main frequency peak, on the basis of dominant frequencies in the spectrum over the channels giving the sources in the hippocampus. The absolute values were time-locked to the stimulus onset and averaged, and the averaged signals were low-pass filtered at 10 Hz to smooth the TSE curves. The increases and decreases of the TSE curves correspond to event-related synchronization (ERS, enhanced rhythmic activity) and desynchronization (reduced rhythmic activity), respectively (Pfurtscheller, 1992). TSE curves were selected at the same subset channels of each hemisphere as those in source modeling giving the hippocampal source of each hemisphere. Based on these TSE curves, the hippocampal source of each hemisphere was confirmed with the same manner as source modeling. Further, using the signal-space projection method, the SSP component of the TSE curve for the hippocampal source of each hemisphere was extracted from the whole TSE curves. Finally, the SSP component of the TSE curve at a single channel with the local signal maximum was used for statistical analysis. The effects of various conditions were evaluated by integrating the TSE curves over a period of 50 ms, containing the peak of TSE curve.

Statistical analysis

Two-factor factorial ANOVA and Fisher's protected least significant difference post hoc test were applied to compare the latencies and spectral power strengths of the M400 sources and the relative levels of Cho and Cr. The factors analyzed were the target picture and laterality. Significance was set at $P < 0.05$.

Results

Task performance

All subjects easily performed the counting task (over 98% accuracy). The total number of target stimuli in MRS and MEG measurement per a recording session was 30 and 45. The number of off-line averaged epochs in MEG measurement was about 40 after rejecting the contaminated epochs.

MRS data

In this study, unpleasant and pleasant pictures of babies' faces were presented to normal subjects in random order, and the subject was asked to silently count the number of times the target picture was shown. Either the unpleasant or pleasant picture served as the target picture. Fig. 1 shows typical averaged ^{1}H-MR spectra time-locked to the onset of the target stimulus from the right hippocampal region of a subject during the activation condition in which the unpleasant picture was presented as the target stimulus (left) and typical averaged ^{1}H-MR spectra obtained during the resting

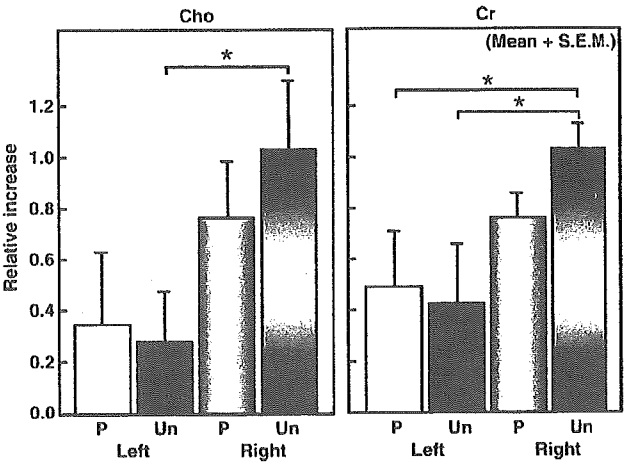

Fig. 2. Relative increases in the levels of Cho (left) and Cr (right) during the activation condition (with either unpleasant or pleasant pictures) in comparison with the respective level during the resting condition in the left and right hippocampal regions. P, pleasant target picture; Un, unpleasant target picture. Each bar represents the mean ± SEM of each session of pleasant or unpleasant target picture in the 10 subjects. *$P < 0.05$.

condition (right). The location of the VOI in the right hippocampal region of this subject in the MR-guided image is shown in Fig. 1 (middle). Three peaks for Cho, Cr, and NAA were detected at the positions of 3.20, 3.00, and 2.00 ppm, respectively. Compared with the amplitudes and integrated values of the peaks for Cho, Cr, and NAA during the resting condition, those measured during the activation condition were elevated. There were no significant differences in the level of NAA in the hippocampal region between the left and right hemispheres; between the resting and activation conditions; nor between the pleasant and unpleasant pictures as the target stimulus.

Fig. 2 shows the relative increases in the levels of Cho (left) and Cr (right) during the activation condition in comparison with the respective level during the resting condition in the left and right hippocampal regions for each target. There were interactions between the relative increase of neurochemicals (Cho and Cr) and hippocampal side ($P < 0.013$ for Cho, $P < 0.017$ for Cr). For the unpleasant target, the relative increase in the level of Cho in the right hippocampal region was significantly larger than that for either the unpleasant or the pleasant target in the left hippocampal region (170–180%, $P < 0.05$). The relative increase in the level of Cr in the right hippocampal region was significantly larger than that for either the unpleasant or the pleasant target in the left hippocampal region (150–160%, $P < 0.05$ for both). For the pleasant target, the relative increases in the levels of Cho and Cr were larger in the right than in the left hippocampal region, although the differences were not significant. There were no significant differences in the relative increases in Cho or Cr in each hippocampal region between the unpleasant and pleasant targets. There was no interaction between the relative increasing level of NAA and hippocampal side.

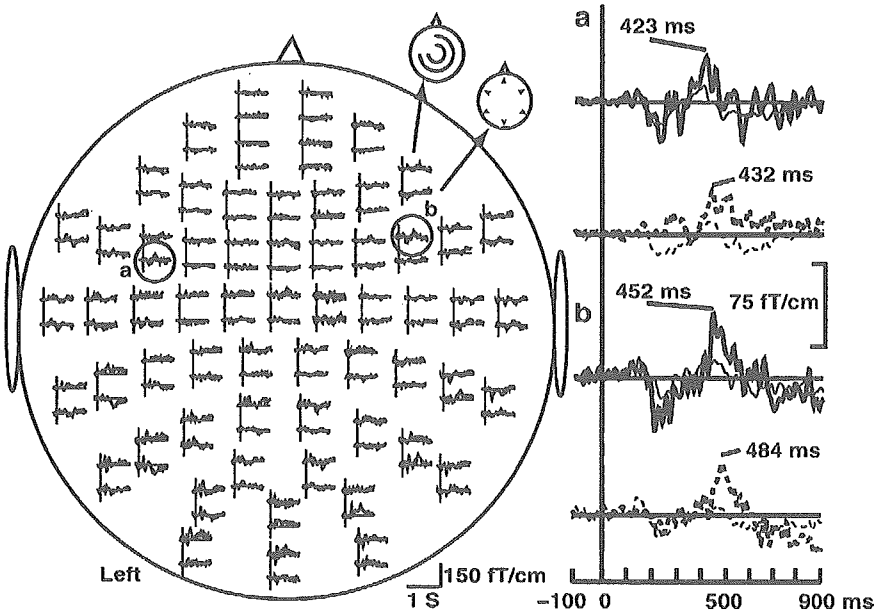

Fig. 3. Magnetoencephalographic responses to unpleasant and pleasant targets in a representative subject. (Left) Whole-scalp magnetic responses to unpleasant targets from the subject. The head viewed from above and the upper and lower traces of each response pair show the latitudinal and longitudinal derivatives of the magnetic field perpendicular to the helmet at the measurement site. (Right) Signals from the left and right anterolateral channels (a and b) are enlarged on the right, where the traces from the target responses (thick lines) and nontarget responses (thin lines) are superimposed. Solid lines, unpleasant stimuli; dotted lines, pleasant stimuli.

MEG signals

Fig. 3 (left) shows typical MEG signals from a representative subject upon presentation of unpleasant targets. During detection of unpleasant and pleasant target pictures, prominent responses were observed at the anterior, anterolateral, central, and posterior channels over each hemisphere in all subjects. Fig. 3 (right) shows the evoked magnetic responses to the target and nontarget stimuli from the anterolateral channels of each hemisphere, superimposed on traces from the responses to the target and nontarget stimuli of the unpleasant and pleasant pictures. The magnetic responses evoked by the unpleasant targets were larger in amplitude than those evoked by the pleasant targets. These patterns of magnetic waveforms were similar across all subjects.

Source distribution

At the main response peaks, the magnetic field patterns were dipolar over several regions of both hemispheres and suggested the presence of five main source areas (the middle frontal, hippocampal, superior temporal, inferior parietal, and occipital areas) in each hemisphere. Fig. 4 shows that the main sources of the magnetic signals in response to unpleasant targets in subject 1 were located in the occipital area [Brodmann area (BA) 19] (left: peaked at a mean of 156 ms, and right: 158 ms), superior temporal gyrus (BA 22) (214 ms and 223 ms), middle frontal area (BA 9/46) (271 ms and 236 ms), hippocampus (404 ms and 431 ms), and inferior parietal lobule (BA40) (417 ms and 476 ms). The pleasant targets activated these same regions in subject 1. Sources for M400 in response to both the unpleasant and the pleasant targets were consistently obtained in BA 19,

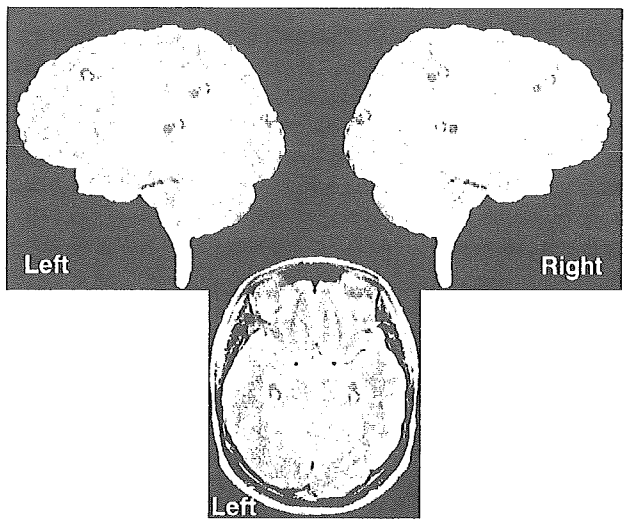

Fig. 4. Main source locations of the magnetic signals in a subject in response to presentation of the unpleasant (red circle) or pleasant targets (dotted red circle), superimposed on the subject's three-dimensional MR image. (Upper left and right) The brain surface viewed from the left and right sides, respectively. (Bottom) An axial view including the hippocampal region of each hemisphere.

Table 1
Source locations of main MEG response peaks in Talairach coordinates (mean ± SEM, 10 subjects)

	Left hemisphere				Right hemisphere			
	x	*y*	*z*	*n*	*x*	*y*	*z*	*n*
Unpleasant target (n = 10)								
Middle frontal area	−50 ± 6	31 ± 5	27 ± 4	2	53 ± 3	34 ± 4	25 ± 3	5
Hippocampal area	−29 ± 2	−12 ± 3	12 ± 2	10	23 ± 4	−13 ± 3	−11 ± 3	9
Sup. temporal area	−60 ± 3	−35 ± 6	12 ± 3	2	57 ± 4	−37 ± 5	15 ± 4	3
Inf. parietal area	−52 ± 4	−35 ± 4	34 ± 3	9	55 ± 2	−40 ± 4	32 ± 3	9
Fusiform gyrus					33	−56	−8	1
Occipital area	−28 ± 5	−85 ± 6	18 ± 3	10	30 ± 2	−88 ± 2	17 ± 3	10
Pleasant target (n = 10)								
Middle frontal area	−49 ± 4	31 ± 6	28 ± 3	3	43 ± 3	36 ± 5	34 ± 3	5
Hippocampal area	−30 ± 3	−19 ± 5	14 ± 2	10	29 ± 3	−20 ± 3	−13 ± 2	9
Sup. temporal area	−58 ± 3	−38 ± 3	15 ± 3	3	56 ± 3	−40 ± 5	14 ± 5	3
Inf. parietal area	−54 ± 3	−34 ± 4	36 ± 3	9	53 ± 2	−39 ± 4	35 ± 3	8
Fusiform gyrus	−27	−60	6	1				
Occipital area	−29 ± 4	−87 ± 3	19 ± 2	10	29 ± 4	−82 ± 3	20 ± 2	10

Note. Coordinates *x* (left to right), *y* (posterior to anterior) and *z* (inferior to superior) are in millimeters from an origin point situated at the anterior commissure. Results are means ± SEM among the subjects whose number is given by *n*.

BA 40, and the hippocampal region of each hemisphere in all subjects, but were not always obtained in BA 22 and BA 9/46 among the subjects (Table 1). The left fusiform gyrus was activated in one subject upon presentation of the pleasant target (182 ms), and the right fusiform gyrus was activated in another subject during presentation of the unpleasant target (194 ms). Table 1 summarizes the ECD locations of M400 in the subjects based on the Talairach coordinate system (Talairach and Tournoux, 1988).

TSE curves

In all subjects, the averaged amplitude spectra for the magnetic fields showed dominant 10-Hz frequency at the posterior channels, and 3.5–7.5 and 8–12 Hz at the anterolateral channels. Fig. 5A shows amplitude spectra calculated from the same channels that show the local maximum at the anterolateral channels in subject 2. The amplitude spectra around 3.5–7.5 Hz elevated more during discrimination of the unpleasant target pictures than the pleasant target pictures, on both hemispheres.

Based on the dominant frequencies of the individual rhythms, the TSE analysis was applied with frequency bands of 3.5–7.5 and 8–12 Hz. The contour maps of the absolute changes of TSE at the peaks of rebound and suppression show the prominent rebound of 3.5–7.5 Hz and suppression of 8–12 Hz at the anterolateral channels of both hemispheres. Fig. 5B shows the TSE curves of θ (3.5–7.5 Hz) and α (8–12 Hz) bands (θ and α TSE) in the hippocampus of each hemisphere of the same subject whose results are shown in Figs. 3 and 4. The θ TSE curves started to increase at about 250 ms and peaked at 400–450 ms, and these latencies are similar to the onset and peak latencies, respectively, of M400. The θ TSE curves having the largest peak value were obtained in the right hippocampus for the unpleasant targets. The α TSE curves showed the largest event-related desynchronization at a latency close to the M400 peak, upon presentation of both the unpleasant and the pleasant targets. The α and θ TSE curves showed similar patterns in that their peaks were earlier in the left than in the right hippocampus for both unpleasant and pleasant targets and were earlier for unpleasant targets than for pleasant targets across the subjects, although the difference was not statistically significant (Fig. 5C). Fig. 5D shows the relative changes in the peak amplitude of the TSE curve relative to that in the resting state. There was an interaction between the relative increase in θ TSE amplitude and hippocampal side ($P < 0.05$). Both the θ and the α TSE curves of the hippocampus of each hemisphere showed larger relative changes for the unpleasant than for the pleasant targets. For the unpleasant targets, the relative change in θ synchronization was significantly larger in the right than in the left hippocampus ($P < 0.05$) and, overall, was larger than that for the pleasant targets ($P < 0.05$ for the right hippocampus, $P < 0.01$ for the left hippocampus). The relative change in θ synchronization in the left hippocampus was larger for unpleasant than for pleasant targets (*ns*). The α TSE curves did not show any significant differences between the activation and resting conditions nor between the left and right sides.

Discussion

In this study, brain activation was measured both neurophysiologically and neurochemically during the discrimination of target stimuli conveying emotional information. The four main, important, methodological features of this study were: (a) use of combined MEG and MRS to measure event-related activity in the human hippocampus; (b) MRS

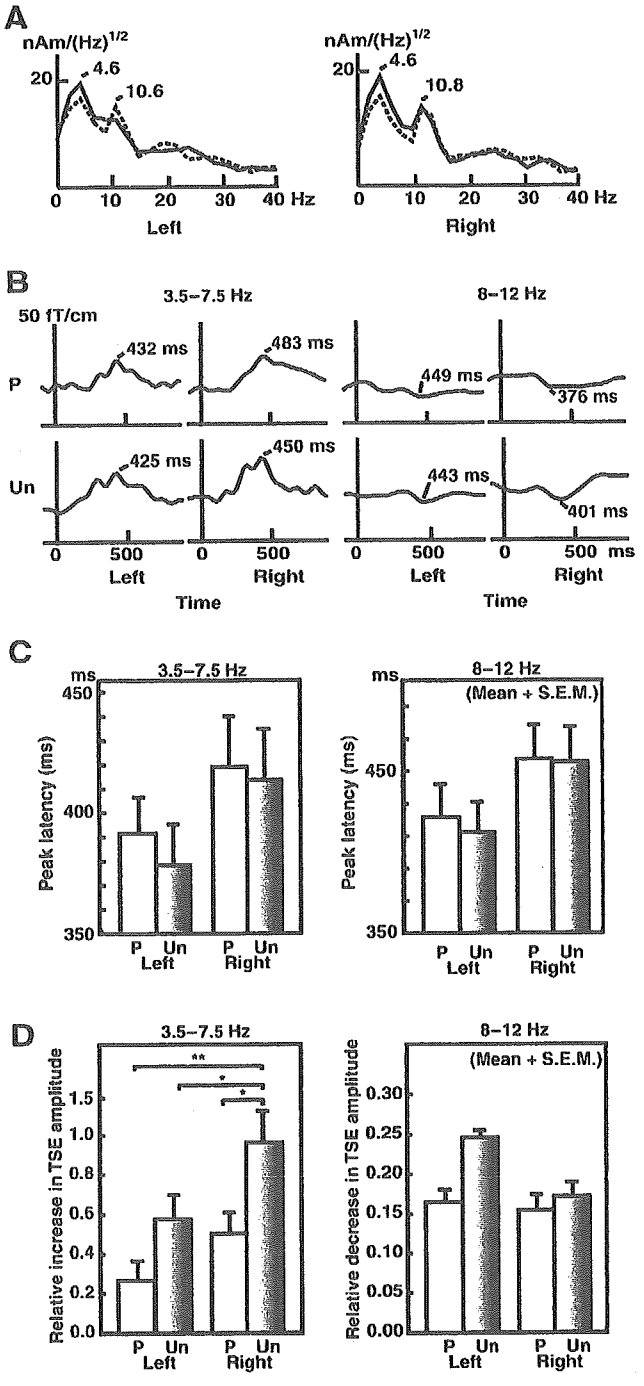

Fig. 5. (A). Changes in the θ and α bands in the left and right anterolateral channels during the discrimination task. (B) TSE curves of θ (3.5–7.5 Hz) and α (8–12 Hz) bands (θ and α TSEs) related to the target pictures, at the hippocampal region of both hemispheres in subject 1. The onset of the target stimulus was at time 0 ms. (C) Comparison of the peak latencies of the θ (3.5–7.5 Hz) and α (8–12 Hz) TSEs upon presentation of unpleasant or pleasant targets in the left and right channels across subjects. Each bar represents the mean ± SEM. (D) Relative change in the amplitude of TSE upon presentation of the pleasant or unpleasant target relative to that of the prestimulated state. The integration time for the TSE curves was 50 ms, containing the peak of TSE curve. The relative increases and decreases in the amplitude of TSE are shown separately. P, pleasant target picture; Un, unpleasant target picture. Each bar represents the mean ± SEM. $^{**}P < 0.01$, $^{*}P < 0.05$.

scanning time-locked to the stimulus onset with a suitable delay between trigger onset and scan timing, which was based on our MEG data and our previous study showing the dynamic changes in neurochemical metabolism (Nistitani and Maeno, 2002); (c) noninvasive estimation of the dynamics of the main chemical transmitters in the hippocampal region by comparing the results obtained during the activation and resting conditions; (d) evaluation of the hippocampal event-related synchronization and desynchronization by MEG.

Event-related synchronization in the hippocampus

The present MEG study demonstrated brain activity during the discrimination of visual stimuli conveying emotional information in several regions: the occipital, inferior parietal, middle frontal, superior temporal, and hippocampal regions of each hemisphere. The prefrontal, inferior parietal, and superior temporal cortices are part of a network for attentional control (Hopfinger et al., 2000; Miller, 2000; Driver and Vuilleumier, 2001), and the hippocampal regions play an important role in the updating of memory template and cognition (Donchin, 1979; Vargha-Khadem et al., 1997; Meslum, 1998; Bernstein et al., 2001; Rapcsak et al., 2001).

Hippocampal activity was studied by ERS and event-related MRS. To engage the attention and memory functions of the brain, the tasks of target discrimination and counting the number of target stimuli were used in this study. The finding that the amplitude of M400 and ERS (in terms of θ activity) in the hippocampus was larger in the right than in the left hippocampus while detecting unpleasant targets is in agreement with other previous studies that showed hemispheric lateralization of functions related to emotional information (Silberman and Weingartner, 1986; Adolphs, 1999). Furthermore, the current results corroborate experimental evidence suggesting that the medial temporal region, including the hippocampus and adjusting region, plays an important role in the updating of memory template, short-term memory processing, attention, and cognition (Donchin, 1979; Vargha-Khadem et al., 1997; Meslum, 1998). The present result of ERS suggests that the θ cells in the hippocampal region were activated during the discriminating task, since the ERS of the hippocampal θ rhythm reflects the excitatory postsynaptic potentials in CA1/CA3 (Nunez et al., 1987; Fried et al., 1997; Wiebe and Staubli, 2001). Furthermore, since memory processing is affected by the activity of cholinergic neurons, the present result is consistent with previous studies showing that the hippocampal θ rhythm is elicited by cholinergic neurons (Bland, 1986; Huerta and Lisman, 1993, Monmaur et al., 1997; Fischer et al., 1999; Keita et al., 2000).

Event-related MRS

The approach used in the present study offers a noninvasive means of analyzing the dynamic changes in neurochemical metabolism evoked by a stimulus. Furthermore, the level of dynamic neurochemical metabolism was not estimated by the integrated values of Cho and Cr, but by their relative increases in comparison with the respective values in the resting condition. These ratios reflect the real-time changes in neurochemical metabolism induced by the stimulus. In contrast, the MRS technique in conventional studies has been used to estimate the static state of neurochemical metabolism after structural changes have occurred in the brain; these studies are performed to supplement the clinical diagnosis of patients and to gain an understanding of a particular pathological state (Kario et al., 1999). Recent studies have attempted to elucidate the relationship between neurochemical metabolism and cognitive function, but were not successful in accurately associating brain function with a specific cognitive process, because the MRS and cognitive tests were performed separately (e.g., Ferrier et al., 2000; Sawrie et al., 2000).

Our other study using ^{1}H-MRS showed the neurochemical dynamics in the human hippocampus while the subjects performed a task similar to that in the present study (Nistitani and Maeno, 2002). NAA has been designated a neuronal marker and is currently an axonal marker as well (Miller, 1991; Ross and Bluml, 2001). NAA is synthesized in the mitochondria and is involved in a number of neurobiological processes including the production of ATP, which is required for propagation of the depolarizing action potential (Miller, 1991; Simmons et al., 1991; Urenjak et al., 1992). Thus, the integrated value of NAA closely reflects neuronal function rather than the state of the cell membrane, and the concentration of NAA reflects neural viability (Namer et al., 1999). However, in our other study, we found that in contrast with the levels of Cho and Cr, the NAA level was relatively constant during performance of the task (Nishitani and Maeno, 2002). This result is supported by the fact that the half-life of NAA in the gray matter is over several minutes (Danielsen and Ross, 1999).

The relative increases in Cho and Cr observed in this study reflect the concentration and the neurochemical metabolism of Cho and Cr in the hippocampal region, because there were no structural changes in the brains of the normal subjects and the concentration of NAA was nearly constant during performance of the task. The relative increase in Cr, which generally corresponds to energy metabolism in the mitochondrial respiratory chain, during the discrimination of emotional pictures may reflect increased excitatory activity in the hippocampus. Most of the Cho found in a neuron due to high affinity transport is used in the synthesis of acetylcholine, which plays an important role in memory and cognitive processes (Fibiger, 1991). A relative increase in Cho does not reflect cell membrane metabolism caused by a structural change, but rather it reflects Cho derived from acetylcholine which is released in the hippocampus CA1/CA3 in response to unpleasant stimuli (Acquas et al., 1996; Stilman et al., 1997). Cholinergic neurons induce an oscillatory θ rhythm in the hippocampus (Huerta and Lisman, 1993; Keita et al., 2000). θ cells in the hippocampus are involved in memory processing in the hippocampus (Wiebe and Staubli, 2001). The present results suggest facilitation of updating memory template and matching the visual stimuli with the target picture during the cognitive task in the hippocampal region, especially in the right side, and are in agreement with the results obtained in previous studies (Silberman and Weingartner, 1986; Adolphs, 1999).

Conclusions

The current findings suggest that this newly devised method combining event-related MEG with MRS can be used to noninvasively elucidate the dynamic features of neurophysiology and neurochemical metabolism and represents a promising approach for improving our understanding of brain mechanisms and for clinically examining brain functions in patients with brain diseases.

Acknowledgments

The author thanks Prof. H. Shibasaki for precious comments, Mr. M. Maeno for collecting data, and Mr. K. Maruyama and Mr. J. Okamoto for modification of the MRS proceeding programs. This study was financially supported by Grants-in-Aid for Research on Brain Science (H12-023), for Research on Psychiatric and Neurological Diseases and Mental Health (H14-005) from the Japan Ministry of Health, Labor, and Welfare, and for Scientific Research (B) 15300111 from the Japan Society for the Promotion of Sciences.

References

Acquas, E., Wilson, C., Fibiger, H.C., 1996. Conditioned and unconditioned stimuli increase frontal cortical and hippocampal acetylcholine release: effects of novelty, habituation, and fear. J. Neurosci. 16, 3089–3096.

Adolphs, R., Damasio, H., Tranel, D., Damasio, A.R., 1996. Cortical systems for the recognition of emotion in facial expressions. J. Neurosci. 16, 7678–7687.

Adolphs, R., 1999. Social cognition and the human brain. Trends Cogn. Sci. 12, 469–479.

Bernstein, L.J., Beig, S., Siegenthaler, A.L., Grady, C.L., 2001. The effect of encoding strategy on the neural correlates of memory for faces. Neuropsychologia 40, 86–98.

Bland, B.H., 1986. The physiology and pharmacology of hippocampal formation theta rhythms. Prog. Neurobiol. 26, 1–26.

Bottomley, P.A., 1987. Spatial localization in NMR spectroscopy in vivo. Ann. N. Y. Acad. Sci. 508, 333–348.

Bottomley, P.A., Edelstein, W.A., Foster, J.H., 1985. In vivo solvent-suppressed localized hydrogen nuclear magnetic resonance spectros-

copy: a window to metabolism? Proc. Natl. Acad. Sci. USA 821, 2148–2153.

Danielsen, E.R., Ross, B., 1999. Magnetic Resonance Spectroscopy: Diagnosis of Neurological Diseases. Dekker, New York.

Donchin, E., 1979. Event-related potentials: a tool in the study of human information processing, in: Begleiter, H. (Ed.), Evoked Brain Potentials and Behavior, Plenum, New York, pp. 13–88.

Driver, J., Vuilleumier, P., 2001. Perceptual awareness and its loss in unilateral neglect and extinction. Cognition 79, 39–88.

Ferrier, C.H., Alarcon, G., Glover, A., Koutroumanidis, M., Morris, R.G., Simmons, A., Elwes, R.D.C., Cox, T., Binnie, C.D., Polkey, C.E., 2000. *N*-Acetylaspartate and creatine levels measured by 1H MRS relate to recognition memory. Neurology 55, 1874–1883.

Fibiger, H.C., 1991. Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. Trends Neurosci. 14, 220–223.

Fischer, Y., Gahwilder, B.H., Thompson, S.M., 1999. Activation of intrinsic hippocampal theta oscillations by acetylcholine in rat septo-hippocampal cocultures. J. Physiol. 519, 405–413.

Fried, I., MacDonald, K.A., Wilson, C.L., 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron 18, 753–765.

Haase, A., Frahm, J., Hänicke, W., Matthaei, D., 1985. ^{1}H NMR chemical shift selective (CHESS) imaging. Phys. Med. Biol. 30, 341–344.

Halgren, E., Squires, N.K., Wilson, C.L., Rohrbaugh, J.W., Babb, T.L., Crandall, P.H., 1980. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 210, 803–805.

Hämäläinen, M., Hari, R., Ilmoniemi, R., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev. Mod. Phys. 65, 413–497.

Haxby, J.V., Ungerleider, L.G., Horwitz, B., Maisog, J.M., Rapoport, S.I., Grady, C.L., 1996. Face encoding and recognition in the human brain. Proc. Natl. Acad. Sci. USA 93, 922–927.

Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

Huerta, P., Lisman, J.E., 1993. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364, 723–725.

Ioannides, A.A., Liu, M.J., Liu, L.C., Bamidis, P.D., Hellstrand, E., Stephan, K.M., 1995. Magnetic field tomography of cortical and deep processes: examples of "real-time mapping" of averaged and single trial MEG signals. Int. J. Psychophysiol. 20, 161–75.

Kario, K., Matsuo, T., Hoshide, S., Umeda, Y., Shimada, K., 1999. Effect of thrombin inhibition in vascular dementia and silent cerebrovascular disease: An MR spectroscopy study. Stroke 30, 1033–1037.

Keita, M.S., Frankel-Kohn, L., Bertrand, N., Lecanu, L., Monmaur, P., 2000. Acetylcholine release in the hippocampus of the urethane anaesthetized rat positively correlates with both peak theta frequency and relative power in the theta band. Brain Res. 887, 323–334.

Kikuchi, Y., Endo, H., Yoshizawa, S., Kait, M., Nishimura, C., Tanaka, M., Kumagai, T., Takeda, T., 1997. Human cortico-hippocampal activity related to auditory discrimination revealed by neuromagnetic field. NeuroReport 8, 1657–61.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. International Affective Picture System (IAPS): Technical Manual and Affective Ratings, The Center for Research in Psychophysiology. University of Florida, Gainesville.

Meslum, M.M., 1998. From sensation to cognition. Brain 121, 1013–1052.

Miller, E., 2000. The neural basis of top-down control of visual attention in prefrontal cortex, in: Monsell, S., Driver, J. (Eds.), Control of Cognitive Processes: Attention and Performance, MIT Press, Cambridge, MA, pp. 511–534.

Miller, B.L., 1991. A review of chemical issues in ^{1}H NMR spectroscopy: *N*-acetyl-L-aspartate, creatine and choline. NMR Biome 4, 47–52.

Monmaur, P., Collet, A., Puma, C., Frankel-Kohn, L., Sharif, A., 1997. Relations between acetylcholine release and electrophysiological characteristics of theta rhythm: a microdialysis study in the urethane-anesthetized rat hippocampus. Brain Res. Bull. 42, 141–146.

Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J., 1998. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 121, 47–57.

Namer, I.J., Bolo, N.R., Sellal, F., Nguyen, V.H., Nedelec, J.F., Hirsch, E., Marescaux, C., 1999. Combined measurements of hippocampal *N*-acetyl-aspartate and T2 relaxation time in the evaluation of mesial temporal lobe epilepsy: correlation with clinical severity and memory performances. Epilepsia 40, 1424–1432.

Nishitani, N., Nagamine, T., Fujiwara, N., Yazaawa, S., Shibasaki, H., 1998. Cortical-hippocampal auditory processing identified by magnetoencephalography. J. Cogn. Neurosci. 10, 231–247.

Nishitani, N., Ikeda, A., Nagamine, T., Honda, M., Mikuni, M., Taki, W., Kimura, J., Shibasaki, H., 1999a. The role of the hippocampus in auditory processing studied by event-related electric potentials and magnetic fields in epilepsy patients before and after temporal lobectomy. Brain 122, 687–707.

Nishitani, N., Uutela, K., Shibasaki, H., Hari, R., 1999b. Cortical visuomotor integration during eye pursuit and eye-finger pursuit. J. Neurosci. 19, 2647–2657.

Nishitani, N., Hari, R., 2000. Temporal dynamics of cortical representation for action. Proc. Natl. Acad. Sci. USA 97, 913–918.

Nishitani, N., Hari, R.2002. Viewing lip forms: cortical dynamics. Neuron 36, 1211–1220.

Nishitani, N., Maeno, M. 2002. Non-invasive estimation of in vivo neurochemical dynamics. NeuroImage, S1039.

Nunez, A., Garcia-Austt, E., Bubo Jr., W., 1987. Intracellular theta-rhythm generation on identified hippocampal pyramids. Brain Res. 416, 289–300.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Pfurtscheller, G., 1992. Event-related synchronization (ERS): an electrophysiological correlate of cortical areas at rest. Electroencephalogr. Clin. Neurophysiol. 83, 62–69.

Raij, T., Uutela, K., Hari, R., 2000. Audiovisual integration of letters in the human brain. Neuron 28, 617–625.

Rapcsak, S.Z., Nielsen, L., Littrell, L.D., Glisky, E.L., Kaszniak, A.W., Laguna, J.F., 2001. Face memory impairments in patients with frontal lobe damage. Neurology 57, 1168–1175.

Ross, B., Bluml, S., 2001. Magnetic resonance spectroscopy of the human brain. Anat. Rec. 265, 54–84.

Salmelin, R., Hari, R., 1994. Spatiotemporal characteristics of sensorimotor MEG rhythms related to thumb movement. Neuroscience 60, 537–550.

Sawrie, S.M., Martin, R.C., Gilliam, F.G., Faught, E., Maton, B., Hugg, J.W., Bush, N., Sinclair, K., Kuzniecky, R.I., 2000. Visual confrontation naming and hippocampal function: A neural network study using quantitative ^{1}H magnetic resonance spectroscopy. Brain 123, 770–780.

Silberman, E.K., Weingartner, H., 1986. Hemispheric lateralization of functions related to emotion. Brain Cogn. 5, 322–353.

Simmons, M.L., Frondoza, C.G., Coyle, J.T., 1991. Immunocytochemical localization of *N*-acetyl-aspartate with monoclonal antibodies. Neuroscience 45, 37–45.

Stilman, M.J., Shukitt-Hale, B., Coffey, B.P., Levy, A., Lieberman, H.R., 1997. In vivo hippocampal acetylcholine release during exposure to acute stress. Stress 1, 191–200.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotactic Atlas of the Human Brain. Thieme, Stuttgart.

Tesche, C.D., Uusitalo, M.A., Ilmoniemi, R.J., Huotilainen, M., Kajola, M., Salonen, O., 1995. Signal-space projection of MEG data characterize both distributed and well-localized neuronal sources. Electroencephalogr. Clin. Neurophysiol. 95, 189–200.

Tesche, C.D., Karhu, J., Tissari, S.O., 1996. Non-invasive detection of neural population activity in human hippocampus. Cogn. Brain Res. 4, 39–47.

Tesche, C.D., 1997. Non-invasive detection of ongoing neuronal population activity in normal human hippocampus. Brain Res. 749, 53–60.

Tesche, C.D., Karhu, J., 2000. Theta oscillations index human hippocampus activation during a working memory task. Proc. Natl. Acad. Sci. USA 97, 919–924.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., Mishkin, M., 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277, 376–380.

Urenjak, J., Williams, S.R., Gadian, D.G., Noble, M., 1992. Specific expression of *N*-acetylaspartate in neurons, oligodendrocyte-type-2 astrocyte progenitors, and immature oligodendrocytes in vitro. J. Neurochem. 59, 55–61.

Uusitalo, M.A., Ilmoniemi, R.J., 1997. Signal-space projectionmethod for separating MEG or EEG into components. Med. Biol. Eng. Comput. 35, 136–140.

Wiebe, S.P., Staubli, U.V., 2001. Recognition memory correlates of hippocampal theta cells. J. Neurosci. 21, 3955–3967.

Abnormal Imitation-Related Cortical Activation Sequences in Asperger's Syndrome

Nobuyuki Nishitani, MD, PhD,[1,2] Sari Avikainen, MD,[1] and Riitta Hari, MD, PhD[1,3]

Subjects with Asperger's syndrome (AS) are impaired in social interaction and imitation, but the underlying brain mechanisms are poorly understood. Because the mirror-neuron system (MNS) that matches observed and executed actions has been suggested to play an important role in imitation and in reading of other people's intentions, we assessed MNS functions in 8 adult AS subjects and in 10 healthy control subjects during imitation of still pictures of lip forms. In the control subjects, cortical activation progressed in 30 to 80-millisecond steps from the occipital cortex to the superior temporal sulcus, to the inferior parietal lobe, and to the inferior frontal lobe, and finally, 75 to 90 milliseconds later, to the primary motor cortex of both hemispheres. Similar activation sites were found in AS subjects but with slightly larger scatter. Activation of the inferior frontal lobe was delayed by 45 to 60 milliseconds and activations in the inferior frontal lobe and in the primary motor cortex were weaker than in control subjects. The observed abnormal premotor and motor processing could account for a part of imitation and social impairments in subjects with AS.

Ann Neurol 2004;55:558–562

Autism-spectrum disorders are characterized by impairments of social communication, often attributed to a lack of understanding of other people's mental states. Recent research suggests that mirror neurons, first discovered in monkey frontal area F5, are important for some aspects of social cognition, especially for understanding the intentions of other people.[1–3] Mirror neurons are activated both when subjects view another person's motor acts and when they perform similar movements themselves.

Certain areas of the human mirror-neuron system (MNS), especially Broca's region (the human homolog of monkey F5) and the primary motor cortex, seem essential for imitation.[4–8] Because imitation is important for development of proper understanding of other people's minds,[9] the common observation that autistic people have poor imitation skills makes the MNS one plausible candidate to support social interaction.[10–12]

We previously observed that the primary motor cortex of subjects with Asperger's syndrome (AS) is rather normally activated during both observation and execution of finger manipulation.[10] However, those results do not exclude dysfunction of other parts of the MNS. In this study, we followed cortical activation sequences when AS and healthy subjects imitated orofacial gestures presented as still pictures; the setup was similar to our previous study on healthy subjects.[7]

Subjects and Methods

Subjects and Experimental Setup

Eight Finnish subjects fulfilling the diagnostic International Classification of Diseases (ICD)–10 criteria[13] for Asperger syndrome (six men and two women; age range, 19–45 years; mean, 29.9 years) and 10 Finnish healthy control subjects (four men, and six women; age range, 23–28 years; mean 24 years) participated in the study. All control subjects and seven AS subjects were right-handed; one AS subject was ambidextrous. Informed consent was obtained from each subject after full explanation of the study, and the local ethics committee had approved the study protocol. Three different still pictures were projected once every 3.6 to 4.4 seconds for 551msec, in a random order, on a screen 90cm in front of the subject (Fig 1); all stimuli were of same luminance, contrast, and size (15 × 20cm). The subjects were asked to imitate the lip forms as soon and accurately as possible. A short rehearsal period before the actual measurement ensured that the subjects understood the given instructions and were able to perform the task.

Recordings and Analysis

The recording and analysis methods of magnetoencephalography (MEG) were similar to those extensively used in our

From the [1]Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Espoo, Finland; [2]Cognitive Sciences Section, Department of Sensory and Communicative Disorders, Research Institute, National Rehabilitation Center for Persons with Disabilities, Tokorozawa, Japan; and [3]Department of Clinical Neurophysiology, Helsinki University Central Hospital, Helsinki, Finland.

Received Jul 3, 2003, and in revised form Dec 3. Accepted for publication Dec 8, 2003.

Published online Mar 1, 2004, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20031

Address correspondence to Dr Hari, Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, P.O. Box 2200, FIN-02015 HUT, Espoo, Finland. E-mail: hari@neuro.hut.fi

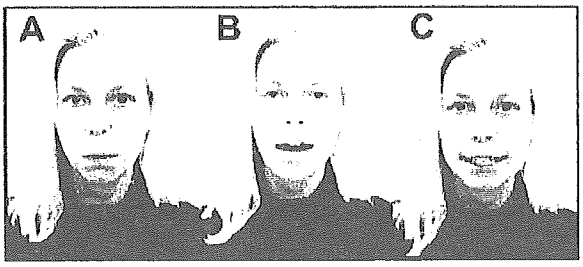

Fig 1. Still pictures of three orofacial gestures: (A) lip protrusion, (B) lip opening, and (C) contraction of both sides of mouth.

previous studies.[6,7] Bipolar surface electromyograms (EMGs) were recorded from the orbicular muscle of mouth in five of eight AS subjects and in all control subjects, and vertical and horizontal electrooculograms were recorded from all subjects. The recording passband was 0.1 to 600Hz and the sampling rate was 600Hz. The analysis period extended from 300msec before to 1,000msec after the stimulus onset, with a 100msec prestimulus period as the baseline. Epochs with blinks and excessive eye movements were rejected on the basis of electrooculograms

The averaged signals were digitally low-pass filtered at 40Hz. The current sources of the spatial signal patterns were modeled as equivalent current dipoles (ECDs).[14] The ECDs that best explained the most dominant signals were obtained from least-squares fits applied on the data of 20 to 30 channels around the local signal maxima. Only ECDs accounting for greater than 80% of the field variance, and with confidence volumes less than $1cm^3$, were accepted for further analysis. The ECDs were superimposed on the subject's own magnetic resonance imaging (MRI) surface rendering after alignment of the MEG-MRI coordinate systems.[14] The source locations were transformed to the Talairach's standard brain space.[6,7,15] In the statistical analysis, both t test and χ^2 test were applied, and the activations of undetectable sources in a particular brain area were assumed to be 0nAm in strength.

Results

Subjects' Performance

The onset latencies of the mouth EMGs did not differ between the subject groups (mean ± SEM, 393 ± 27msec after the stimulus onset in AS subjects and 384 ± 9msec in the control group).

However, the EMGs lasted significantly longer in the AS subjects than in the control group (890 ± 47 vs 466 ± 20 ms; $p < 0.001$; Fig 2A). The performance of the ambidextrous subject did not differ from the other AS subjects.

Activated Brain Areas

In agreement with the results of our previous study on healthy Japanese subjects,[7] five main activation areas were identified on the basis of the field patterns and the consequent source analysis in both subject groups.

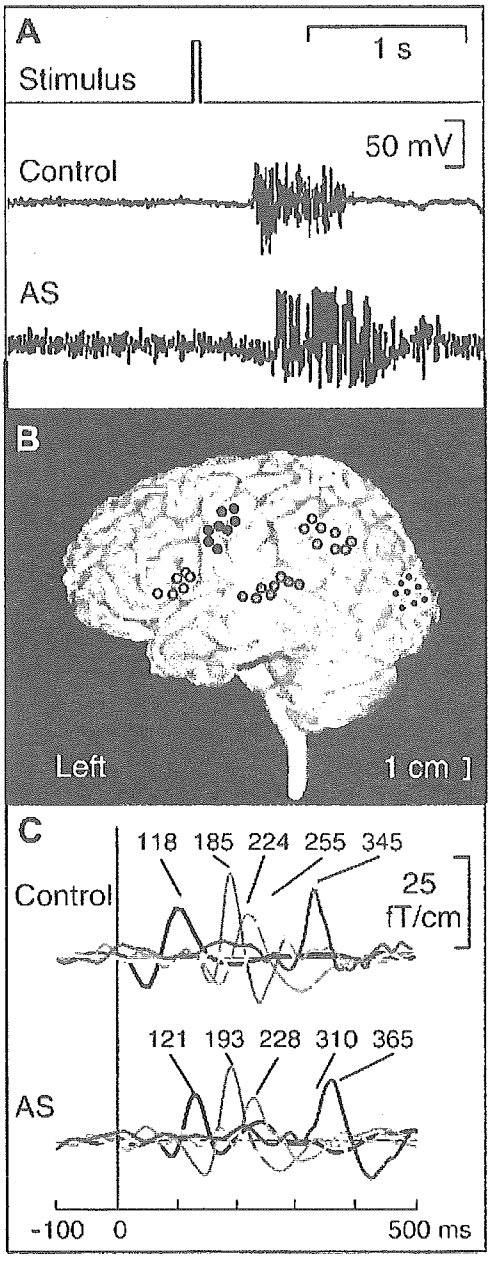

Fig 2. (A) Stimulus timing and electromyograms (EMGs) from the mouth muscle of a control subject and an Asperger's syndrome (AS) subject. (B) The main source locations of all AS subjects superimposed on Talairach's standard brain. Each symbol refers to one AS subject showing activation in that brain area. (C) Magnetoencephalographic (MEG) signals of the control and AS subject from five areas on the left hemisphere. The signals were averaged time-locked to the onset of the visual stimulus. Occ = occipital; STS = superior temporal sulcus; IPL = inferior parietal lobule; IF = inferior frontal, M1 = primary motor cortex.

Figure 2B shows the scatter of active brain areas in all AS subjects. The source clusters agree with activation of the occipital cortex (Occ), the region of the superior temporal sulcus (STS), the inferior parietal lobule (IPL), the inferior frontal area (IF, Broca's area), and the primary motor cortex (M1). The Table gives the coordinates of all activations in the two groups. In the control group, all five areas were consistently activated, whereas in the AS subjects the left IF was activated only in six subjects and the right IF area only in three; this hemispheric difference was statistically significant (χ^2 test; $p < 0.01$).

Activation Timing and Source Strengths

Figure 2C shows responses of one control and one AS subject from the five main activation areas in the left hemisphere. The earliest signals peak at 118 to 121msec at the occipital area, and thereafter the latencies increase systematically to STS, to IPL, to IF, and to M1. The time difference between IPL and IF signals is clearly longer in the AS subject than in the control subject.

Figure 3 shows the mean (±SEM) peak latencies at the left hemisphere across all subjects. The duration of the whole activation sequence from occipital area to M1 cortex was approximately 230msec in the control subjects and approximately 245msec in the AS group. In both groups, the peak activations from occipital cortex to STS and from STS to IPL were separated by 30 to 80msec ($p < 0.05$ for both intervals); consequently, the latencies did not differ between the groups at these three first areas of the activation chain. However, from IPL to IF, the interval in the left hemisphere was 60msec longer ($p < 0.01$) for AS than control subjects.

In the right hemisphere, peak latencies were similar, but IF signals were seen only in three of eight AS subjects. M1 activations followed IF activation by 75 to 90msec in the control subjects ($p < 0.01$ for the timing difference between these two areas) and by 35–50msec in AS subjects (not significant) in both hemispheres. The M1 latency difference between the groups did not reach statistical significance (difference of 45msec on the left and of 25msec on the right).

The source strengths did not differ between the groups in occipital, STS, IPL areas. Instead, both IF and M1 activations were significantly weaker in AS

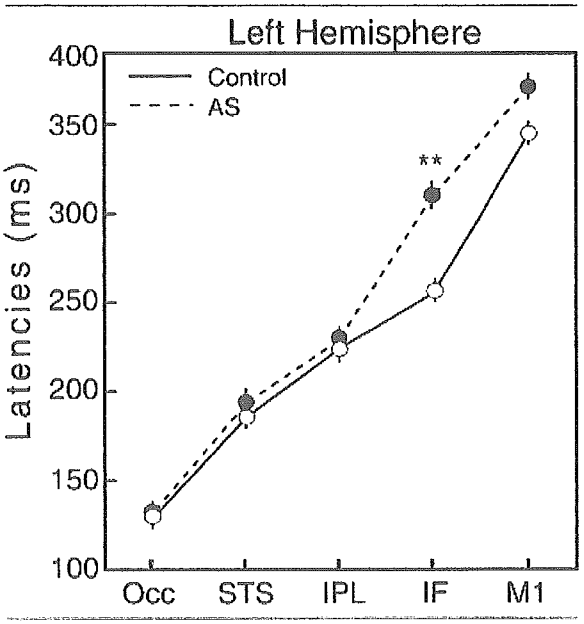

*Fig 3. Peak latencies (mean ± SEM) at the left hemisphere Occ, STS, IPL, IF, and M1 regions across all subjects. **p < 0.01. AS = Asperger's syndrome; Occ = occipital; STS = superior temporal sulcus; IPL = inferior parietal lobule; IF = inferior frontal, M1 = primary motor cortex.*

Table. Source Locations of Main MEG Response Peaks in Talairach Coordinates (mean ± SEM)

	Left Hemisphere					Right Hemisphere				
Subjects	*x*	*y*	*z*	BA	N	*x*	*y*	*z*	BA	N
AS subjects (N = 8)										
Occipital	−18 ± 6	−84 ± 4	15 ± 4	18	8	21 ± 6	−83 ± 5	12 ± 4	18	8
Superior temporal	−56 ± 4	−39 ± 8	5 ± 2	22	8	50 ± 2	−40 ± 7	6 ± 2	22	6
Inferior parietal	−48 ± 4	−50 ± 6	36 ± 5	40	8	40 ± 6	−53 ± 5	41 ± 5	40	7
Inferior frontal	−46 ± 2	18 ± 5	9 ± 3	44/45	6	47 ± 3	18 ± 2	5 ± 3	44/45	3
Primary motor	−47 ± 5	−15 ± 4	36 ± 6	4	8	46 ± 2	−21 ± 4	34 ± 5	4	6
Control subjects (N = 10)										
Occipital	−16 ± 3	−89 ± 4	16 ± 5	18	10	15 ± 5	−88 ± 4	16 ± 5	18	10
Superior temporal	−55 ± 4	−47 ± 5	10 ± 4	22	10	52 ± 6	−47 ± 5	12 ± 3	22	8
Inferior parietal	−44 ± 7	−51 ± 4	39 ± 3	40	8	46 ± 5	−51 ± 3	40 ± 4	40	7
Inferior frontal	−46 ± 6	19 ± 3	14 ± 4	44/45	9	47 ± 4	19 ± 4	13 ± 5	44/45	10
Primary motor	−55 ± 5	−13 ± 4	38 ± 3	4	9	53 ± 2	−15 ± 2	36 ± 4	4	10

Coordinates *x* (left-to-right), *y* (posterior-to-anterior), *z* (inferior-to-superior) are in millimeters from origin situated at the anterior commissure.
BA = Brodmann's area.

than control subjects. The median values were 50% smaller ($p < 0.05$) in the left IF, 75% smaller ($p < 0.01$) in the right IF, 57% smaller ($p < 0.01$) in the left MI, and 50% ($p < 0.05$) smaller in the right M1.

Plotting the individual source strengths as a function of response latency in Figure 4 indicates separate clusters for the two groups. The median values of the source strengths per latency (unit nanoampere · meter/msec) differed between the groups at both areas ($p < 0.01$ on the left, $p < 0.02$ on the right).

Discussion

Our results demonstrate slight, but statistically significant, abnormalities in the cortical activation chain of AS subjects while they imitate orofacial gestures presented as still pictures. The activations were normal in strength and timing at the early steps of the sequence, that is, in occipital, STS, and IPL regions. Normal STS activation speaks against any significant deficit of high-level visual analysis in the AS group; because STS has an important role in processing of social visual cues and of biological motion.[16,17]

The main abnormality was observed in the Broca's area, on the left, and in its counterpart in the right hemisphere. These IF activations were spatially more scattered in AS than control subjects, and the signals were delayed and reduced in strength; moreover, activation was less frequently seen in the right than the left IF region.

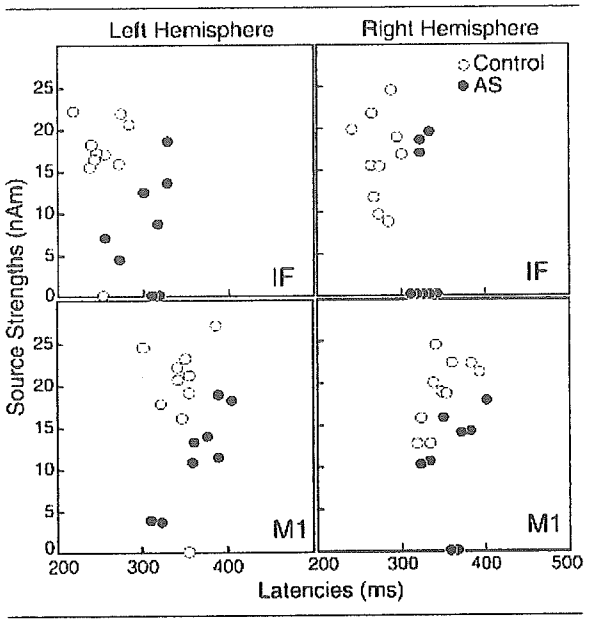

Fig 4. The relationship between the source strength and latency at the IF and M1 areas of both hemispheres for all subjects. In case of an absent source, the source with strength of OnAm was plotted on the median value of the latency of each group. Occ = occipital; STS = superior temporal sulcus; IPL = inferior parietal lobule; IF = inferior frontal, M1 = primary motor cortex.

Because AS subjects have normal language development, it is unlikely that the abnormal IF activation would reflect language-related dysfunction of the Broca's region; more plausible connections would be related to deficits in imitation.[18,19] The prolonged duration of the mouth EMG in AS subjects agrees with this interpretation. Note that the EMG onset latencies did not differ between the groups and that the MEG response latencies were similar at the initial stages of the activation chain (occipital cortex, STS, and IPL). Thus, it is unlikely that the IF and M1 abnormalities could be explained by some general behavioral differences between the groups.

F5 mirror neurons have been suggested to form an important interface between forward and inverse models of motor control;[20] the inverse models match the intended actions/goals and the motor commands, whereas the forward models predict the sensory outcome of the motor act.[21] Our data do not allow differentiation between an abnormality in the IPL–IF connection and an intrinsic IF disorder. The latter is supported by anatomical data that demonstrate a reversed asymmetry of the IF region in autistic subjects, with 27% larger IF area on the right in contrast with the 17% larger IF area on the left in healthy subjects.[22] However, similar data are not available for AS subjects who are more verbal than deeply autistic subjects.

Several authors have proposed that imitation is based on mirror neurons or on the mirror-neuron system that links action recognition and execution and possibly also is involved in action understanding.[1,23,24] A more sophisticated understanding of other minds ("theory-of-mind") is considered to rely on orbitofrontal and anterior medial frontal (AMF) areas.[25,26] Autistic subjects have reduced volume of the right AMF and significantly decreased AMF metabolism during theory-of-mind tasks.[27–29] Future studies should unravel the modulatory influences from the prefrontal theory-of-mind regions on MNS circuitries.

These results of AS subjects suggest a right-hemisphere dominant dysfunction of the IF and M1 parts of their MNS. Interestingly, patients with right frontotemporal lesions are deficient in tasks requiring attribution of mental states,[30] and deficits of social communication and social intelligence in AS subjects have been attributed to right-hemisphere dysfunction.[31] The human IF is connected to the orbitofrontal cortex via corticocortical pathways. Especially interesting in the present context are reciprocal connections between IF, orbitofrontal cortex, and AMF via the basal ganglia[32–34]; these circuits are involved in mediating behavioral plans and action sequences.[35]

In conclusion, our results imply abnormal imitation-related cortical activation sequences in the frontal or

parietofrontal circuitries of AS subjects, suggesting that MNS dysfunction can account for a part of their imitation and social impairments.

This study was supported by the Academy of Finland (R.H.), the Human Frontier Science Program Organization Grant (RG 39-98, P.I.V.G.), the Sigrid Jusélius Foundation (R.H.), and Grants for Comprehensive Research on Aging and Health (H15-22) from the Japanese Ministry of Health Labour and Welfare (N.N.), and a Grant-in-Aid for Scientific Research (B) (15300111, N.N.) from the Japan Society for the Promotion of Science.

MRIs were acquired at the Department of Radiology of the Helsinki University Central Hospital, Finland. We thank M. Illman for assistance in the measurements.

References

1. Rizzolatti G, Fogasi L, Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci 2001;2:661–670.
2. Passingham R. The frontal lobe and voluntary action. Oxford: Oxford University Press, 1993.
3. Petrides M, Pandya DN. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller F; Grafman J, eds. Handbooks of neuropsychology. Vol 11. Amsterdam: Elsevier Science, 1994:17–58.
4. Hari R, Forss N, Avikainen S, et al. Activation of human primary motor cortex during action observation: a neuromagnetic study. Proc Natl Acad Sci USA 1998;95:15061–15065.
5. Hari R, Levänen S, Raij T. Timing of human cortical functions during cognition: role of MEG. Trends Cogn Sci 2000;4: 455–462.
6. Nishitani N, Hari R. Temporal dynamics of cortical representation for action. Proc Natl Acad Sci USA 2000;97:913–918.
7. Nishitani N, Hari R. Viewing lip forms: cortical dynamics. Neuron 2002;36:1211–1220.
8. Rizzolatti G, Fadiga L, Gallese V, et al. Premotor cortex and the recognition of motor actions. Cogn Brain Res 1996;3: 131–141.
9. Rogers SJ, Pennington BF. A theoretical approach to the deficits in infantile autism. Dev Psychopathol 1991;3:137–162.
10. Avikainen S, Kulomäki T, Hari R. Normal movement reading in Asperger subjects. Neuroreport 1999;10:3467–3470.
11. Gallese V, Goldman A. Mirror neurons and the simulation theory of mind-reading. Trends Cogn Sci 1998;2:493–501.
12. Williams JHG, Whiten A, Suddendorf T, et al. Imitation, mirror neurons and autism. Neurosci Biobehav Rev 2001;25: 287–295.
13. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnosis Criteria for Research. Geneva: World Health Organization, 1993.
14. Hämäläinen M, Hari R, Ilmoniemi R, et al. Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. Reviews Modern Physics 1993;65:413–497.
15. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart: Thieme, 1988.
16. Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. Trends Cogn Sci 2000;4:267–278.
17. Blakemore S-J, Decety J. From the perception of action to the understanding of intention. Nat Rev Neurosci 2001;2: 561–567.
18. Avikainen S, Wohlschläger A, Liuhanen S, et al. Impaired mirror-image imitation in Asperger and high-functioning autistic subjects. Curr Biol 2003;13:339–341.
19. Smith IM, Bryson SE. Imitation and action in autism: a critical review. Psychol Bull 1994;116:259–273.
20. Carr L, Iacoboni M, Dubeau MC, et al. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci USA 2003;100:5497–5502.
21. Miall RC. Connecting mirror neurons and forward models. Neuroreport 2003;14:2135–2137.
22. Herbert MR, Harris GJ, Adrien KT, et al. Abnormal asymmetry in language association cortex in autism. Ann Neurol 2002; 52:588–596.
23. Hari R, Nishitani N. From viewing of movements to imitation and understanding of other persons' acts: MEG studies of the human mirror-neuron system. In: Kanwisher N, Duncan J, eds. Attention and performance. Oxford: Oxford University Press, 2004.
24. Wohlschläger A, Bekkering H. Is human imitation based on a mirror-neuron system? Some behavioral evidence. Exp Brain Res 2002;143:335–341.
25. Baron-Cohen S, Ring H. A model of the mindreading system: neuropsychological and neurobiological perspectives. In: Origins of an understanding mind. Mitchell P, Lewis C, eds. Mahwah, NJ; Erlbaum, 1994:183–207.
26. Gallagher LH, Frith CD. Functional imaging of "theory of mind." Trends Cogn Sci 2003;7:77–83.
27. Castelli F, Frith C, Happé F, et al. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain 2002;125:1839–1849.
28. Happé F, Ehlers S, Fletcher P, et al. Theory of mind in the brain: evidence form a PET scan study of Asperger syndrome. Neuroreport 1996;8:197–201.
29. Haznedar MM, Buchsbaum MS, Wei T-C, et al. Limbic circuity in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am J Psychiatry 2000;157:1994–2001.
30. Happé F, Brownell H, Winner E. Acquired "theory of mind" impairments following stroke. Cognition 1999;70:211–240.
31. Ellis H, Gunter HL. Asperger syndrome: a simple matter of white matter? Trends Cogn Sci 1999;3:192–200.
32. Cavada C, Company T, Tejedor J, et al. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 2000;10:220–242.
33. Haber SN, Kunishio K, Mizobuchi M, et al. The orbital and medial prefrontal circuit through the primate basal ganglia. J Neurosci 1995;15:4851–4867.
34. Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci 2001;16:291–310.
35. Koechlin E, Danek A, Burnod Y, et al. Medial prefrontal and subcortical mechanisms underlying the acquisition of motor and cognitive action sequences in humans. Neuron 2002;35: 371–381.

Broca's Region: From Action to Language

Broca's region, classically considered a motor speech-production area, is involved in action understanding and imitation. It also seems to help in sequencing of actions. Broca's region might have evolved for interindividual communication, both by gestures and speech.

Nobuyuki Nishitani,[1] Martin Schürmann,[2] Katrin Amunts,[3] and Riitta Hari[2,4]

[1]Cognitive Functions Section, Department of Rehabilitation for Sensory Functions, Research Institute, National Rehabilitation Centre for Persons with Disabilities, Tokorozawa, Japan; [2]Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Espoo, Finland; [3]Institute of Medicine, Forschungszentrum Jülich, Jülich, Germany; and [4]Department of Clinical Neurophysiology, University of Helsinki, Helsinki, Finland; hari@neuro.hut.fi

In his now classic report from 1861, Pierre Paul Broca described a man who was unable to speak although his tongue and lip movements were not impaired. The man, later called "Monsieur Tan," was able to say only "tan" and utter a swear word. He had paralysis on his right side but seemed to be intelligent and not impaired in other aspects. On autopsy, a fluid-filled cavity was found in his left frontal lobe, just anterior to the motor cortex of mouth and tongue (36). Lesions to what is nowadays called Broca's region lead to nonfluent, sparse, dysprosodic, and agrammatical speech (19). This deficit contrasts the "sensory" aphasia caused by damage to the left parietotemporal (Wernicke's) region.

In contrast to the early concept of Broca's region as an exclusive speech-production area, today's view comprises much wider language-related functions (14) as well as other communication-related functions. Recent studies have shown that Broca's region contains representations of hand actions and orofacial gestures. In this brief review, we will focus on the motor functions of Broca's region. We start by describing the anatomy and connections of Broca's region, and then we discuss the role of this brain area in action execution, observation, and understanding and the relationship of these functions to imitation. Finally, we will speculate about why Broca's region is involved in so many apparently different functions.

Structure and Connectivity of Broca's Region

Anatomy and histology

Broca's region and its right-hemisphere homolog (FIGURE 1) include Brodmann's cytoarchitectonic areas (BA) 44 and 45; they occupy the pars opercularis and pars triangularis of the inferior frontal gyrus (IFG) in the dominant hemisphere

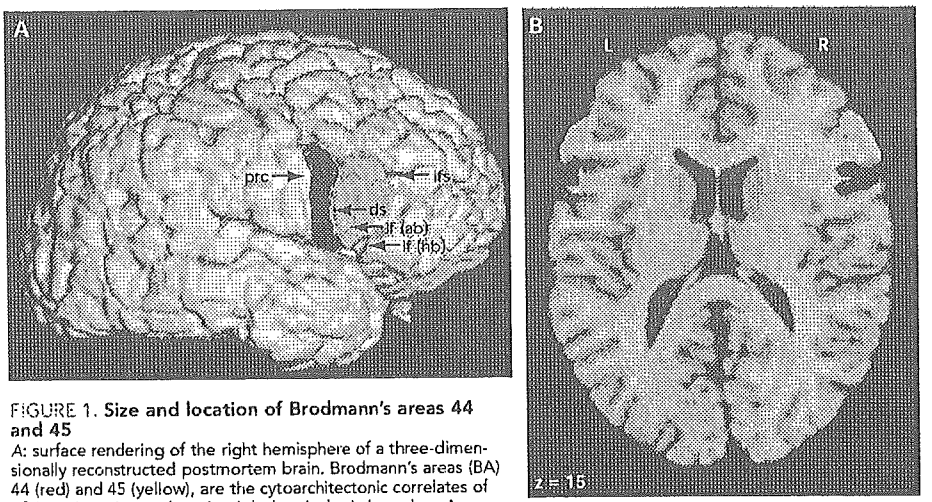

FIGURE 1. **Size and location of Brodmann's areas 44 and 45**

A: surface rendering of the right hemisphere of a three-dimensionally reconstructed postmortem brain. Brodmann's areas (BA) 44 (red) and 45 (yellow), are the cytoarchitectonic correlates of of Broca's region and are its right-hemispheric homolog. Areas of both hemispheres were delineated in histological sections of a total of 10 brains and were superimposed on a lateral view of the right hemisphere, where the sulcal pattern is more "typical" than in the left hemisphere (2, 4). B: 50% probabilistic maps of BA 44 (red) and 45 (yellow) after warping of the 10 magnetic resonance images of the postmortem brains and their cytoarchitectonic areas to the "MNI reference brain" (http://www.fz-juelich.de/ime/ime_start, http://www.bic.mni.mcgill.ca/). The maps show only those voxels of the reference space that overlapped in 5 or more out of 10 brains. prc, Precentral sulcus; ifs, inferior frontal sulcus; ds, diagonal sulcus; lf, lateral fissure; ab, ascending branch of the lf; hb, horizontal branch of the lf.

1548-9213/05 8.00 ©2005 Int. Union Physiol. Sci./Am. Physiol. Soc.

(the left in 95% of the population). The widely used Brodmann map (16) represents a simplified drawing of only one typical brain, and later histological studies have indicated considerable individual variation in the size and extent of areas 44 and 45 with respect to the individual sulcal topography; for example, area 44 volume may differ across individuals even by a factor of ten (2, 4). Broca's region matures later than, for example, the primary sensorimotor cortices, as is evident from both the histological fine structure (3) and from cortical thickness maps based on magnetic resonance imaging (37).

Although areas 44 and 45 differ in their cytoarchitecture (2), they share, for example, the presence of very large pyramidal cells in deep layer III and in layer V, the lack of a clear border between layers II and III, and the low cell density in layer VI (2). However, whereas area 44 is "dysgranular" (containing a thin layer IV of small granular cells with pyramidal cells from deep layer III and upper layer V intermingled with those of layer IV), area 45 has densely packed granular cells in layer IV ("granular" area) (2, 4, 65). Although Rizzolatti and Arbib (82) consider area 44 analogous to monkey area F5, the homology between the human area 44 and the monkey F5 has not yet been demonstrated in a strict sense.

Hemispheric asymmetry

Areas 44 and 45 can be found in both hemispheres, but nearly all patients with Broca's aphasia have lesions in the left inferior frontal cortex. This clinical observation raises the question of whether and how far Broca's region and its right-hemispheric counterpart differ anatomically and functionally.

Anatomic asymmetry. The volume of the histologically defined area 44 is larger in the left than in the right hemisphere, whereas area 45 is more symmetric (2, 30). Moreover, the cytoarchitecture of both areas shows significant interhemispheric differences (5).

In great apes, the inferior frontal region corresponding to human Broca's region is larger in the left than in the right hemisphere (18), suggesting that the neuroanatomic substrates for left-hemisphere dominance in vocalization developed as early as five million years ago, long before speech emerged. It has been suggested that vocalizations were gradually incorporated into the gestural system, and in the subsequent switch from manual gesture to vocal language the left hemisphere could have taken dominance for both speech and manual action (21).

Functional asymmetry. The dominance of the left-hemispheric area 44/45 in language-related functions is well established (14). It is far less clear whether area 44/45 is asymmetric in other communication-related functions (to be reviewed in the sections below). For example, the right IFG is activated during voluntary inhibition of imitative and overlearned responses (15) as well as during perceptual sequencing tasks (97). The right IFG is also activated when people try to make sense of ambiguous emotional expression in face images but not when they view and judge pictures of ambiguous gender (73, 78). Both left and right IFG are activated during detection of errors in musical syntax (63). Furthermore, both left and right IFG are essential for imitation (44). Finally, data on imagery of movement suggest a left-hemispheric dominance of area 44 for egocentric movements but a right-hemispheric dominance of the same area for movement characteristics in space (11). A systematic review of functional asymmetry is beyond the scope of this article. Below, findings about "Broca's region" refer to the left hemisphere, and activation of the right-hemisphere counterpart will be mentioned separately, when needed. "Area 44/45" will refer to either hemisphere.

Connections of Broca's region

The available data on brain connectivity derive mainly from tracing and electrophysiological experiments in monkeys, from which they have been extrapolated to the human brain. Some recent studies have applied diffusion tensor imaging to directly analyze connectivity in the living human brain. The major inputs and outputs of areas 44 and 45 differ to some extent, emphasizing the different functional roles of these two areas.

According to data from monkey F5, the human IFG (bilaterally) is likely to be connected to the anterior intraparietal cortex, the superior temporal sulcus (STS), the parietal cortex (area PF in monkeys), the cerebellum, and Wernicke's area (reviewed in Ref. 6). In contrast to many other brain functions, conclusions based on primate research must be considered with particular caution when the anatomy and physiology of language processing are concerned. Electrophysiological experiments in primates have implicated both a dorsal and a ventral pathway connecting Wernicke's area to Broca's region (54, 89). Such connections in the human brain have recently been confirmed by using diffusion tensor imaging and tractography (80). A dorsal pathway, including the arcuate fasciculus, was distinguished from a more ventral route, including the external capsule and the uncinate fasciculus. Interestingly, the connections were stronger in the dominant than in the nondominant hemisphere. Although studies on tractography in the human brain do not demonstrate the existence of anatomic, synaptic connectivity, they are indica-

tors of the existence of anatomic pathways between brain areas. The functional connectivity of Broca's region, evident, for example, in covariance analysis of functional magnetic resonance imaging (fMRI), is task specific and much more widely spread than the anatomic connectivity would predict (42). Of course, covarying activation does not necessarily imply a network of directly connected nodes.

Broca's Region with a Mosaic of Functions

Below we briefly discuss various functions that have been ascribed to Broca's region and/or its right-hemisphere counterpart. It should be noted, however, that activation of any area in a brain imaging study does not mean that the neural substrate of the mentioned functions is seated (only) there; rather, it indicates that the activated area is involved in, or may be an important node in, a widely distributed neuronal network. It is most likely that Broca's region consists of partly overlapping subsystems that support various functions, ranging from motor imagery (11, 35) to object manipulation and grasping (13), to motor preparation (59, 90), and to planning (25).

We will proceed from the classical functions of Broca's region in speech production and language to more basic functions in perceptual sequencing, action understanding, and imitation.

Language and speech

In her extensive review of fMRI studies of language areas, Bookheimer (14) showed that areas 44 and 45 subserve different functions. The IFG is often activated bilaterally but shows left-hemispheric dominance during tasks requiring naming (91), judgments of phonology (43, 100), semantics (4, 29, 101), and syntax (9, 28, 29, 43). Broca's region is also activated during acquisition of grammatical rules, discrimination of speech sounds, production of words, estimation of time intervals, and reproduction of rhythms (14). Thus Broca's region seems to be involved in both perception and production of speech. We will claim below that this role of Broca's region as an interface of action and perception can be generalized to nonverbal functions.

Language production and understanding also involve prosody, one of the few language-related processes with right-hemisphere dominance (68, 70). The interaction of the two hemispheres, however, seems to be more complex than has been assumed previously. Integrating evidence from neuroimaging, psycholinguistics, neurology, and neurophysiology, Friederici and Alter (27) proposed that segmental, lexical, and syntactic information is processed in different frontotemporal networks in the left hemisphere (including the temporo-parieto-occipital junction, parts of the IFG, and the superior temporal lobe). In contrast, the processing of intonation would be supported by a temporofrontal circuit in the right hemisphere, consisting mainly of the frontal operculum and regions in the superior temporal gyrus. The strict right-hemispheric lateralization of the processing of intonational information can be modulated by stimulus or task demands via the corpus callosum. It was suggested that single regions within the described networks obtain their specific role for the processing of particular aspects of language via interaction with other areas.

Perception-action link for communication: mirror neurons

Communication, both verbal and nonverbal, requires that the interacting individuals "stay tuned." Because the conspecifics certainly are very similar in their main characteristics, it is then also mandatory that each subject's action and perception rely on closely linked neuronal circuitries---one individual's output is the other (similar) individual's input.

Interesting "mirror neurons" were discovered some years ago in frontal area F5 of the monkey cortex. These neurons are active during execution of object-related hand actions, but they are also active, importantly, when the monkey is just observing similar acts (23, 31, 84–86). For example, the mirror neurons are activated when the monkey takes a raisin from a tray and also when he views another monkey or the human experimenter doing the same. No information is yet available about possible hemispheric lateralization of the monkey mirror neurons.

Mirror neurons have visuomotor properties, being sensitive to goal-related motor acts (102), but they can also be activated by sounds that imply actions (55, 57). Importantly, the mirror neurons do not only react to visual input and then project, via some transformational step, to motor-output-related neurons but are also part of a system that forms a neuronal representation of the observed motor acts. Similar to F5, the rostral part of the inferior parietal cortex contains neurons that are active during action observation and execution (32); this region receives input from the STS, which is known to contain neurons responding to biological motion (for review, see Ref. 1).

In search of a human mirror-neuron system (MNS), human counterparts of the monkey mirror neurons were first looked for with PET, which follows oxygen consumption in the brain (40, 59, 86). Broca's region was activated when the subject observed, imagined, and imitated the examiner

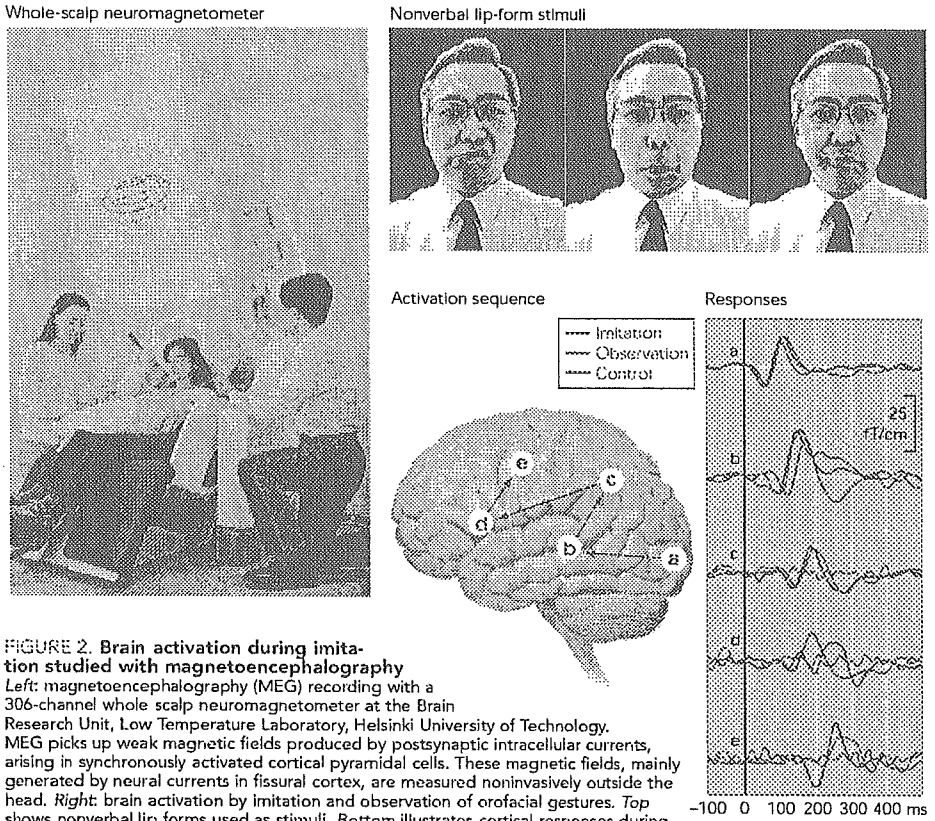

FIGURE 2. **Brain activation during imitation studied with magnetoencephalography**
Left: magnetoencephalography (MEG) recording with a 306-channel whole scalp neuromagnetometer at the Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology. MEG picks up weak magnetic fields produced by postsynaptic intracellular currents, arising in synchronously activated cortical pyramidal cells. These magnetic fields, mainly generated by neural currents in fissural cortex, are measured noninvasively outside the head. *Right*: brain activation by imitation and observation of orofacial gestures. *Top* shows nonverbal lip forms used as stimuli. *Bottom* illustrates cortical responses during imitation (red) and observation (green) of nonverbal orofacial gestures. The responses recorded from 5 locations are indicated, and the cortical activation, shown on the schematic brain, progresses from the occipital visual area to the superior temporal sulcus, to the inferior parietal areas, then to Broca's region in the inferior frontal cortex, and finally to the primary motor cortex. Similar activation areas and temporal sequences were seen also in the right hemisphere. The blue traces refer to control stimuli (landscapes that activated only the two first steps). Modified from Ref. 77.

using a precision grasp to enclose an object or to move his/her hand. Thus Broca's region could contain neurons similar to the monkey mirror neurons. The activation sequence associated with online imitation and with observation of another person's movements also included the STS (76, 88).

The monkey F5 mirror neurons are also activated by orofacial gestures, and therefore a recent magnetoencephalography (MEG) study (77) applied still pictures of verbal and nonverbal lip forms that the subject had to observe, imitate, or make in a self-paced manner (FIGURE 2). In all conditions and in both hemispheres, the activation spread from occipital cortex (peak activation 120 ms after the picture onset) in 20- to 60-ms steps to the STS (the strongest activation), the inferior parietal lobule, the inferior frontal lobe (Broca's region), and, 80–100 ms later, to the primary motor cortex. Because the STS is not activated when the subject makes movements his- or herself, it can be considered only as influencing the (motor) MNS.

Assuming that the observed MNS activation sequence would be related to the link between a sender and a receiver of an action-related message, some abnormalities could be expected in subjects who have abnormal imitation skills and difficulties in understanding motor-act-based intentions of other subjects. Such deficits are observed in high-functioning autistic (Asperger syndrome) subjects, who in fact displayed delayed and diminished activation in Broca's region (75) during imitation (FIGURE 3). Moreover, activation was in many subjects absent in the right hemisphere.

Within the MNS, the close link between perception and action seems to be realized in functions of Broca's region. Such a link may well be important in facilitating communication between an agent and an observer due to shared sensory and motor representations. Along similar lines, Liberman and Mattingly (62) strongly advocated a motor theory of

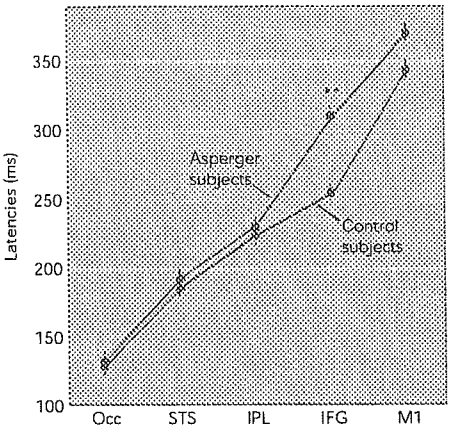

FIGURE 3. **Mean peak latencies in the left hemisphere of control subjects and Asperger subjects during imitation of lip forms**
There were no significant differences in the duration of the whole activation sequence from the occipital area (Occ) via superior temporal sulcus (STS) to the primary motor cortex (M1) between both groups. The activation interval from the inferior parietal lobule (IPL) to Broca's region (inferior frontal gyrus; IFG) was statistically significantly longer for Asperger subjects than for control subjects; the statistically significant difference is marked with asterisks. Modified from Ref. 75.

speech, meaning that the listener perceives the speech sounds in terms of how they are articulated rather than in terms of their acoustic characteristics.

In line with left-hemisphere control for speech, orofacial gestures show a right hemimouth dominance in babies during babbling, as opposed to smiling (45). Corresponding results have been observed in humans (McGurk effect attenuated when the speaker's right hemimouth is covered; Ref. 74) and in marmosets (right hemimouth dominance for social contact calls as opposed to expressions of negative emotion; Ref. 46).

An action-perception link seems especially important during language acquisition: when the child listens to a new word, s/he automatically tries to imitate it, thereby forming a close temporal link between sensing (hearing) and acting (articulating). Language acquisition through imitation of speech sounds could well be supported by the acoustic mirror neurons in F5/Broca's region (57, 83). The close connection between speech perception and imitation/production becomes manifest also in adults when they modify their accent and syntax according to the speaker with whom they are interacting.

In a combined transcranial magnetic stimulation (TMS) and PET study, auditory speech activated the left IFG, suggesting that this area primes the motor system to respond to heard speech (103), one more hint for a role of Broca's area as an interface between perception and action.

A role of area 44/45 as an interface between perception and action is also suggested by the inhibitory influence of right IFG on certain imitative and overlearned responses (Ref. 15; see Ref. 7 for more general inhibitory functions of right IFG).

To sum up, mirror neurons, as important parts of larger neuronal circuitries, can be considered to transfer action-related information (be it visual or auditory) to knowledge (83). The available information is in line with the view that the MNS supports communicative functions. STS and inferior parietal cortex provide essential input to F5/Broca's region, where the communicative functions of the MNS become manifest.

Action understanding

Rizzolatti and co-workers (83, 87, 88) consider Broca's region essential for action understanding. Support for such an idea comes from studies in which monkey F5 neurons also react when the end part of the movement is obscured when the monkey only knows what is going to happen (102). Furthermore, a part of the F5 mirror neurons are also activated by sounds that are related to actual motor acts and the monkey understands this relationship (57).

Observation of different types of mouth actions activates several brain areas, including the pars opercularis of the IFG and the adjacent ventral premotor cortex, with different patterns and likely via different mechanisms influenced by knowledge of the observed action (12, 17). Interestingly, Broca's region was not activated when the human subjects watched a dog barking, i.e., an action that is not in the observer's motor repertoire (17). In addition to Broca's region and premotor cortex, the primary motor cortex also shows differential activation dependent on action understanding: MEG results about the motor-cortex part of the human MNS suggest that the motor cortex differentiates natural and artificially presented movements (52). Moreover, a recent study of observation of chopstick use demonstrated that the motor cortex is activated more strongly the more often the (Finnish) subjects had used chopsticks during the last year. In other words, a dependence on experience was demonstrated in the motor-cortex part of the MNS (53).

Humans most likely understand another person's actions, and also their motor-act-based intentions, by mapping observed actions, postures, and gaze onto their own motor representations of similar actions. The observed motor sequence may evoke memories and experiences of motor patterns performed earlier. If the observed motor sequence contains recognizable parts that already are included in the observer's own motor vocabulary, it is far

easier to both understand and imitate the new sequence.

Imitation

As a part of the human MNS, Broca's region seems to have an important role in imitation, a capability different from direct copying of the action without understanding its goal. "True" imitation relies on perception-action coupling and allows the imitator to perform totally new motor actions, thereby forming the basis for skill learning (67). In true imitation, the observed motor patterns are directly matched on the observer's own internal motor representations; this is a fundamentally different mechanism from detailed visual analysis, followed by matching of the visual and motor reference frames.

The role of Broca's region in imitation is still under debate; a recent study claimed that most of the previous studies have had too little variability in the imitated actions so that the imitator could have just kept in mind the limited set of movement patterns, repeating them as well as if they were coded with numbers (64). Another possible contaminating factor in studies reporting activation in Broca's region could be covert verbalization ("internal speech") during the motor acts.

In an fMRI study, imitation of action strongly involved the left IFG (49). Imitation of goal-directed actions (as compared with non-goal-directed actions) led to more intense activation of the bilateral IFG (58). In an extensive analysis of seven fMRI studies, Molnar-Szakacs et al. (71) concluded that Broca's region is functionally parcellated so that imitation-related activation occurs at the dorsal and ventral part of the pars opercularis, whereas the pars triangularis is activated only during observation and not during imitation. Accordingly, MEG recordings showed stronger responses of Broca's region (and of the primary motor cortex) during imitation than action observation or execution (75–77); the reason may be either facilitation/enhancement of responses by imitation or the coactivation and summing-up of two different neuronal populations.

As further support for the importance of the IFG in imitation, fMRI activation was stronger during imitation than during simple observation of facial expressions in the IFG, the superior temporal cortex, insula, and amygdala (20), and imitation—but not execution—of finger movements was impaired during repetitive TMS applied over the left and right pars opercularis (44).

Some action patterns are highly contagious. For example, watching another person yawn may trigger the viewer to do the same. In an fMRI study in which subjects watched videotaped yawns vs. nonnameable, nonyawn facial gestures, no yawn-specific activation was observed in Broca's region (98). Thus activation associated with yawn contagiousness seems not to rely on essential parts of the MNS, in line with the nature of contagious yawns as automatically released behavioral acts rather than a truly imitated motor pattern that would require detailed action understanding.

Proponents of the ideomotor theory have noted, as early as the 19th century, that an idea leads to an action, unless it is actively suppressed. Although some of us can view a cold beer on the table without drinking it, patients with frontal lobe lesions may display echoing behavior so that perception leads to an automatic response (61). In healthy subjects, some spinal mechanisms are inhibited at the same time as facilitation occurs at the cortical level (8).

Forward and inverse models

Planning an action, for example reaching for an object, includes expectation of the sensory consequences. "Forward models," considered to underlie such predictions, are thought to involve efference copies that inform the sensory brain areas about the forthcoming sensory input, which then would be compared with the predictions. For example, utterances deviating infrequently from the frequently produced vowels do not elicit change-related responses in the human auditory cortex although the same sounds presented externally (from tape) do so (22). "Inverse models," on the other hand, refer to (e.g., visual) feedback from movements that are needed to reach the object.

Broca's region has been suggested as an interface between inverse and forward models (48), coding the goal of an action (in the dorsal part) and also sending efference copies to the STS (in the ventral part). Specifically, Broca's region would receive visual input from the STS via the parietal cortex and would process it into action plans. A competing hypothesis stresses the role of the posterior parietal cortex as the interface between inverse and forward models (69). The forward and inverse models are useful in conceptualizing sequences of brain activation during online imitation of another person's actions.

It is interesting that the inverse and forward models propose activation sequences very similar to those that have already been demonstrated (for the inverse model case) with MEG; for example, FIGURE 2 pinpointed dynamic activation from the STS to inferior parietal cortex, Broca's region, and finally to the primary motor cortex (77).

Motor and perceptual sequencing

Parsing is essential for understanding any observed actions and for their consequent imitation. Think

for example how while learning a new language we first face great difficulties in segmenting the message into single words. Broca's region could have a role in action segmentation (on the sensory side) and in action sequencing (on the motor side). In support of such a role in representing sequential information, Broca's region is activated during auditory and visual rhythm-monitoring tasks (93) and during attention to timing and speed of moving objects, as opposed to attention to properties of the objects (94–96). Interestingly, IFG is activated by sequences of biological stimuli (such as goal-directed motion) but not during completion of geometric figure sequences (97). Deviation from an expected sequence may explain why Broca's region and its right-hemisphere counterpart are activated when musical syntax is violated (63).

Brain-damage data suggest that hemispheres might have different roles in sequencing: Left-hemisphere lesions preferably affect verbal sequencing, and right-hemisphere lesions affect nonverbal sequencing (14, 56).

Hand gestures and their relation to speech

Speech production and speech-related gestures are connected to such a degree that they have been considered as outlets of the same thought process (39), a view supported by the finding that hand and orofacial gestures are supported by the speech production area, i.e., Broca's region.

Speech-related gestures may occur even when the speaker-gesturer knows that others cannot see the gestures, e.g., during a phone call. Similarly, congenitally blind persons may also gesture when speaking with other blind people (38, 50). The close connections between speech production and hand gestures are also supported by studies of hearing babies born to deaf parents: the infants' hand actions display a similar rhythm to babbling (81). In stutterers, speech-related hand gestures freeze at the same time as the speech is disturbed; however, non-speech-related hand movements can continue normally (66). Along similar lines, observation of grasping movements can influence the observer's simultaneous mouth movements and syllable pronunciation (33, 34).

All of these findings suggest an intimate connection between speech-related hand and face gestures and the production of speech. The corepresentation of speech and gestures in Broca's region could reflect shared evolutionary roots. Accordingly, Rizzolatti and Arbib (82) suggested that hand and orofacial gestures—rather than primate vocalizations—are the precursors of human language; their proposal links earlier gestural theories to recent neurophysiological results about the MNS. The close connection between gestures and speech/language is also evident from the spontaneous emergence of sign languages in isolated societies of deaf persons (99) and of the brain-imaging findings that sign language activates very similar brain regions to those activated by speech (47, 60). Interestingly, Horwitz et al. (47) showed an extensive involvement of area 45 in spoken and signed language, suggesting representation of modality-independent aspects of language generation in the inferior frontal cortex.

Broca's Region: Conclusions and Speculations

Broca's region encompassing Brodmann's cytoarchitectonic areas 44 and 45 in the left hemisphere, with representations of face, head, and hands—but not of foot—may have evolved into a special communication area relying on orofacial gestures and hand movements. That function requires representation and segmentation of rapidly changing motor and sensory patterns and a close matching of these two to form an action-perception interface.

Far beyond its classical language functions, Broca's region contributes to action planning, action observation, action understanding, and imitation. Speech production and comprehension can be considered a highly developed form of action execution/observation matching (see also the motor theory of speech; Ref. 62). The new concepts of "motor cognition" (51) and "sequential cognition" (24) may be useful as first approximations of the wide range of functions subserved by Broca's region.

The role of Broca's region in action understanding, derived from findings of mirror-neuron research, is also supported by the following observations:

1) when subjects view and listen to speaking faces, activation of Broca's region is stronger during incongruent than during congruent audiovisual stimuli (79);

2) when dyslexic subjects passively view words, they show stronger Broca's region activation than do normal-reading subjects (92); and

3) when patients with cochlear prosthesis listen to their native language, they show stronger Broca's region activation than do normal-hearing subjects (72).

In all of these conditions, Broca's region seems to be more strongly activated when the task requires much effort for understanding the sensory message.

As a likely interface for sensory and motor sequencing, Broca's region is in a good position to

support action understanding in general. True imitation can follow only when the action is first parsed and understood. Strong effort for action understanding also recruits top-down influences based on the subject's previous experience, and thus predictive behavior can result (26).

The studies reviewed here converge on a central role of Broca's region as an orchestrator of time-sensitive perceptual and motor functions underlying verbal and nonverbal communication. However, several questions still remain open, such as whether and how specific language functions (e.g., those related to syntax; cf. Refs. 10 and 41) have common evolutionary roots with the perceptual and motor functions supported by Broca's region and to what extent their neuronal correlates overlap. Once the basic functions and neuronal substrates are identified, information is also needed about temporal activation sequences and connectivity to fully unravel the multitude of brain functions to which Broca's region contributes. ❀

References

1. Allison T, Puce A, and McCarthy G. Social perception from visual cues: role of the STS region. *Trends Cogn Sci* 4: 267–278, 2000.
2. Amunts K, Schleicher A, Bürgel U, Mohlberg H, Uylings HB, and Zilles K. Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* 412: 319–341, 1999.
3. Amunts K, Schleicher A, Ditterich A, and Zilles K. Broca's region: cytoarchitectonic asymmetry and developmental changes. *J Comp Neurol* 465: 72–89, 2003.
4. Amunts K, Weiss PH, Mohlberg H, Pieperhoff P, Eickhoff S, Gurd JM, Marshall JC, Shah NJ, Fink GR, and Zilles K. Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—the roles of Brodmann areas 44 and 45. *Neuroimage* 22: 42–56, 2004.
5. Amunts K and Zilles K. Advances in cytoarchitectonic mapping of the human cerebral cortex. *Neuroimaging Clin N Am* 11: 151–169, 2001.
6. Arbib M and Bota M. Language evolution: neural homologies and neuroinformatics. *Neural Netw* 16: 1237–1260, 2003.
7. Aron AR, Robbins TW, and Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 8: 170–177, 2004.
8. Baldissera F, Cavallari P, Craighero L, and Fadiga L. Modulation of spinal excitability during observation of hand actions in humans. *Eur J Neurosci* 13: 190–194, 2001.
9. Ben-Shachar M, Hendler T, Kahn I, Ben-Bashat D, and Grodzinsky Y. The neural reality of syntactic transformations: evidence from functional magnetic resonance imaging. *Psychol Sci* 14: 433–440, 2003.
10. Ben-Shachar M, Palti D, and Grodzinsky Y. Neural correlates of syntactic movement: converging evidence from two fMRI experiments. *Neuroimage* 21: 1320–1336, 2004.
11. Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund HJ, Zilles K, and Seitz RJ. Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. *Hum Brain Mapp* 11: 273–285, 2000.
12. Binkofski F and Buccino G. Motor functions of the Broca's region. *Brain Lang* 89: 362–369, 2004.
13. Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, and Freund HJ. A parieto-premotor network for object manipulation: evidence from neuroimaging. *Exp Brain Res* 128: 210–213, 1999.
14. Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 25: 151–188, 2002.
15. Brass M, Derrfuss J, and von Cramon DY. The inhibition of imitative and overlearned responses: a functional double dissociation. *Neuropsychologia* 43: 89–98, 2005.
16. Brodmann K. *Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Johann Ambrosius Barth, 1909.
17. Buccino G, Lui F, Canessa N, Patteri I, Lagravinese G, Benuzzi F, Porro CA, and Rizzolatti G. Neural circuits involved in the recognition of actions performed by nonconspecifics: an FMRI study. *J Cogn Neurosci* 16: 114–126, 2004.
18. Cantalupo C and Hopkins WD. Asymmetric Broca's area in great apes. *Nature* 414: 505, 2001.
19. Caplan D. *Language: Structure, Processing, and Disorders*. Cambridge, MA: Massachusetts Institute of Technology Press, 1996.
20. Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, and Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci USA* 100: 5497–5502, 2003.
21. Corballis MC. From mouth to hand: gesture, speech, and the evolution of right-handedness. *Behav Brain Sci* 26: 199–208, 2003.
22. Curio G, Neuloh G, Numminen J, Jousmäki V, and Hari R. Speaking modifies voice-evoked activity in the human auditory cortex. *Hum Brain Mapp* 9: 183–191, 2000.
23. Di Pellegrino G, Fadiga L, Fogassi L, Gallese V, and Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res* 91: 176–180, 1992.
24. Dominey PF, Hoen M, Blanc JM, and Lelekov-Boissard T. Neurological basis of language and sequential cognition: evidence from simulation, aphasia, and ERP studies. *Brain Lang* 86: 207–225, 2003.
25. Fincham JM, Carter CS, van Veen V, Stenger VA, and Anderson JR. Neural mechanisms of planning: a computational analysis using event-related fMRI. *Proc Natl Acad Sci USA* 99: 3346–3351, 2002.
26. Flanagan JR and Johansson RS. Action plans used in action observation. *Nature* 424: 769–771, 2003.
27. Friederici AD and Alter K. Lateralization of auditory language functions: a dynamic dual pathway model. *Brain Lang* 89: 267–276, 2004.
28. Friederici AD and Kotz SA. The brain basis of syntactic processes: functional imaging and lesion studies. *Neuroimage* 20, *Suppl* 1: S8–S17, 2003.
29. Friederici AD, Rüschemeyer SA, Hahne A, and Fiebach CJ. The role of left inferior frontal and superior temporal cortex in sentence comprehension: localizing syntactic and semantic processes. *Cereb Cortex* 13: 170–177, 2003.
30. Galaburda AM. La région de Broca: observations anatomiques faites un siècle après la mort de son découvreur. *Rev Neurol (Paris)* 136: 609–616, 1980.
31. Gallese V, Fadiga L, Fogassi L, and Rizzolatti G. Action recognition in the premotor cortex. *Brain* 119: 593–609, 1996.
32. Gallese V, Fogassi L, Fadiga L, and Rizzolatti G. Action representation and the inferior parietal lobule. In: *Attention & Performance XIX. Common Mechanisms in Perception and Action*, edited by Prinz W and Hommel B. Oxford: Oxford University Press, 2002.
33. Gentilucci M. Grasp observation influences speech production. *Eur J Neurosci* 17: 179–184, 2003.
34. Gentilucci M, Benuzzi F, Gangitano M, and Grimaldi S. Grasp with hand and mouth: a kinematic study on healthy subjects. *J Neurophysiol* 86: 1685–1699, 2001.
35. Gerardin E, Sirigu A, Lehericy S, Poline JB, Gaymard B, Marsault C, Agid Y, and Le Bihan D. Partially overlapping neural networks for real and imagined hand movements. *Cereb Cortex* 10: 1093–1104, 2000.
36. Glynn L. *An Anatomy of Thought. The Origin and Machinery of the Mind*. Oxford: Oxford University Press, 1999.
37. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, and Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA* 101: 8174–8179, 2004.