia patients. Subjects were 282 patients with epilepsy-psychosis (36 postictal, 224 interictal, and 22 bimodal psychoses) and 612 schizophrenia patients. Age of onset was compared between the schizophrenia group and the whole epilepsy-psychosis group as well as its subgroups. Effects of sex and family history of psychosis on age of onset were also evaluated. Epilepsy patients developed psychosis later (mean age 30.1) than schizophrenia patients (mean age 26.6). Among epilepsy-psychosis subgroups, postictal psychosis and interictal psychosis showed a later onset than schizophrenia. In interictal psychosis, while chronic schizophrenia-like psychosis occurred at similar age compared to schizophrenia, brief episodic psychosis occurred at later age. Epilepsy-psychosis patients showed no sex difference in age of onset, whereas female schizophrenia patients showed a later onset than male schizophrenia patients. Both the epilepsy and schizophrenia patients with family history of psychosis tended to develop psychosis at an earlier age, although this did not reach statistically significant level. The findings of the study suggest that the nature of epilepsy-psychosis is not fully equivalent to that of schizophrenia.
© 2007 Elsevier B.V. All rights reserved.

* Corresponding author at: Adachi Mental Clinic, Kitano 7-5-12, Kiyota, Sapporo 004-0867, Japan. Tel.: +81 11 8810325; fax: +81 11 8810325.
    E-mail address: adacchan@tky2.3web.ne.jp (N. Adachi).

Introduction

Psychosis is an important issue in the treatment of patients with epilepsy (Trimble, 1991; Mendez et al., 1993). Whereas similarities between the psychoses of epilepsy patients (epilepsy-psychosis) and schizophrenia have long been considered (Trimble, 1991; Sachdev, 1998), the detailed nature of the epilepsy-psychosis still remains unclear. With respect to age of onset of these two psychotic conditions, there have been few comparisons between epilepsy-psychosis and schizophrenia. Schizophrenia tends to develop during a specific age period and with a sex difference at age of onset of psychosis; men showed a single high peak during adolescence to early adulthood, while women showed a second peak of onset after age 40 (Weinbergar, 1987; Hafner et al., 1998). In addition, a family history of illness is often associated with age of onset in schizophrenia patients (Gorwood et al., 1995; Alda et al., 1996) as well as in several neuropsychiatric diseases (Ridley et al., 1986; Weissman et al., 1986). Conversely, epilepsy patients often exhibit psychosis in their late twenties or early thirties (Trimble, 1991; Adachi et al., 2002). Little is known about sex differences and effects of family history of psychosis on age of onset of psychosis. We conducted a large, multi-center, controlled study to compare age of onset of epilepsy-psychosis with that of schizophrenia.

Materials and methods

Definition of psychoses

Psychosis was defined as the presence of hallucinations, delusions, or a limited number of severe behavioral abnormalities in accordance with the ICD-10 (World Health Organization (WHO), 1992). The diagnosis of epilepsy-psychosis required distinct psychotic symptoms in a clear conscious state after the development of epilepsy. This definition of epilepsy-psychosis was originally described by Pond (1957) and has subsequently been used in most studies in epilepsy-psychosis (Slater et al., 1963; Bruens, 1974; Kristensen and Sindrup, 1978; Bredkjaer et al., 1998; Adachi et al., 2000, 2002; Rayport and Ferguson, 2001; Qin et al., 2005). This entity satisfied the ICD-10 criteria for organic hallucinosis (F06.0), organic catatonic disorder (F06.1), or organic delusional disorder (F06.2).

Epilepsy-psychoses were subclassified into three categories: postictal psychosis (PIP), interictal psychosis (IIP), and bimodal psychosis (BMP). (1) PIP was diagnosed when all psychotic episodes occurred within 7 days after a decisive seizure or a cluster of seizures (Logsdail and Toone, 1988; Kanemoto et al., 1996; Adachi et al., 2002, 2007). (2) IIP was diagnosed when all episodes occurred during seizure-free periods or between habitual seizures (Sachdev, 1998; Adachi et al., 2000, 2002). IIP included chronic schizophrenia-like psychosis (at least 1 episode lasted for 1 month or more) and brief interictal psychosis (all episodes disappeared within 1 month) (Slater et al., 1963; Bruens, 1974; Sachdev, 1998; Adachi, 2006). (3) If both postictal and interictal psychotic episodes were observed on different occasions in an individual patient, BMP was diagnosed (Tarulli et al., 2001; Adachi et al., 2003). Psychotic episodes during seizures, such as psychic seizures or nonconvulsive status epilepticus, were excluded.

Study subjects

A total of 282 epilepsy-psychosis patients, who were consecutively registered in our epilepsy-psychosis database in December 1996 were recruited for the study (Adachi et al., 2000, 2002). All patients met the criteria for epilepsy (International League Against Epilepsy (ILAE), 1989) and psychosis (World Health Organization (WHO), 1992). They were followed up regularly at an adult epilepsy clinic in one of five tertiary neuropsychiatry institutions: the National Center Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; or Komagino Hospital. The detailed clinical characteristics of this cohort have been described elsewhere (Adachi et al., 2000, 2002).

We also recruited 612 schizophrenia patients diagnosed in accordance with the ICD-10 (WHO, 1992), who were consecutively enrolled after visiting a psychiatry clinic at one of the five hospitals during the period 1 and 14 November, 1996. Thus, this cohort represents the overall population of schizophrenia patients treated in the five hospitals.

Neither patient with epilepsy-psychosis nor with schizophrenia had evidence of dementing process, a history of substance abuse, or an expanding brain mass lesion during our follow-up periods.

Research items

In all subjects, the following items were investigated: (1) sex, (2) age at the time of the study, (3) age of onset of psychosis; age of onset was defined as the earliest age when a clear psychotic symptom was identified, regardless of whether or not it was preceded by prodromal non-psychotic symptoms and signs (Jablensky et al., 1992). To study differences in sex in late-onset psychosis, we compared the sex ratio in patients who developed psychosis at age 40 or later, and (4) family history of psychosis; any psychotic disorder of the ICD-10 (such as schizophrenia, paranoid disorders, or acute-transient psychosis) (WHO, 1992) in a first-degree relative was regarded as positive family history psychosis, in accordance with the Japanese version of the Family History Research Diagnostic Criteria (Kitamura et al., 1984).

In patients with epilepsy-psychosis, the following items were evaluated additionally: (1) age at onset of epilepsy, (2) epilepsy type (focal, generalized, and unclassified); diagnosed using observed seizure symptoms and EEG and neuroimaging findings in accordance with the International Classifications for Epilepsy (ILAE, 1989), and (3) psychosis subtypes (PIP, IIP, and BMP), as defined above.

Diagnoses and clinical assessments on epilepsy and all psychoses were made by neuropsychiatrists doubly qualified in epileptology and psychiatry. The patient and key informants were interviewed in accordance with the section of History of Onset and Hospitalization, the Japanese edition of the Comprehensive Assessment of Symptoms and History (Andreasen, 1994). Clinical notes were also used to confirm the first psychotic episode, since epilepsy patients had already been treated for epilepsy at the onset of psychosis. The study was approved by the ethics committees of the institutions.

Data analysis

Standard parametric regression analysis and analysis of variance (ANOVA) were used for continuous data. Post hoc Bonferroni test was used for subgroup comparisons; epilepsy-psychosis subtypes (IIP, PIP, and BMP) and IIP subtypes (chronic schizophrenia-like, brief, and unclassified). For comparison among study groups with different mean ages at the time of evaluation, the weighted least squares procedure (age at the examination as weight) was used to reduce the bias of age at the time of evaluation. Age at the time of evaluation correlated significantly with age at onset of psychosis in epilepsy patients ($r = 0.683$, $p = 0.000$) and in schizophrenia patients

$(r = 0.542, p = 0.000)$; the more advanced age at the observation the subjects are, the more advanced age at onset of psychosis was observed. This tendency may be partly due to a limitation of the operational diagnosis; since onset of psychosis in the future cannot be included, age of onset must be earlier than age of the time of evaluation. A Chi square test or Fisher's exact test was used for categorical data. The significance level was set as $p < 0.05$. SPSS 14.0 [SPSS Inc., Chicago, IL] was used for all statistical analyses.

Results

Characteristics of the subjects

The detailed clinical characteristics of the patients with epilepsy-psychosis have been described elsewhere (Adachi et al., 2000, 2002). In short, of the 282 epilepsy-psychosis patients (148 men and 134 women), age at the time of evaluation ranged 17—82 years (mean 40.4, S.D. 13.0); men, 39.9 years (S.D. 12.7) and women, 41.0 years (S.D. 13.2). Age of onset of epilepsy ranged 0—60 years (mean 13.6, S.D. 9.3). Two hundred and thirty patients had focal epilepsy (146 temporal lobe epilepsy, 33 frontal lobe epilepsy, 11 parietal lobe epilepsy, 6 occipital lobe epilepsy, and 34 multi- or undetermined-lobular epilepsy), 45 had generalized epilepsy (29 idiopathic generalized epilepsy and 16 symptomatic generalized epilepsy), and 7 had unclassifiable epilepsy. Two hundred and four patients had generalized tonic-clonic seizures and 186 had complex partial seizures. The epilepsy-psychosis subgroups consisted of IIP ($n = 224$, mean age at the time of evaluation 39.7 years, S.D. 12.7), PIP ($n = 36$, 46.3 years, 13.7), and BMP ($n = 22$, 38.5 years, 12.3). Of the IIP patients, 193 (mean age at the time of evaluation 39.1 years, S.D. 12.1) had chronic schizophrenia-like psychosis, 17 (45.5 years, 14.8) had brief interictal psychosis, and 14 (41.3 years, 16.8) had IIP with insufficient information of the durations. Fifteen patients (mean age 39.8 years, S.D. 12.9) had first-degree relatives with psychosis.

The 612 schizophrenia patients consisted of 310 men and 302 women. Age at the examination ranged 14—82 years (mean age at the time of evaluation 41.1, S.D. 13.4); men, 40.3 years (S.D. 13.0) and women, 42.0 years (13.7). Seventy patients (mean age 42.5 years, S.D. 13.1) had first-degree relatives with psychosis.

Ages of onset of psychosis

Ages of onset are shown for the entire study group and for the subgroups in Table 1. Mean age of onset was significantly later in epilepsy-psychosis than in schizophrenia ($F = 21.6$, $p = 0.000$). There were significant differences in age of onset between subgroups of epilepsy-psychosis and schizophrenia ($F = 16.1$, $p = 0.000$). PIP ($p = 0.000$) and IIP ($p = 0.018$) developed at a later age than did schizophrenia. Likewise, PIP developed later than did IIP ($p = 0.000$) or BMP ($p = 0.001$). Further analysis with subdivisions of IIP (chronic schizophrenia-like, brief episodic, and insufficient information) and schizophrenia showed significant differences in age of onset ($F = 6.9$, $p = 0.000$). Post hoc analysis showed that brief episodic IIP developed at later age than did schizophrenia-like IIP ($p = 0.006$) and schizophrenia ($p = 0.000$).

Age of onset is shown by sex and family history of psychosis for each group in Table 2. No significant difference was observed for all the epilepsy-psychosis patients ($F = 0.04$, $p = 0.834$). In contrast, for the schizophrenia patients, age of onset was significantly later in female than in male patients ($F = 12.4$, $p = 0.000$). Whereas epilepsy patients with late-onset psychosis showed no sex difference (20 men and 22 women, $\chi^2 = 0.27$, $p = 0.508$), late-onset schizophrenia patients showed a significant female preponderance (12 men and 38 women, $\chi^2 = 14.3$, $p = 0.000$). Age of onset in patients with family history of psychosis was slightly earlier than those without in the epilepsy-psychosis group ($F = 2.1$, $p = 0.148$) and in the schizophrenia group ($F = 3.0$, $p = 0.086$), although there was no statistically significant difference.

Discussion

Epilepsy patients developed psychosis at a later age compared to schizophrenia patients. Regarding the subgroups of epilepsy-psychosis, the both IIP and PIP tended to occur at

Table 1   Age of onset of psychosis in patients with epilepsy-psychosis or with schizophrenia

	Observed mean (S.D.)	Adjusted mean (S.E.)	95% CI
Epilepsy-psychosis ($n = 282$)	27.7 (0.7)	30.1 (0.6)[a]	28.9—31.3
Interictal ($n = 224$)	26.8 (10.3)	29.0 (0.7)[b]	27.6—30.3
Chronic schizophrenia-like ($n = 193$)	26.2 (9.8)	28.1 (0.7)[c]	26.7—29.6
Brief episodic ($n = 17$)	33.4 (12.1)	36.1 (2.3)[c]	31.6—40.6
Insufficient information for duration ($n = 14$)	27.4 (13.2)	31.1 (2.7)	25.9—36.3
Postictal ($n = 36$)	34.8 (10.3)	37.4 (1.6)[b]	34.3—40.6
Bimodal ($n = 22$)	25.0 (9.3)	26.8 (2.2)	22.4—31.2
Schizophrenia ($n = 612$)	25.1 (8.7)	26.6 (0.4)[a,b,c]	25.8—27.4

[a] Epilepsy-psychosis vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 21.6$, $p = 0.000$.

[b] Epilepsy-psychosis subgroups vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 16.1$, $p = 0.000$ (post hoc test: interictal psychosis vs. schizophrenia, $p = 0.018$, postictal psychosis vs. schizophrenia, $p = 0.000$).

[c] Interictal psychosis subgroups vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 6.9$, $p = 0.000$ (post hoc test: schizophrenia vs. brief episodic, $p = 0.000$, chronic schizophrenia-like vs. brief episodic, $p = 0.006$).

Table 2 Effects of sex and family history of psychosis on age of onset of psychosis

Sex	Family history	Observed mean (S.D.)	Adjusted mean (S.E.)	95% CI
Epilepsy-psychosis[a]				
Men (n = 148)		27.9 (10.3)	28.1 (1.7)	24.8–31.4
Women (n = 134)		27.5(11.3)	27.8 (1.8)	24.3–31.4
	Positive (n = 15)	24.9 (7.3)	25.7 (3.1)	19.6–31.8
	Negative (n = 267)	27.9 (10.9)	30.3 (0.7)	28.9–31.7
Men	Positive (n = 10)	25.8 (8.4)	25.8 (3.1)	19.6–31.9
Men	Negative (n = 138)	28.1 (10.4)	30.5 (1.0)	28.5–32.4
Women	Positive (n = 5)	23.0 (4.8)	25.5 (3.1)	19.6–31.9
Women	Negative (n = 129)	27.7 (11.5)	30.2 (1.0)	28.1–32.3
Schizophrenia[b]				
Men (n = 310)		24.1 (7.3)	24.5(0.7)	23.1–25.9
Women (n = 302)		26.1(9.9)	27.2(0.7)	25.8–28.5
	Positive (n = 70)	24.1 (7.2)	24.8 (1.1)	22.6–27.0
	Negative (n = 542)	25.2 (8.9)	26.9 (0.4)	26.1–27.7
Men	Positive (n = 36)	23.2 (5.7)	23.5 (1.2)	21.2–25.8
Men	Negative (n = 274)	24.2 (7.5)	25.5 (0.6)	24.4–26.6
Women	Positive (n = 34)	25.0 (8.5)	26.2 (1.2)	23.9–28.5
Women	Negative (n = 268)	26.2 (10.1)	28.2 (0.6)	27.1–29.3

ANOVA with age at evaluation as weight.
[a] Sex, $F = 0.04$, $p = 0.834$; family history, $F = 2.14$, $p = 0.145$; sex × family history, $F = 0.121$, $p = 0.729$.
[b] Sex, $F = 12.4$, $p = 0.000$; family history, $F = 2.9$, $p = 0.088$; sex × family history, $F = 0.03$, $p = 0.858$.

a later age than did schizophrenia. Only the patients with BMP had a comparable onset to the schizophrenia patients. Our findings are concordant with most uncontrolled studies reporting similar age range of onset of epilepsy-psychosis, late twenties or early thirties (Slater et al., 1963; Trimble, 1991). These age ranges appear to be slightly later than the first peak of onset of schizophrenia (early twenties) (Hafner et al., 1998). Although Mendez et al. (1993) showed a comparable age of onset between 62 epilepsy patients (mean 23.6 years) and 62 age-matched schizophrenia patients (mean 24.6 years), they found a later age of onset (mean 28.4 years) in their expanded sample cohort (146 epilepsy-psychosis patients). Epilepsy patients often have multiple risks for developing psychosis, i.e., distinct brain insults, repetitive seizures, and antiepileptic drugs (Adachi et al., 2000; Trimble, 1991), while few schizophrenia patients have these risks. If the congenital vulnerability for developing psychosis was the same for both groups, the acquired risks associated with epilepsy or organic brain damage would be expected to predispose these patients to the development of an early onset of psychosis. However, our findings did not support this notion, suggesting that the underlying vulnerability to psychosis in epilepsy patients does not completely equivalent to that in schizophrenia patients.

With respect to the further subdivisions, chronic schizophrenia-like psychosis occurred at earlier age. Age of onset was similarly slightly earlier in BMP patients. Kanemoto et al. (1996) also reported that chronic IIP occur at an earlier age than do either PIP or episodic IIP. In accordance with the ICD-10 (WHO, 1992), most patients with chronic schizophrenia-like psychosis can be diagnosed as having schizophrenia unless epilepsy was considered. Patients categorized in these narrow diagnostic entities may have high vulnerabilities towards development of psychosis.

According to the neurodevelopmental hypothesis, similar age of onsets, regardless of their etiologies, could exhibit similar psychiatric symptoms (Weinbergar, 1987). Thus, it is possible that these patients with high vulnerabilities have common liabilities to schizophrenia patients. However, this should be argued with cautions. Several studies (Mellers et al.,1998; Maier et al., 2000) has demonstrated some pathophysiological differences between schizophrenia-like psychosis in epilepsy and schizophrenia. The reliability of subdivision with clinical course has not yet been thoroughly confirmed; an individual epilepsy-psychosis patient often shows both episodic and chronic psychoses on different occasions in the course of their illness (Onuma et al., 1992; Cockerell et al., 1996; Adachi et al., 2003; Adachi, 2006). If our patients with brief IIP were to develop chronic schizophrenia-like psychosis afterwards, the mean age of onset might shift later than that observed in the current study.

Epilepsy-psychosis patients showed no sex difference in age of onset. This appeared to be due partially to the smaller proportion of late-onset psychosis in female epilepsy patients, as opposed to the female preponderance for late-onset schizophrenia. A protective effect of estrogen in the brain has been proposed to explain the sex difference in the development of schizophrenia (Hafner et al., 1998). In epilepsy patients, several factors, such as seizure frequency, duration of epilepsy, and antiepileptic drugs, are correlated with neuroendocrine levels (Leiderman et al., 1990) and may account for the difference. The serum luteinizing hormone level is elevated after seizures in both men and women with epilepsy (Dana-Haeri et al., 1983). Furthermore, in epilepsy patients with psychopathology, baseline serum gonadotrophine levels were lower than those in epilepsy patients without psychopathology, and levels were

more volatile after seizures (Dana-Haeri and Trimble, 1984). These epilepsy-related factors may disrupt endocrinologic regulation, thus diminishing any sex effect. However, this is not entirely clear, as these factors have also been reported to be associated with the development of psychosis in epilepsy patients (Adachi et al., 2000, 2002; Trimble, 1991).

The both epilepsy and schizophrenia patients with family history of psychosis developed psychosis at an earlier age, although there was no statistical difference. Whether family history of psychosis is a risk factor to psychosis in epilepsy patients has long been discussed (Trimble, 1991; Adachi, 2006). In contrast to the Slater's negative observations (Slater et al., 1963), several large control studies (Adachi et al., 2000, 2002; Qin et al., 2005) have recently shown the possibility of genetic vulnerability to psychosis in epilepsy-psychosis patients. Whereas effects of family history on age of onset are controversial in schizophrenia studies (Kendler et al., 1996), our findings may be in line with some studies showing that schizophrenia patients with a family history had an earlier onset than those without (Gorwood et al., 1995; Alda et al., 1996). It is concordant that individuals with a high familial liability to various neuropsychiatric diseases develop their first symptom at a young age (Ridley et al., 1986; Klein et al., 1999). Patients with the genetic vulnerability to psychosis, regardless of having epilepsy, are likely to develop their psychotic episode at an earlier age.

Our significant findings of differences in age of onset between epilepsy-psychosis and schizophrenia need to be interpreted with caution to our definition of epilepsy-psychosis. In the current study, we studied patients who developed psychosis after the onset of epilepsy in accordance with the most popular definition of epilepsy-psychosis. Since Pond's initial description (1957), most large studies on epilepsy-psychoses have dealt subjects which developed epilepsy prior to psychosis (Slater et al., 1963; Kristensen and Sindrup, 1978; Mendez et al., 1993; Bredkjaer et al., 1998; Adachi et al., 2000, 2002; Qin et al., 2005). It can ensure the specificity of diagnosis for causal relation between epilepsy and psychosis, rather than psychosis simply related to brain damage or concurrence of non-organic psychosis (Pond, 1957; Slater et al., 1963; Bruens, 1974; Trimble, 1991; Rayport and Ferguson, 2001). However, this definition is rather operative based on limited observations in the early periods (Pond, 1957; Slater et al., 1963; Bruens, 1974). The significance of epileptic process on the development of epilepsy-psychosis has not been fully demonstrated (Adachi, 2006). Further studies are required to clarify as to whether patients who developed psychosis, either organic or functional, after the onset of epilepsy are equivalent to our subjects.

Other limitations may also be considered in the current study. First, the subclassification for epilepsy-psychosis, in particular IIP, remain controversial (Adachi, 2006). We employed the diagnostic criteria covering different characteristics of epilepsy-psychosis subgroups. We believe they are the most comprehensive criteria among those used in previous studies. Thus, our finding may be partially inconsistent with those that resulted from studies using narrow criteria. Second, because our study subjects were looked after in specialist clinics, they were inevitably patients who suffer from difficult-to-manage epilepsy, psychosis, or

both. Thus our findings may not directly apply to those in more general settings. Third, the WHO 10-country study (Jablensky et al., 1992) showed that age of onset of schizophrenia is influenced by multiple interacting factors including sex, premorbid personality traits, family history of psychosis, and marital status. Premorbid personality and marital status were not considered in the present study. Although we have no reason to believe that they would significantly bias our data, this remains a limitation in our study. Further analyses based on our findings are required to clarify the nature of epilepsy-psychosis.

References

Adachi, N., 2006. Epilepsy and psychosis. Issues on clinical research in epilepsy psychosis. Seishin Shinkeigaku Zasshi 108, 260—265 (in Japanese).

Adachi, N., Matsuura, M., Okubo, Y., Oana, Y., Takei, N., Kato, M., Hara, T., Onuma, T., 2000. Predictive variables for interictal psychosis in epilepsy. Neurology 55, 1310—1314.

Adachi, N., Matsuura, M., Hara, T., Oana, Y., Okubo, Y., Kato, M., Onuma, T., 2002. Psychoses and epilepsy: are interictal and postictal psychoses distinct clinical entities? Epilepsia 43, 1574—1582.

Adachi, N., Kato, M., Sekimoto, M., Ichikawa, I., Akanuma, N., Uesugi, H., Matsuda, H., Ishida, S., Onuma, T., 2003. Recurrent postictal psychoses after remission of interictal psychosis: further evidence of bimodal psychosis. Epilepsia 44, 1218—1222.

Adachi, N., Ito, M., Kanemoto, K., Akanuma, N., Okazaki, M., Ishida, S., Sekimoto, M., Kato, M., Kawasaki, J., Tadokoro, Y., Oshima, T., Onuma, T., 2007. Duration of postictal psychotic episodes. Epilepsia 48, 1531—1537.

Alda, M., Ahrens, B., Lit, W., Dvorakova, M., Labelle, A., Zvolsky, P., Jones, B., 1996. Age of onset in familial and sporadic schizophrenia. Acta Psychiatr. Scand. 93, 447—450.

Andreasen, N.C., 1994. In: Okazaki, Y., Kitamura, T., Anzai, N., Shima, S., Ohta, T. (Eds.), Comprehensive Assessment of Symptoms and History (CASH). Seiwa Shoten Publishers, Tokyo (Japanese edition translated).

Bredkjaer, S.R., Mortensen, P.B., Parnas, J., 1998. Epilepsy and non-organic non-affective psychosis. Br. J. Psychiatry 172, 235—238.

Bruens, J.H., 1974. Psychoses in epilepsy. In: Vinken, P.J., Bruyn, G.W. (Eds.). Handbook of Clinical Neurology, vol. 15. North-Holland publishing co., North Holland, Amsterdam, pp. 593—610.

Cockerell, O., Moriarty, J., Trimble, M., Sander, J.W.A.S., Shorvon, S.D., 1996. Acute psychological disorders in patients with epilepsy: a nation-wide study. Epilepsy Res. 25, 119—131.

Dana-Haeri, J., Trimble, M.R., 1984. Prolactin and gonadotrophin changes following partial seizures in epileptic patients with and without psychopathology. Biol. Psychiatry 19, 329—336.

Dana-Haeri, J., Trimble, M.R., Oxley, J., 1983. Prolactin and gonadotrophin changes following generalized and partial seizures. J. Neurol. Neurosurg. Psychiatry 46, 331—335.

Gorwood, P., Leboyer, M., Jay, M., Payan, C., Feingold, J., 1995. Gender and age at onset in schizophrenia: impact of family history. Am. J. Psychiatry 152, 208—212.

Hafner, H., Hambrecht, M., Loffler, P., Munk-Jorgensen, P., Riecher-Rossler, A.I., 1998. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. Psychol. Med. 28, 351—365.

ILAE, 1989. Commission on classification and terminology of the international league against epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30, 389—399.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., Day, R., Bertelsen, A., 1992. Schizophrenia: Mani-

festations, Incidence and Course in Different Cultures: A World Health Organization 10-Country Study. Psychol Med Monograph (Suppl. 20). Cambridge University Press, Cambridge.

Kanemoto, K., Kawasaki, J., Kawai, I., 1996. Postictal psychosis: a comparison with acute interictal and chronic psychoses. Epilepsia 37, 551–556.

Kendler, K.S., Karkowski-Shuman, L., Walsh, D., 1996. Age at onset in schizophrenia and risk of illness in relatives. Results from the Roscommon Family Study. Br. J. Psychiatry 169, 213–218.

Kitamura, T., Shima, S., Sekino, E., Kato, M., 1984. Reliability study on Family History-Research Diagnostic Criteria (FH-RDC) by using case vignettes. Jpn. J. Soc. Psychiatry 7, 308–312 (in Japanese).

Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Thase, M.E., Rush, A.J., LaVange, L., Harrison, W.M., Keller, M.B., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, familiy history and treatment response. J. Affect. Disord. 55, 149–157.

Kristensen, O., Sindrup, E.H., 1978. Psychomotor epilepsy and psychosis. I. Physical aspects. Acta Neurol. Scand. 57, 361–369.

Leiderman, D.B., Csernansky, J.G., Moses Jr., J.A., 1990. Neuroendocrinology and limbic epilepsy: relationships to psychopathology, seizure variables, and neuropsychological function. Epilepsia 31, 270–274.

Logsdail, S.J., Toone, B.K., 1988. Post-ictal psychoses. A clinical and phenomenological description. Br. J. Psychiatry 152, 246–252.

Maier, M., Mellers, J., Toone, B., Trimble, M., Ron, M.A., 2000. Schizophrenia, temporal lobe epilepsy and psychosis: an *in vivo* magnetic resonance spectroscopy and imaging study of the hippocampus/amygdale complex. Psychol. Med. 30, 571–581.

Mellers, J.D.C., Adachi, N., Takei, N., Cluckie, A., Toone, B.K., Lishman, W.A., 1998. SPET study of verbal fluency in schizophrenia and epilepsy. Br. J. Psychiatry 173, 69–74.

Mendez, M.F., Grau, R., Doss, R.C., Taylor, J.L., 1993. Schizophrenia in epilepsy: seizure and psychosis variables. Neurology 43, 1073–1077.

Onuma, T., Adachi, N., Hisano, T., Uesugi, S., 1992. 10-year follow-up study of epilepsy with psychosis. Jpn. J. Psychiatry Neurol. 45, 360–361.

Pond, D.A., 1957. Psychiatric aspects of epilepsy. J. Ind. Med. Prof. 3, 1421–1451.

Qin, P., Xu, H., Laursen, T.M., Vestergaard, M., Moriensen, P.B., 2005. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study. Br. Med. J. 331, 23–25.

Rayport, M., Ferguson, S.M., 2001. Psychosis of epilepsy. An integrated approach. In: Ettinger, A.B., Kanner, A.M. (Eds.), Psychiatric Issues in Epilepsy. A Practical Guide to Diagnosis and Treatment. Lippincott Williams & Wilkins, Philadelphia, pp. 73–94.

Ridley, R.M., Baker, H.F., Crow, T.J., 1986. Transmissible and transmissible neurodegenerative disease: similarities in age of onset and genetics in relation of aetiology. Psychol. Med. 16, 199–207.

Sachdev, P., 1998. Schizophrenia-like psychosis and epilepsy: the status of the association. Am. J. Psychiatry 155, 325–336.

Slater, E., Beard, A.W., Glithero, E., 1963. The schizophrenia-like psychoses of epilepsy. Br. J. Psychiatry 109, 95–150.

Tarulli, A., Devinsky, O., Alper, K., 2001. Progression of postictal to interictal psychosis. Epilepsia 42, 1468–1471.

Trimble, M.R., 1991. The Psychoses of Epilepsy. Raven Press, New York.

Weinbergar, D.R., 1987. Implications of normal brain development for pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–667.

Weissman, M.M., Merikangas, K.R., Wickramaratne, P., Kidd, K.K., Prusoff, B.A., Leckman, J.F., Pauls, D.L., 1986. Understanding the clinical heterogeneity of major depression using family data. Arch. Gen. Psychiatry 43, 430–434.

World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.

Regular Article

Relationship between exploratory eye movement, P300, and reaction time in schizophrenia

Sakae Takahashi, MD, PhD,[1]* Eiichi Tanabe, MD, PhD,[1] Teiichiro Sakai, MD, PhD,[1] Masato Matsuura, MD, PhD,[2] Eisuke Matsushima, MD, PhD,[3] Shigeru Obayashi, MD, PhD[4] and Takuya Kojima, MD, PhD[1]

[1]*Department of Neuropsychiatry, Nihon University School of Medicine,* [2]*Section of Biofunctional Informatics, Graduate School of Allied Health Sciences, Tokyo Medical and Dental University,* [3]*Section of Liaison Psychiatry and Palliative Medicine and* [4]*Section of Psychiatry and Behavioral Sciences, Graduate School of Tokyo Medical and Dental University, Tokyo, Japan*

Aims: Exploratory eye movement (EEM), P300 and reaction time (RT) tests may relate to the important parts of information processing in the human brain. Therefore the aim of the present study was to compare EEM, P300 and RT test data in schizophrenic and normal control groups to investigate whether schizophrenic patients have information processing abnormalities. In addition, the potential correspondence between the three tests was examined in order to investigate the information processing dysfunctions seen in schizophrenic patients.

Methods: The EEM, P300 and RT performances were recorded in 34 schizophrenic and 36 normal control subjects. Ten parameters were measured: four from the EEM test (number of eye fixations, total eye scanning length, cognitive search score and responsive search score [RSS]); two from the P300 test (amplitude and latency); and four from the RT test (simple reaction time, index of reaction time crossover [IRT-crossover], set index and coefficient of variation).

Results: These parameters in the schizophrenic patients differed significantly from those in the control group. Additionally, there was a significant correlation between the RSS and the IRT-crossover in the schizophrenic patients.

Conclusion: The present group comparisons (schizophrenia vs normal controls) are consistent with previous studies in that the abnormalities in EEM, P300 and RT tests in schizophrenic patients were able to be replicated. Moreover, based on the former psychological theory, it is reasonable to propose that the RSS is associated with the IRT-crossover. The present results may contribute to elucidation of the pathophysiological signature of schizophrenia.

Key words: exploratory eye movement, P300, reaction time, schizophrenia.

DISTURBANCES IN INFORMATION processing in the brain have played a central role in understanding schizophrenia since early in the 20th century.[1,2] Cognitive dysfunction in schizophrenia has been the subject of in-depth empirical analysis.

Abnormalities in eye movement, event-related potentials (ERP), reaction time (RT), continuous performance task and skin conductance orienting response have been proposed to reflect disturbances in information processing.[3]

Our group has studied eye movements while subjects freely view stationary horizontal S-shaped figures. This method is called the exploratory eye movement (EEM) test. We have demonstrated that disturbances in EEM test were usually found in schizophrenic patients.[4] Abnormalities in ERP, especially the P300, are among the most robust biologic

Correspondence: Sakae Takahashi, MD, PhD, Nihon University School of Medicine Department of Neuropsychiatry, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. Email: sakae@med.nihon-u.ac.jp

observations in schizophrenia.[5] The P300 has been performed frequently in many laboratories worldwide. RT disturbances are another replicable finding in schizophrenia. Several studies have verified that schizophrenic patients have RT test disturbances.[3,6] Based on these findings, we considered that EEM, P300 and RT were putative biological indicators of liability to schizophrenia. Moreover, with regard to the three tests, it has been reported that EEM may reflect the information processing in relation to Neisser's anticipatory schemata; P300 may index the updating of memory systems; and RT may link cognitive function with reference to Shakow's major set. Precisely, it is possible that these three tests relate the important parts of information processing in the human brain. Therefore, the aim of the present study was to conduct EEM, P300 and RT tests in schizophrenic patients and normal controls, to investigate whether schizophrenic patients have information processing abnormalities. In addition, we examined the potential correspondence between the three tests to investigate the information processing dysfunctions seen in schizophrenic patients.

METHODS

Subjects

Thirty-four subjects with schizophrenia and 36 normal controls were included in the present study. The schizophrenia subjects (21 male, 13 female) had a mean age of 26.9 ± 4.9 years; mean duration of illness was 4.2 ± 3.9 years; mean age at onset was 22.8 ± 5.4 years; mean years of education was 12.8 ± 2.2 years. All schizophrenic subjects met the DSM-IV criteria for schizophrenia.[7] The diagnosis was based on structured clinical interviews for DSM-IV. Each interview was administered by two experienced psychiatrists. All schizophrenic patients were receiving an average daily dosage of 10.8 ± 9.0 mg of a haloperidol equivalent neuroleptic medication. No schizophrenia subjects had ever undergone electroconvulsive shock treatment. Classifying the schizophrenic patients into DSM-IV subtypes, there were seven disorganized types, 17 paranoid types, four residual types and six undifferentiated types. We performed the exploratory eye movement, P300 and RT tests on the schizophrenic subjects after they recovered from acute symptoms. All subjects in the present study understood the investigator's instructions clearly. The normal control subjects (18 male, 18

female; mean age 26.7 ± 3.6 years; mean years of education 16.4 ± 2.2 years) were age- and sex-matched with the schizophrenic subjects. With regard to the mean years of education, there was a significant difference between schizophrenic patients and normal controls. The normal controls were drawn from healthy volunteers who consisted of hospital staff, students from Nihon University and members of Tokyo-based drug companies. The normal controls had no specific history of mental illness according to DSM-IV criteria and were taking no psychiatric medications. None of the schizophrenic patients or normal controls had any evidence of substance or alcohol abuse or organic brain pathology. The present study was approved by the Ethics Committees of Nihon University, Tokyo, Japan. Informed consent was obtained from each patient and normal control subjects after the nature of study had been fully explained.

Exploratory eye movement

A standard test of EEM using an NAC V-type eye mark recorder (NAC, Tokyo, Japan) was carried out. Three horizontal S-shaped figures were projected on to a screen (Fig. 1). The method is briefly described as follows.

1) The subject was shown the original S-shaped figure (Fig. 1a) for 15 s. Immediately after viewing it, he/she was asked to draw the original S-shaped figure.
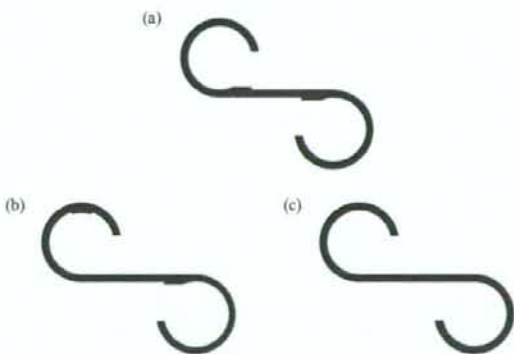

Figure 1. Three horizontal S-shaped figures in the exploratory eye movement (EEM) test. More detailed descriptions of these figures (a, b and c) have been presented in our previous studies.[4,8,9]

2) (i) The subject was instructed to compare a figure with the original figure (Fig. 1a) and was then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 1b), for 15s; (ii) after 15 s had elapsed and with the figure still in view, the subject was asked whether it differed from the original figure and, if it did, how it differed; (iii) after the subject had replied and while the figure was still being shown, he/she was asked 'Are there any other differences?'.

3) Step 2(i–iii) was repeated with a figure without bumps (Fig. 1c).

We analyzed the subject's eye movements while they were viewing the horizontal S-shaped figures. Based on the analysis, we obtained four parameters: number of eye fixations (NEF), total eye scanning length (TESL), cognitive search score (CSS) and responsive search score (RSS). We consider that the RSS may be the most specific parameter of schizophrenia in the EEM test. We obtain the RSS based on the data of eye movements during the 5 s immediately after the question 'Are there any other differences?' is asked in step 2(iii). More detailed descriptions of the EEM test methods have been presented in our previous studies.[4,8,9]

P300

ERP were recorded based on the standard auditory odd-ball paradigm. Tone pips were delivered binaurally through headphones at a stimulus intensity of 60 dB and a tone duration of 100 ms, with a rise and fall time of 10 ms. Subjects were asked to count silently, with eyes closed, infrequent high-pitched tones (2000 Hz) pseudo-randomly presented with a series of frequent low-pitched tones (1000 Hz). Two hundred and fifty tones were presented with interstimulus intervals of 0.6/s, and the ratio of high- to low-pitch tones was 1:4 (50:200).

ERP recordings were obtained using three silver/silver chloride disc electrodes with a linked-ear reference according to the international 10–20 system (Fz, Cz, Pz). The electroencephalogram was filtered using a bandpass of 0.5–60 Hz. Horizontal electrooculogram (EOG) was recorded from electrodes placed at the right and left external canthi. Vertical EOG was recorded using right eye supra- and infraorbital electrodes. Horizontal and vertical EOG were used to monitor and control eye movement and
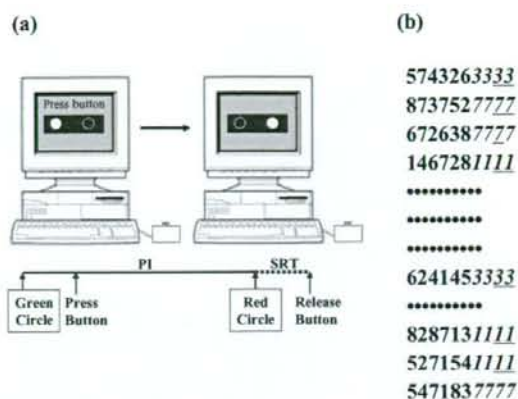

Figure 2. (a) Reaction time test apparatus and (b) preparatory interval (PI) array. SRT, simple reaction time.

blink artifacts. In addition, these were used to reject EOG artifacts, and trials were excluded when the voltage exceeded ±100 μV.

Fifty trials with the high-pitched tones were averaged with a sweep time of 700 ms including a 100 ms prestimulus baseline. The P300 peak latency and amplitude were measured from baseline to peak and were defined as the data point at the Pz electrode with the largest positive voltage from 250 to 550 ms. The sampling time was 6 ms.

Reaction time

RT was calculated based on the methods of Steffy and Galbraith.[10] As shown in Fig. 2(a), the RT task apparatus consisted of a computer linked to a control button. The subject reclined in a chair in front of the display monitor. When the subject pressed the button, a green circle immediately appeared on the left side of the display. The subject held it down, and after a preparatory interval (PI), the green circle disappeared and a red circle appeared on the right side of the display. The subject was required to release the button as quickly as possible after the appearance of the red circle. The lag time between the appearance of the red circle and the release of the button was measured as the simple reaction time (SRT). This RT task consisted of a series of 120 trials that included a regular series and an irregular series (Fig. 2b). The regular series consisted of 12 sets of four isotemporal

trials with 1, 3 or 7 s PI (Fig. 2b, italic font). The irregular series consisted of 12 sets of six anisotemporal trials with eight PI, from 1 to 8 s (Fig. 2b, plain font). These eight PI were given in pseudo-random order. As can be seen in Fig. 2(b), the regular and irregular series were presented alternately.

According to DeAmicis and Cromwell, we calculated the index of reaction time crossover (IRT-crossover) utilizing mean SRT with formula (1) given here.[11] Rodnick and Shakow reported that reaction time crossover (RT-crossover) phenomenon may be a marker for process schizophrenia.[12] This phenomenon was transformed to the index (IRT-crossover: difference between the average SRT for regular trials and for irregular trials at the 7 s PI) using the DeAmicis and Cromwell method.[11] They found that 25 ms was the optimal cut-off point between schizophrenic patients and normal controls from the inspection of the data in individual subjects. Since then, some investigators have indicated that the optimal cut-off point is 10 ms or 25 ms.[13,14] Thus, it has been considered that the optimal cut-off point of IRT-crossover between schizophrenic patients and normal controls is still not determined. Using a DeAmicis and Cromwell method,[11] we inspected the present data and found that the maximum difference between schizophrenia patients and normal controls was obtained using a cut-off point of 15 ms. For this reason, if the IRT-crossover score was ≥15 ms, we defined it as abnormal.

On the basis of the procedures of Rodnick and Shakow, we calculated the set index (SI) utilizing mean SRT with formula (2) given here.[12] They found that this single criterion of mean RT level differentiated most of the schizophrenia patients from the normal controls, but there was still some overlap despite the fact that a significant difference existed between the two groups. They attempted to create an index using the data from the RT to achieve more satisfactory differentiation between patients and normal controls, and finally obtained the SI. There was no overlap between schizophrenia patients and normal controls with SI in their study. In the present study the construction of the trial arrangement differentiated from their method. The task procedure in the present study followed the Steffy and Galbraith method, which was modified to show the RT-crossover most frequently. Steffy and Galbraith did not calculate the SI.[10] In the present study, in order to calculate the SI based on the data of the trial arrangement of Steffy and Galbraith, we slightly adjusted the

Rodnick and Shakow formula. Therefore, although we tried to stay as close to this as possible, our SI formulas differed slightly from the original Rodnick and Shakow work.[12]

To investigate intra-trial response variability, we calculated the coefficient of variation (CV) of data from all trials with formula (3) given here. If the CV was >95% upper of confidence interval of the normal control group, we defined it as abnormal.

$$\text{IRT-crossover} = M7R - M7I \qquad (1)$$

where M7R is the mean RT for each trial on regular condition with a PI of 7 s, the regular condition is the last two trials of the regular series were defined as the regular condition (Fig. 2b, underlined italic font); M7I, is the mean RT for each trial on irregular condition with a PI of 7 s, the irregular condition is all trials of the irregular series, and the first trial of the regular series were defined as the irregular condition (Fig. 2b, plain and italic font).

$$\text{SI} = MH \times (M7R + M7I) + M1R^2 + M3R \qquad (2)$$

where MH is the highest of several RT means for each trial obtained at any PI (1, 2, 3, 4, 5, 6, 7 or 8) under either condition (regular or irregular). M7R and M7I are the same as defined above. M1R is the mean RT for each trial on regular condition with a PI of 1 s, M3R is the mean RT for each trial on a regular condition with a PI of 3 s.

$$\text{CV} = SD7I + M7I \qquad (3)$$

where SD7I is the standard deviation of RT for each trial on irregular condition with a PI of 7 s. M7I is same as defined above.

It is possible that these three tests may have been effected by the time of day. To ensure consistency, all three tests were done for each subject on the same day. Further, each of the three tests was performed for each subject at the same time of day. The order of test performances was as follows: (i) RT, (ii) EEM, and (iii) P300. These three tests were done according to this order in almost all subjects.

Statistical analysis

All EEM, P300 and RT measurements failed to meet the criteria for normality (Wilks–Shapiro test). Therefore, these data were examined using a nonparametric method. Group differences (schizophrenia group vs normal control group) on all EEM

and P300 parameters and the SRT of the RT test were assessed using the Mann–Whitney *U*-test. Because the IRT-crossover and the CV in the RT test data were converted to categorical data, these data were compared using the 2 × 2 contingency table. Moreover, because the RT-crossover table included cells that had a low expected frequency, the RT-crossover was compared using Fisher's exact test. In contrast, because the CV table did not include cells that had a low expected frequency, the CV was compared using the χ^2 test. Statistical significance was set at $P < 0.01$. Relationships between EEM, P300 and RT variables were tested using the Spearman rank–order correlation test. In order to examine these relationships, we used numerical variables as opposed to categorical variables with regard to RT-crossover and CV parameters. This is primarily due to the fact that numerical variables yield a more detailed outcome.

RESULTS

Schizophrenic patients versus normal controls

Table 1 shows the results of EEM, P300 and RT tests for the two groups.

Exploratory eye movement

The NEF and TESL were significantly lower in the schizophrenic group compared to that of the normal control group. The schizophrenic group had significantly lower CSS and RSS than the normal control group.

P300

There was a significant increase in the latency and a reduction in the amplitude of P300 in the schizophrenic group compared with that in the normal control group.

Reaction time

The SRT and SI in the schizophrenic group were significantly higher than those in the normal control group. There were nine patients (25.7%) in the schizophrenic group who had an abnormal RT-crossover, but there was only one subject (3%) in the normal control group who had an abnormal RT-crossover. Concerning CV, 24 schizophrenic patients (70.6%), but only nine normal controls (25.0%) demonstrated any abnormality. There was a significant difference between the schizophrenic patients and the normal controls with regard to RT-crossover and CV.

EEM, P300 and RT tests

Tables 2,3 illustrate the rank–order (Spearman) correlation between EEM, P300 and RT in schizophrenia and normal controls. As can be seen, the RSS of the

Table 1. EEM, P300 and RT parameters in schizophrenia and normal controls

		Schizophrenic patients ($n = 34$)	Controls ($n = 36$)
EEM	NEF	28.1 ± 7.5	36.8 ± 6.7*
	TESL (cm)	434.3 ± 167.2	619.8 ± 146.4*
	CSS	4.5 ± 1.0	6.2 ± 0.9*
	RSS	7.4 ± 1.4	10.4 ± 1.9*
P300	LAT (ms)	373.3 ± 32.6	346.7 ± 24.0*
	AMP (µV)	6.6 ± 2.8	9.1 ± 2.9*
RT	SRT (ms)	229.7 ± 48.4	164.0 ± 23.7*
	SI	465.3 ± 121.2	349.1 ± 88.4*
	RT-Cross	9 (26.5%)	1 (2.8%)[†]
	CV	24 (70.6%)	9 (25.0%)[‡]

*$P < 0.01$ (Mann–Whitney *U*-test), [†]$P < 0.01$ (Fisher's exact test), [‡]$P < 0.01$ (χ^2 test).
Mean ± SD.
AMP, amplitude; CSS, cognitive search score; CV, coefficient of variation; EEM, exploratory eye movement; LAT, latency; NEF, number of eye fixations; RSS, responsive search score; RT, reaction time; RT-Cross, reaction time crossover; SI, set index; SRT, simple reaction time; TESL, total eye scanning length.