とし、上下（または逆）方向に突起が移動できるようにして仮現運動刺激も可能とする。

PC 操作を指点字として出力させる装置は、スクリーンリーダソフトから出力される点字ディスプレイ用コードを PIC(Peripheral Interface Controller)により取り込み、指点字出力へと変換する。PIC はマイクロコンピュータの１種であり、簡易な装置として作成が可能である。

なお、装置の使用評価に協力いただく障害者および晴眼者には予め装置の動作原理、動作環境等を説明し、必ず事前に承諾をとることとする。PC 操作にはワープロソフトによる文書作成を含むため、臨床評価中にはプライバシーの保護には特に配慮する。

C．研究結果

脳活動賦活用の６指刺激装置は各指単独または同時刺激が可能であり、各指内の刺激も 1 点突起による単一刺激でなく、8 点（2 点 4 列）の刺激または、上下（または逆）方向に突起が移動するような仮現運動刺激も可能となった（図１）。

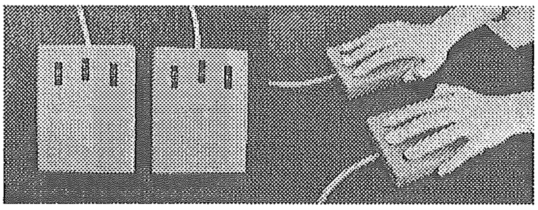


図１　６指刺激装置

ＰＣ操作内容の指点字呈示機は図２に示すようにコンパクトな装置として開発できた。指点字の呈示は図３に示したコネクタから偏芯モータを利用して行う。コネクタ上部の LED は確認用の点灯に用いる。先行研究から、1 文字に対する最適な振動刺激時間は約 200ms であることが示されているため振動時間は固定とするが、文字と文字の刺激休止間隔は利用者の希望にあわせられるように可変とした。

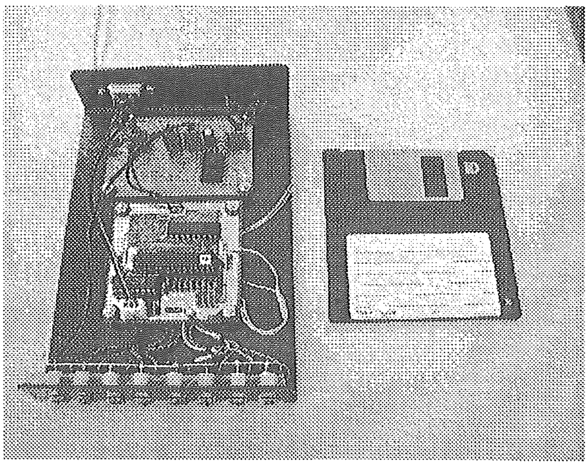


図２　PIC を用いた指点字呈示機

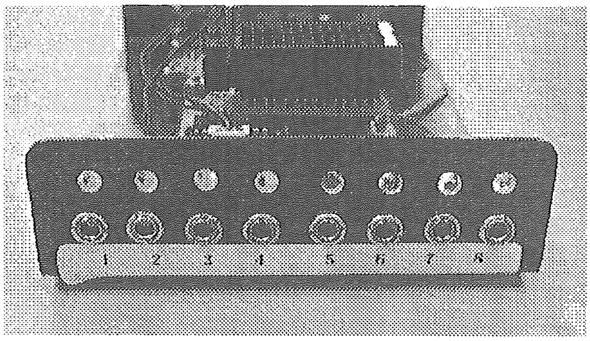


図３　指点字刺激モータ用コネクタ

D．考察

盲ろう者の方に試用してもらった結果、指先に振動モータをつけた場合、指点字の刺激は判別できるが同時にキーボード上で 6 点入力操作をするのには困難が伴う、という意見があった。6 点入力用のキーは標準キーボードとは別なスイッチを用意するなどの工夫が必要となろう。また、カーソルキーなども 6 点入力用のキーと同様に標準キーボードとは独立させた方が操作性は向上すると考えられる。PC 操作がリアルタイムにフィードバックされる点については好評であった。

E．結論

脳活動賦活用の６指刺激装置の開発に平行して、ＰＣ操作内容を指点字として呈示できる装置も開発した。盲ろう者の試用により、6 点入力用

キーやカーソルキーなどの入力に関するキー整備を行うことで操作性の向上が期待できることが判明した。

F．健康危惧情報

特になし。

G．研究発表

1．論文発表

1）伊藤和幸．透明文字盤 Etran 方式の PC 利用による代替について．電子情報通信学会福祉情報工学研究会技術研究報告書．104：1－4，2004．

2）田中久美子，伊藤和幸．重度身障者のための１ボタン自然言語入力システムに向けて．電子情報通信学会福祉情報工学研究会技術研究報告書．104：43-47，2004．

3）伊藤和幸，山本智子．ＰＣ利用によるＥｔｒａｎ方式の意思伝達方法．第１９回リハ工学カンファレンス講演論文集．19：97－98，2004．

4）坂尻正次，伊藤和幸，富田英雄，伊福部達．盲ろう者のＰＣ利用を目的としたかな呈示機．19：99－100，2004．

5）伊藤和幸．仮名パターンの表現方法とその効果．第２０回ライフサポート学会予稿集．20：67－68，2004．

6）Sakajiri, M., Okada, S., Ito, K., Sadakane, A., Sugiyama, N., Tomita, H., Ifukube, T. A Tactile Display System in the Use of a PC for Individuals Who Are Deaf-Blinds. 9th International Conference, ICCHP 2004. 1129-1136, 2004.

7）伊藤和幸．IT 利用に必要な支援～リハ工学（研究者の立場から）．リハビリテーションエンジニアリング．19：31－34，2004．

8）伊藤和幸，伊福部達．ビデオキャプチャ画像処理による視線検出及び石伝達装置への応用．電子情報通信学会論文誌(D)．J88-D-I：527－535，2005．

9）樋口宜男，伊藤英一，伊藤和幸，奥 英久，河合俊宏，田中芳則，寺師良輝，中山 剛，畠中 規，森 大毅．コミュニケーション支援のための肢体不自由者の身体特性に関する研究．文部科学省研究補助金「特定領域研究」障害者・高齢者のコミュニケーション機能に関する基礎研究．57-66，2005．

１０） 伊藤和幸．カナ呈示による盲ろう者向けパソコン操作支援機器．人と福祉を支える技術フォーラム 2005．

2．学会発表

1）坂尻正次，伊藤和幸，富田英雄，伊福部達，盲ろう者のＰＣ利用を目的としたかな呈示機，第１９回リハ工学カンファレンス，Vol.19，pp.99-100，2004．

2）伊藤和幸．“仮名パターンの表現方法とその効果”．第２０回ライフサポート学会．東京都，2004-09．ライフサポート学会，第２０回ライフサポート学会講演予稿集．2004，p.67-68.

3）Sakajiri, M., Okada, S., Ito, K., Sadakane, A., Sugiyama, N., Tomita, H., Ifukube, T. “A Tactile Display System in the Use of a PC for Individuals Who Are Deaf-Blinds”. 9th International Conference, ICCHP 2004, Paris, France, 2004-07-07/7-09, p.1129-1136.

H．知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

（別添５）

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
山下英尚・山脇成人	高齢者の気分障害	日本老年精神医学会	老年精神医学講座；各論	ワールドプランニング	東京	2004	131-149

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nishitani, N., Schürmann. M., Amunts, K., Hari, R	"Broca's region: From action to Language".	Physiology	20(1)	60-69	2005
Nishitani, N., Avikainen, S., Hari, R.	Abnormal imitation-related cortical activation sequences in Asperger's syndrome	Ann Neurol	55(4)	558-562	2004
西谷信之	脳磁図による脳機能の解明	Frontiers in Medicine	56(2)	12-16	2005
Shirao,N., Okamoto,Y., Mantani,T., Okamoto,Y. Yamawaki,S.	Gender differences in brain activity generated by unpleasant word stimuli concerning body image: an fMRI study.	The British Journal of Psychiatry	186	48-53	2005
Tanaka SC, Doya K, Okada G, UedaK, Okamoto Y, Yamawaki S	Prediction of immediate and future rewards differentially re-cruits cortico-basal ganglia loops.	Nat Neurosci.	7(8)	887-93.	2004
Asahi S, Okamoto Y, Okada G, Yamawaki S, Yokota N.	Negative correlation between right prefrontal activity during response inhibition and impulsiveness: a fMRI study.	Eur Arch Psychiatry Clin Neurosci	254	245-51	2004
山脇成人，山下英尚	高齢うつ病の現状と課題	ジェロントロジーホライズン	17(1)	71-75	2005
山脇成人，山下英尚	高齢者の抗不安薬の使い方	Modern Physician	24(6)	1031-1034	2004
山脇成人，山下英尚	抗うつ薬の中断による離脱症候群	日本医事新報	4192	92-93	2004
岡本泰昌，山下英尚，上田一貴，白尾直子，山脇成人	ストレスの適応破綻の脳内メカニズム fMRI と MEG を用いた脳機能画像解析	心身医学	44(3)	185-192	2004

岡田剛，岡本泰昌，山下英尚，上田一貴，旭修司，山脇成人	うつ病患者の前頭葉機能に及ぼす抗うつ薬の効果:fMRI を用いた検討	精神薬療研究年報	36	248-253	2004
岡本泰昌，白尾直子，上田一貴，世木田幹，山下英尚，山脇成人	ストレス適応の脳内メカニズム	精神神経学雑誌	106(3)	365-371	2004
Mantani T, Okamoto Y, Shirao N, Okada G, Yamawaki S.	Reduced activation of posterior cingulate cortex during imagery in subjects with high degrees of alexithymia: an fMRI study	Biol. Psychiatry			in press
Yamashita H, Okamoto Y, Morinobu S, Yamawaki S. Kahkonen S.	Visual emotional stimuli modulation of auditory sensory gating studied by magnetic P50 suppression.	Eur Arch Psychiatry Clin Neurosci.			in press
山脇成人，山下英尚	血管性うつ病と痴呆の鑑別	臨床と研究			in press
Sakajiri, M., Okada, S., Ito, K., Sadakane, A., Sugiyama, N., Tomita, H., Ifukube, T.	A Tactile Display System in the Use of a PC for Individuals Who Are Deaf-Blinds	9th International Conference, ICCHP 2004		1129-1136	2004
伊藤和幸，伊福部達	ビデオキャプチャ画像処理による視線検出及び石伝達装置への応用	電子情報通信学会論文誌(D)	J88-D- (2)	527-535	2005
伊藤和幸，山本智子	透明文字盤 Etran 方式の PC 利用による代替について	電子情報通信学会福祉情報工学研究会技術研究報告書	104(93)	1-4	2004
田中久美子，伊藤和幸	重度身障者のための１ボタン自然言語入力システムに向けて	電子情報通信学会福祉情報工学研究会技術研究報告書	104(235)	43-47	2004
伊藤和幸	ＰＣ利用によるＥｔｒａｎ方式の意思伝達方法	第１９回リハエ学カンファレンス講演論文集	19	97-98	2004
坂尻正次，伊藤和幸，富田英雄，伊福部達	盲ろう者のＰＣ利用を目的としたかな呈示機	第１９回リハエ学カンファレンス講演論文集	19	99-100	2004

伊藤和幸	仮名パターンの表現方法とその効果	第２０回ライフサポート学会予稿集	20	67-68	2004
伊藤和幸	IT利用に必要な支援～リハ工学（研究者の立場から）	リハビリテーションエンジニアリング	19(32)	31-34	2004
樋口宜男,伊藤英一，伊藤和幸，奥 英久，河合俊宏,田中芳則，寺師良輝，中山 剛，畠中 規,森 大毅	コミュニケーション支援のための肢体不自由者の身体特性に関する研究	文部科学省研究補助金「特定領域研究」障害者・高齢者のコミュニケーション機能に関する基礎研究		57-66	2005
伊藤和幸	カナ呈示による盲ろう者向けパソコン操作支援機器	人と福祉を支える技術フォーラム 2005			2005

PHYSIOLOGY 20: 60-69, 2005; 10.1152/physiol.00043.2004

Broca's Region: From Action to Language

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

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.

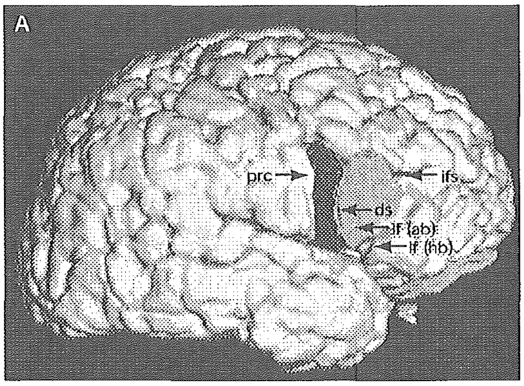
In his now classic report from 1861, Pierre Paul Broca described a man who was unable to speak although his tongue and lip movements were not impaired. The man, later called "Monsieur Tan," was able to say only "tan" and utter a swear word. He had paralysis on his right side but seemed to be intelligent 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



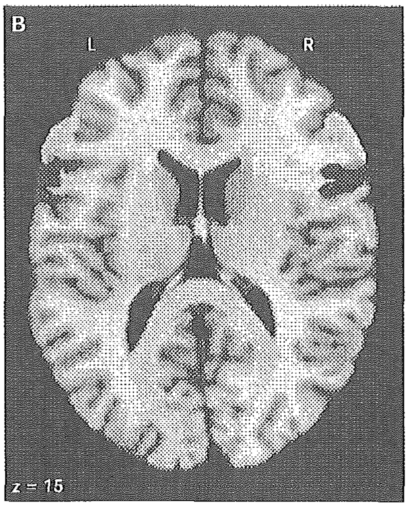


FIGURE 1. **Size and location of Brodmann's areas 44 and 45**
A: surface rendering of the right hemisphere of a three-dimensionally reconstructed postmortem brain. Brodmann's areas (BA) 44 (red) and 45 (yellow), are the cytoarchitectonic correlates of of Broca's region and are its right-hemispheric homolog. 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 indicators 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

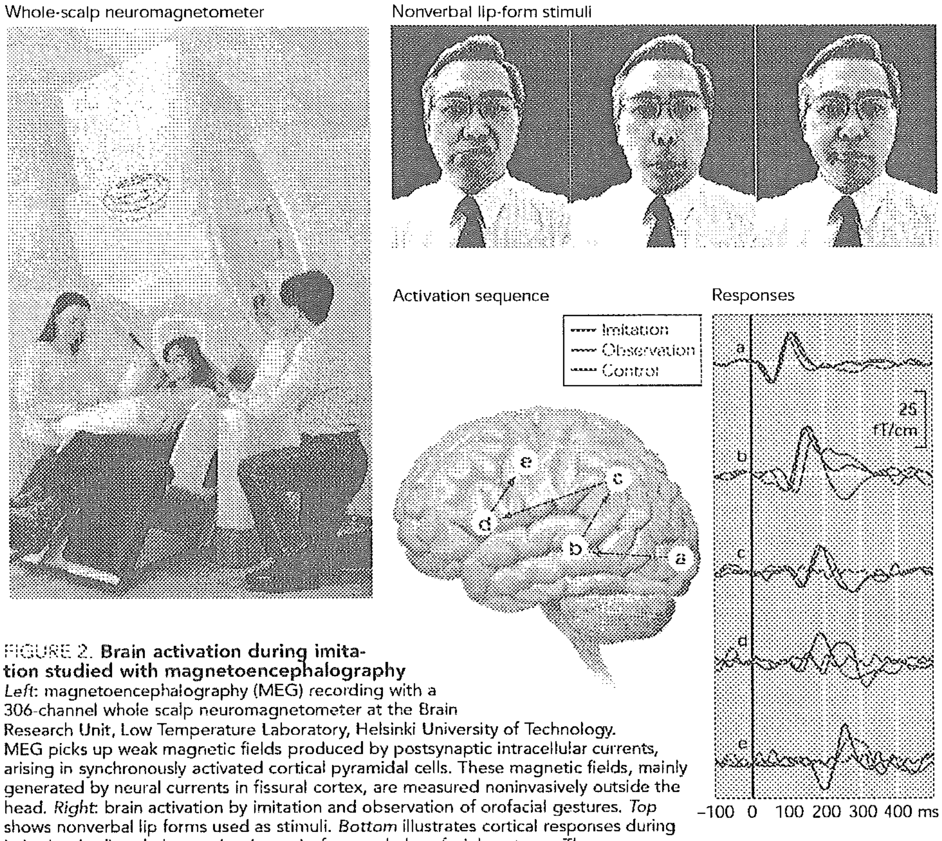


FIGURE 2. **Brain activation during imitation studied with magnetoencephalography**
Left: magnetoencephalography (MEG) recording with a 306-channel whole scalp neuromagnetometer at the Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology. MEG picks up weak magnetic fields 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

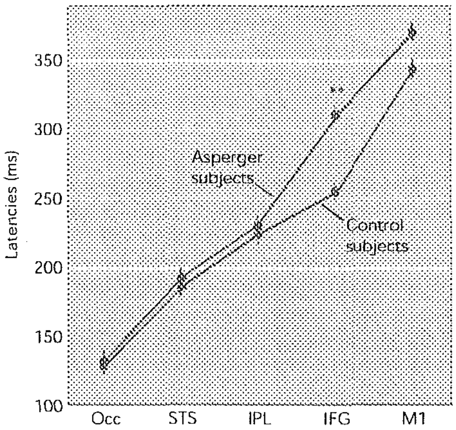


FIGURE 3. **Mean peak latencies in the left hemisphere of control subjects and Asperger subjects during imitation of lip forms**
There were no significant differences in the duration of the whole activation sequence from the occipital area (Occ) via superior temporal sulcus (STS) to the primary motor 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 apres 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.

38. Goldin-Meadow S. The resilience of language. *New York*: Psychology Press, 2003.

39. Goldin-Meadow S. The role of gesture in communication and thinking. *Trends Cogn Sci* 3: 419–429, 1999.

40. Grafton ST, Arbib MA, Fadiga L, and Rizzolatti G. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Exp Brain Res* 112: 103–111, 1996.

41. Grodzinsky Y. The neurology of syntax: language use without Broca's area. *Behav Brain Sci* 23: 1–71, 2000.

42. He AG, Tan LH, Tang Y, James GA, Wright P, Eckert MA, Fox PT, and Liu Y. Modulation of neural connectivity during tongue movement and reading. *Hum Brain Mapp* 18: 222–232, 2003.

43. Heim S, Opitz B, and Friederici AD. Distributed cortical networks for syntax processing: Broca's area as the common denominator. *Brain Lang* 85: 402–408, 2003.

44. Heiser M, Iacoboni M, Maeda F, Marcus J, and Mazziotta JC. The essential role of Broca's area in imitation. *Eur J Neurosci* 17: 1123–1128, 2003.

45. Holowka S and Petitto LA. Left hemisphere cerebral specialization for babies while babbling. *Science* 297: 1515, 2002.

46. Hook-Costigan MA and Rogers LJ. Lateralized use of the mouth in production of vocalizations by marmosets. *Neuropsychologia* 36: 1265–1273, 1998.

47. Horwitz B, Amunts K, Bhattacharyya R, Patkin D, Jeffries K, Zilles K, and Braun AR. Activation of Broca's area during the production of spoken and signed language: a combined cytoarchitectonic mapping and PET analysis. *Neuropsychologia* 41: 1868–1876, 2003.

48. Iacoboni M, Kaplan J, and Wilson S. A neural architecture for imitation and intentional relations. In: *Imitation and Social Learning in Robots, Humans, and Animals: Behavioural, Social and Communicative Dimensions*, edited by Nehaniv C and Dautenhahn K. Cambridge, UK: Cambridge University Press. In press.

49. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, and Rizzolatti G. Cortical mechanisms of human imitation. *Science* 286: 2526–2528, 1999.

50. Iverson JM and Goldin-Meadow S. Why people gesture when they speak. *Nature* 396: 228, 1998.

51. Jackson PL and Decety J. Motor cognition: a new paradigm to study self-other interactions. *Curr Opin Neurobiol* 14: 259–263, 2004.

52. Järveläinen J, Schürmann M, Avikainen S, and Hari R. Stronger reactivity of the human primary motor cortex during observation of live rather than video motor acts. *Neuroreport* 12: 3493–3495, 2001.

53. Järveläinen J, Schürmann M, and Hari R. Activation of the human primary motor cortex during observation of tool use. *Neuroimage* 23: 187–192, 2004.

54. Kaas JH and Hackett TA. 'What' and 'where' processing in auditory cortex. *Nat Neurosci* 2: 1045–1047, 1999.

55. Keysers C, Kohler E, Umiltà MA, Nanetti L, Fogassi L, and Gallese V. Audiovisual mirror neurons and action recognition. *Exp Brain Res* 153: 628–636, 2003.

56. Kim Y, Royer F, Bonstelle C, and Boller F. Temporal sequencing of verbal and nonverbal materials: the effect of laterality of lesion. *Cortex* 16: 135–143, 1980.

57. Kohler E, Keysers C, Umiltà MA, Fogassi L, Gallese V, and Rizzolatti G. Hearing sounds, understanding actions: action representation in mirror neurons. *Science* 297: 846–848, 2002.

58. Koski L, Wohlschläger A, Bekkering H, Woods RP, Dubeau MC, Mazziotta JC, and Iacoboni M. Modulation of motor and premotor activity during imitation of target-directed actions. *Cereb Cortex* 12: 847–855, 2002.

59. Krams M, Rushworth MF, Deiber MP, Frackowiak RS, and Passingham RE. The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 120: 386–398, 1998.

60. Levänen S, Uutela K, Salenius S, and Hari R. Cortical representation of sign language: comparison of deaf signers and hearing non-signers. *Cereb Cortex* 11: 506–512, 2001.

61. Lhermitte F. 'Utilization behaviour' and its relation to lesions of the frontal lobes. *Brain* 106: 237–255, 1983.

62. Liberman AM and Mattingly IG. The motor theory of speech perception revised. *Cognition* 21: 1–36, 1985.

63. Maess B, Koelsch S, Gunter TC, and Friederici AD. Musical syntax is processed in Broca's area: an MEG study. *Nat Neurosci* 4: 540–545, 2001.

64. Makuuchi M. Is Broca's area crucial for imitation? *Cereb Cortex*. In press.

65. Matelli M and Luppino G. Functional anatomy of human motor cortical areas. In: *Handbook of Neuropsychology*, edited by Boller F and Grafman J. Amsterdam: Elsevier, 1997, p. 9–26.

66. Mayberry RI and Jacques J. Gesture production during stuttered speech: insights into the nature of gesture-speech integration. In: *Language and Gesture*, edited by McNeill D. Cambridge, UK: Cambridge University Press, 2000, p. 199–214.

67. Meltzoff AN and Decety J. What imitation tells us about social cognition: a rapprochement between developmental psychology and cognitive neuroscience. *Philos Trans R Soc Lond B Biol Sci* 358: 491–500, 2003.

68. Meyer M, Alter K, Friederici AD, Lohmann G, and von Cramon DY. FMRI reveals brain regions mediating slow prosodic modulations in spoken sentences. *Hum Brain Mapp* 17: 73–88, 2002.

69. Miall RC. Connecting mirror neurons and forward models. *Neuroreport* 14: 2135–2137, 2003.

70. Mitchell RL, Elliott R, Barry M, Cruttenden A, and Woodruff PW. The neural response to emotional prosody, as revealed by functional magnetic resonance imaging. *Neuropsychologia* 41: 1410–1421, 2003.

71. Molnar-Szakacs I, Iacoboni M, Koski L, and Mazziotta J. Functional segregation within pars opercularis of the inferior frontal gyrus: evidence from fMRI studies of imitation and action observation. *Cereb Cortex*. In press.

72. Naito Y, Okazawa H, Honjo I, Takahashi H, Kawano M, Ishizu K, and Yonekura Y. Cortical activation during sound stimulation in cochlear implant users demonstrated by positron emission tomography. *Ann Otol Rhinol Laryngol Suppl* 166: 60–64, 1995.

73. Nakamura K, Kawashima R, Ito K, Sugiura M, Kato T, Nakamura A, Hatano K, Nagumo S, Kubota K, Fukuda H, and Kojima S. Activation of the right inferior frontal cortex during assessment of facial emotion. *J Neurophysiol* 82: 1610–1614, 1999.

74. Nicholls ME, Searle DA, and Bradshaw JL. Read my lips: asymmetries in the visual expression and perception of speech revealed through the McGurk effect. *Psychol Sci* 15: 138–141, 2004.

75. Nishitani N, Avikainen S, and Hari R. Abnormal imitation-related cortical activation sequences in Asperger's syndrome. *Ann Neurol* 55: 558–562, 2004.

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

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

78. Nomura M, Iidaka T, Kakehi K, Tsukiura T, Hasegawa T, Maeda Y, and Matsue Y. Frontal lobe networks for effective processing of ambiguously expressed emotions in humans. *Neurosci Lett* 348: 113–116, 2003.

79. Ojanen V, Möttönen R, Pekkola J, Jääskeläinen IP, and Sams M. Processing of audiovisual speech in the Broca's area. Under revision.

80. Parker GJM, Luzzi S, Alexander DC, Wheeler-Kingshott CAM, Ciccarelli O, and Lambon Ralph MA. Lateralization of ventral and dorsal auditory-language pathways in the human brain. *Neuroimage*. In press.

81. Petitto LA, Holowka S, Sergio LE, and Ostry D. Language rhythms in baby hand movements. *Nature* 413: 35–36, 2001.

82. Rizzolatti G and Arbib MA. Language within our grasp. *Trends Neurosci* 21: 188–194, 1998.

83. Rizzolatti G and Craighero L. The mirror-neuron system. *Annu Rev Neurosci* 27: 169–192, 2004.

84. Rizzolatti G, Fadiga L, Fogassi L, and Gallese V. Resonance behaviors and mirror neurons. *Arch Ital Biol* 137: 85–100, 1999.

85. Rizzolatti G, Fadiga L, Gallese V, and Fogassi L. Premotor cortex and the recognition of motor actions. *Brain Res Cogn Brain Res* 3: 131–141, 1996.

86. Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, and Fazio F. Localization of grasp representations in humans by PET: 1. Observation versus execution. *Exp Brain Res* 111: 246–252, 1996.

87. Rizzolatti G, Fogassi L, and Gallese V. Motor and cognitive functions of the ventral premotor cortex. *Curr Opin Neurobiol* 12: 149–154, 2002.

88. Rizzolatti G, Fogassi L, and Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2: 661–670, 2001.

89. Romanski LM, Tian B, Fritz JB, Mishkin M, Goldman-Rakic PS, and Rauschecker JP. Reply to "'What', 'where' and 'how' in auditory cortex'." *Nat Neurosci* 3: 966, 2000.

90. Rushworth MF, Krams M, and Passingham RE. The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. *J Cogn Neurosci* 13: 698–710, 2001.

91. Salmelin R, Hari R, Lounasmaa OV, and Sams M. Dynamics of brain activation during picture naming. *Nature* 368: 463–465, 1994.

92. Salmelin R, Service E, Kiesilä P, Uutela K, and Salonen O. Impaired visual word processing in dyslexia revealed with magnetoencephalography. *Ann Neurol* 40: 157–162, 1996.

93. Schubotz RI, Friederici AD, and von Cramon DY. Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI. *Neuroimage* 11: 1–12, 2000.

94. Schubotz RI and von Cramon DY. A blueprint for target motion: fMRI reveals perceived sequential complexity to modulate premotor cortex. *Neuroimage* 16: 920–935, 2002.

95. Schubotz RI and von Cramon DY. Functional organization of the lateral premotor cortex: fMRI reveals different regions activated by anticipation of object properties, location and speed. *Brain Res Cogn Brain Res* 11: 97–112, 2001.

96. Schubotz RI and von Cramon DY. Predicting perceptual events activates corresponding motor schemes in lateral premotor cortex: an fMRI study. *Neuroimage* 15: 787–796, 2002.

97. Schubotz RI and von Cramon DY. Sequences of abstract nonbiological stimuli share ventral premotor cortex with action observation and imagery. *J Neurosci* 24: 5467–5474, 2004.

98. Schürmann M, Hesse MD, Stephan KE, Saarela M, Zilles K, Hari R, and Fink GR. Yearning to yawn: the neural basis of contagious yawning. *Neuroimage*. In press.

99. Senghas A, Kita S, and Ozyurek A. Children creating core properties of language: evidence from an emerging sign language in Nicaragua. *Science* 305: 1779–1782, 2004.

100. Thierry G, Boulanouar K, Kherif F, Ranjeva JP, and Démonet JF. Temporal sorting of neural components underlying phonological processing. *Neuroreport* 10: 2599–2603, 1999.

101. Thompson-Schill SL, D'Esposito M, Aguirre GK, and Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc Natl Acad Sci USA* 94: 14792–14797, 1997.

102. Umiltà MA, Kohler E, Gallese V, Fogassi L, Fadiga L, Keysers C, and Rizzolatti G. I know what you are doing. A neurophysiological study. *Neuron* 31: 155–165, 2001.

103. Watkins K and Paus T. Modulation of motor excitability during speech perception: the role of Broca's area. *J Cogn Neurosci* 16: 978–987, 2004.

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

Published by Wiley-Liss, Inc., through Wiley Subscription Services

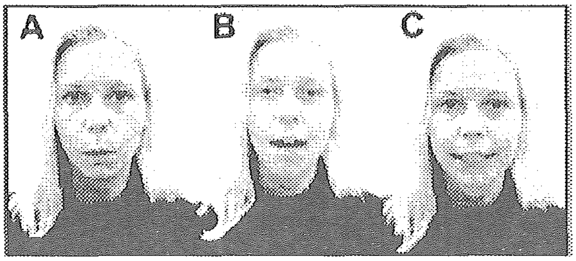


Fig 1. Still pictures of three orofacial gestures: (A) lip protrusion, (B) lip opening, and (C) contraction of both sides of mouth.

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.

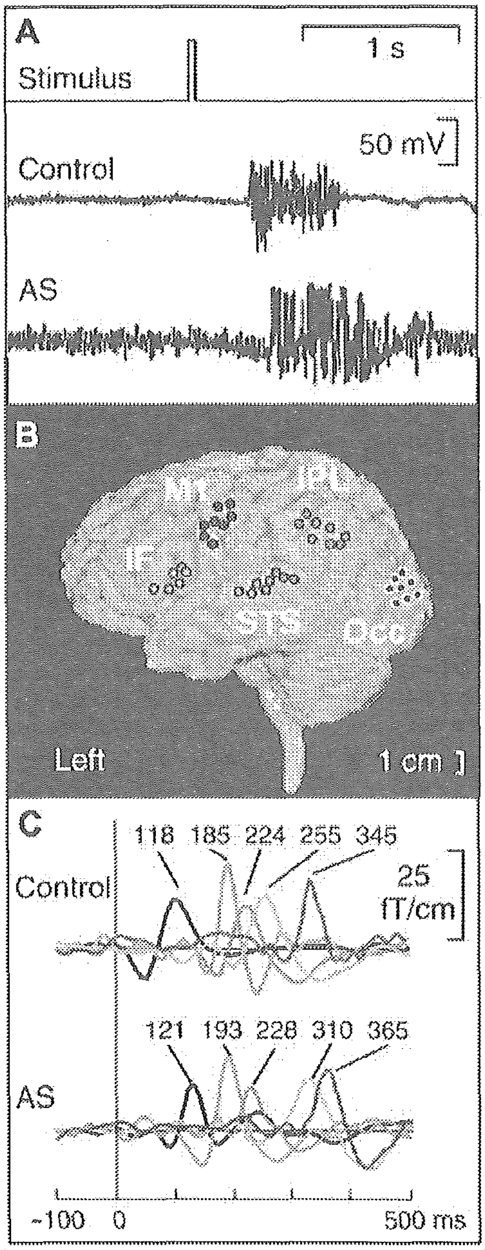


Fig 2. (A) Stimulus timing and electromyograms (EMGs) from the mouth muscle of a control subject and an Asperger's syndrome (AS) subject. (B) The main source locations of all AS subjects superimposed on Talairach's standard brain. Each symbol refers to one AS subject showing activation in that brain 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).

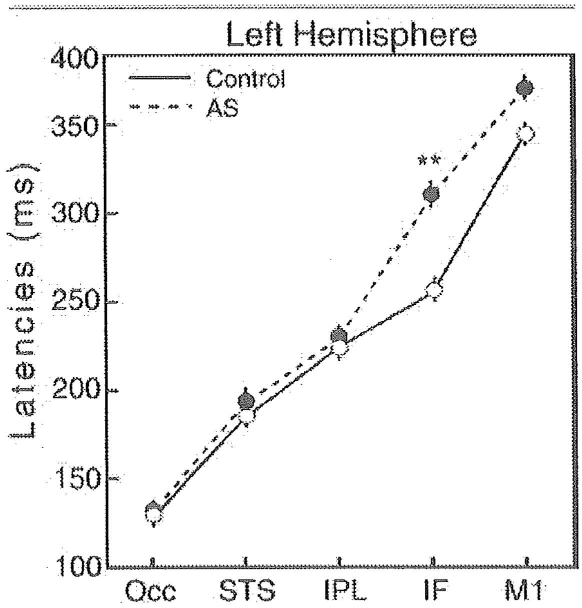


*Fig 3. Peak latencies (mean ± SEM) at the left hemisphere Occ, STS, IPL, IF, and M1 regions across all subjects. **p < 0.01. AS = Asperger's syndrome; Occ = occipital; STS = superior temporal sulcus; IPL = inferior parietal lobule; IF = inferior frontal, M1 = primary motor cortex.*

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

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.

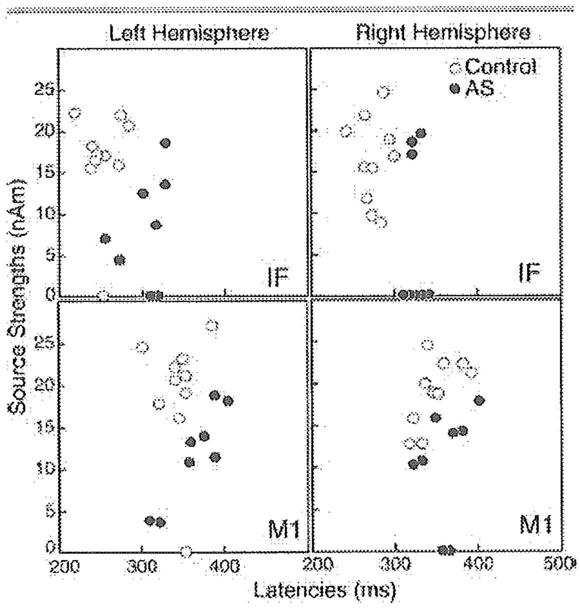


Fig 4. The relationship between the source strength and latency at the IF and M1 areas of both hemispheres for all subjects. In case of an absent source, the source with strength of OnAm was plotted on the median value of the latency of each group. Occ = occipital; STS = superior temporal sulcus; IPL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