tex plasticity, which are—with few exceptions (*81*)—poorly understood. Although complex, a mechanistic, cellular-level explanation of S1 map plasticity appears increasingly tractable and would constitute a major step toward understanding cortical information storage.

References and Notes

1. H. Van der Loos, T. A. Woolsey, *Science* **179**, 395 (1973).
2. D. J. Simons, P. W. Land, *Nature* **326**, 694 (1987).
3. D. V. Buonomano, M. M. Merzenich, *Annu. Rev. Neurosci.* **21**, 149 (1998).
4. T. A. Woolsey, H. Van der Loos, *Brain Res.* **17**, 205 (1970).
5. G. T. Finnerty, L. S. Roberts, B. W. Connors, *Nature* **400**, 367 (1999).
6. K. Fox, *Neuroscience* **111**, 799 (2002).
7. M. Brecht *et al.*, *J. Neurosci.* **24**, 9223 (2004).
8. C. C. Petersen, *Pflugers Arch.* **447**, 126 (2003).
9. D. Feldmeyer, V. Egger, J. Lubke, B. Sakmann, *J. Physiol.* **521**, 169 (1999).
10. R. A. Silver, J. Lubke, B. Sakmann, D. Feldmeyer, *Science* **302**, 1981 (2003).
11. D. Feldmeyer, J. Lubke, R. A. Silver, B. Sakmann, *J. Physiol.* **538**, 803 (2002).
12. T. Shimogori, V. Banuchi, H. Y. Ng, J. B. Strauss, E. A. Grove, *Development* **131**, 5639 (2004).
13. T. Fukuchi-Shimogori, E. A. Grove, *Science* **294**, 1071 (2001).
14. R. S. Erzurumlu, P. C. Kind, *Trends Neurosci.* **24**, 589 (2001).
15. S. Glazewski, K. Fox, *J. Neurophysiol.* **75**, 1714 (1996).
16. M. E. Diamond, W. Huang, F. F. Ebner, *Science* **265**, 1885 (1994).
17. E. A. Stern, M. Maravall, K. Svoboda, *Neuron* **31**, 305 (2001).
18. D. B. Polley, E. Kvasnak, R. D. Frostig, *Nature* **429**, 67 (2004).
19. G. W. Knott, C. Quairiaux, C. Genoud, E. Welker, *Neuron* **34**, 265 (2002).
20. D. O. Hebb, *Organization of Behavior* (Wiley, New York, 1949).
21. H. Wallace, K. Fox, *J. Neurobiol.* **41**, 58 (1999).
22. E. Siucinska, M. Kossut, *Cereb. Cortex* **6**, 506 (1996).
23. A. Skibinska, S. Glazewski, K. Fox, M. Kossut, *Exp. Brain Res.* **132**, 134 (2000).
24. C. B. Allen, T. Celikel, D. E. Feldman, *Nat. Neurosci.* **6**, 291 (2003).
25. G. M. Shepherd, T. A. Pologruto, K. Svoboda, *Neuron* **38**, 277 (2003).
26. S. Glazewski, K. P. Giese, A. Silva, K. Fox, *Nat. Neurosci.* **3**, 911 (2000).
27. M. Kossut, *Exp. Brain Res.* **123**, 110 (1998).
28. D. L. Maier, G. M. Grieb, D. J. Stelzner, J. S. McCasland, *Exp. Neurol.* **184**, 737 (2003).
29. X. Wang, M. M. Merzenich, K. Sameshima, W. M. Jenkins, *Nature* **378**, 71 (1995).
30. M. A. Lebedev, G. Mirabella, I. Erchova, M. E. Diamond, *Cereb. Cortex* **10**, 23 (2000).
31. A. Schierloh, M. Eder, W. Zieglgansberger, H. U. Dodt, *Eur. J. Neurosci.* **20**, 1118 (2004).
32. E. Welker, S. B. Rao, J. Dorfl, P. Melzer, H. van der Loos, *J. Neurosci.* **12**, 153 (1992).
33. M. A. Castro-Alamancos, *Prog. Neurobiol.* **74**, 213 (2004).
34. D. B. Polley, C. H. Chen-Bee, R. D. Frostig, *Neuron* **24**, 623 (1999).
35. E. L. Bienenstock, L. N. Cooper, P. W. Munro, *J. Neurosci.* **2**, 32 (1982).
36. G. G. Turrigiano, S. B. Nelson, *Curr. Opin. Neurobiol.* **10**, 358 (2000).
37. D. E. Feldman, R. A. Nicoll, R. C. Malenka, *J. Neurobiol.* **41**, 92 (1999).
38. K. Fox, B. L. Schlaggar, S. Glazewski, D. D. O'Leary, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 5584 (1996).
39. V. Rema, M. Armstrong-James, F. F. Ebner, *J. Neurosci.* **18**, 10196 (1998).
40. W. A. Myers, J. D. Churchill, N. Muja, P. E. Garraghty, *J. Comp. Neurol.* **418**, 373 (2000).
41. H. T. Cline, *Curr. Opin. Neurobiol.* **11**, 118 (2001).
42. K. J. Bender, J. Rangel, D. E. Feldman, *J. Neurosci.* **23**, 8759 (2003).
43. K. J. Bender, S. Deshmukh, D. E. Feldman, in *Development and Plasticity in Sensory Thalamus and Cortex,* W. Guido, Ed. (Academic Press, in press).
44. K. J. Bender, C. B. Allen, D. E. Feldman, *Soc. Neurosci. Abstr.* 26.3 (2005).
45. T. Takahashi, K. Svoboda, R. Malinow, *Science* **299**, 1585 (2003).
46. E. Foeller, D. E. Feldman, *Curr. Opin. Neurobiol.* **14**, 89 (2004).
47. T. W. Margrie, M. Brecht, B. Sakmann, *Pfleugers Arch.* **444**, 491 (2002).
48. M. Brecht, M. Schneider, I. Manns, *The Plasticity of the Sensory-Motor Cortices,* F. Ebner, Ed. (CRC Press, in press).
49. Y. Dan, M. M. Poo, *Neuron* **44**, 23 (2004).
50. D. E. Feldman, *Neuron* **27**, 45 (2000).
51. T. Celikel, V. A. Szostak, D. E. Feldman, *Nat. Neurosci.* **7**, 534 (2004).
52. D. E. Shulz, V. Ego-Stengel, E. Ahissar, *J. Physiol.* (Paris) **97**, 431 (2003).
53. G. Feng *et al.*, *Neuron* **28**, 41 (2000).
54. W. Denk, J. H. Strickler, W. W. Webb, *Science* **248**, 73 (1990).
55. B. Lendvai, E. A. Stern, B. Chen, K. Svoboda, *Nature* **404**, 876 (2000).
56. D. B. Chklovskii, B. W. Mel, K. Svoboda, *Nature* **431**, 782 (2004).
57. F. Engert, T. Bonhoeffer, *Nature* **399**, 66 (1999).
58. Q. Zhou, K. J. Homma, M. M. Poo, *Neuron* **44**, 749 (2004).
59. E. S. Ruthazer, H. T. Cline, *J. Neurobiol.* **59**, 134 (2004).
60. M. Maravall, I. Y. Koh, W. B. Lindquist, K. Svoboda, *Cereb. Cortex* **14**, 655 (2004).
61. F. R. Volkmar, W. T. Greenough, *Science* **176**, 1445 (1972).
62. J. T. Trachtenberg *et al.*, *Nature* **420**, 788 (2002).
63. J. Grutzendler, N. Kasthuri, W. B. Gan, *Nature* **420**, 812 (2002).
64. E. J. Green, W. T. Greenough, B. E. Schlumpf, *Brain Res.* **264**, 233 (1983).
65. P. W. Hickmott, P. A. Steen, *Nat. Neurosci.* **8**, 140 (2005).
66. A. K. McAllister, L. C. Katz, D. C. Lo, *Annu. Rev. Neurosci.* **22**, 295 (1999).
67. L. C. Katz, C. J. Shatz, *Science* **274**, 1133 (1996).
68. I. Bureau, G. M. Shepherd, K. Svoboda, *Neuron* **42**, 789 (2004).
69. C. Darian-Smith, C. D. Gilbert, *Nature* **368**, 737 (1994).
70. R. Yuste, T. Bonhoeffer, *Annu. Rev. Neurosci.* **24**, 1071 (2001).
71. A. J. Holtmaat *et al.*, *Neuron* **45**, 279 (2005).
72. Y. Zuo, A. Lin, P. Chang, W. B. Gan, *Neuron* **46**, 181 (2005).
73. M. Matsuzaki, N. Honkura, G. C. Ellis-Davies, H. Kasai, *Nature* **429**, 761 (2004).
74. H. Markram, J. Lubke, M. Frotscher, A. Roth, B. Sakmann, *J. Physiol.* (London) **500** (part 2), 409 (1997).
75. V. Braitenberg, A. Schuz, *Anatomy of the Cortex* (Springer-Verlag, Berlin, 1991).
76. G. W. Davis, C. M. Schuster, C. S. Goodman, *Neuron* **17**, 669 (1996).
77. S. Ramón y Cajal, *Nuevo concepto de la Histología de los Centros nerviosos* (Barcelona, 1893).
78. T. Dittgen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 18206 (2004).
79. K. Haas, W. C. Sin, A. Javaherian, Z. Li, H. T. Cline, *Neuron* **29**, 583 (2001).
80. T. W. Margrie *et al.*, *Neuron* **39**, 911 (2003).
81. D. J. Simons, *The Barrel Cortex of Rodents*, E. G. Jones, I. T. Diamond, Eds. (Plenum, New York, 1995), pp. 262–298.
82. Y. Zuo, G. Yang, E. Kwon, W.-B. Gan, *Nature* **436**, 261 (2005).

83. We thank C. Hansel and A. Lee for manuscript comments. This work was supported by NIH R01 NS046652 and the McKnight Foundation (D.F.) and the Erasmus University Rotterdam, a Vidi grant from Netherlands Organization for Scientific Research, and Human Frontier Science Program grants (M.B.).

10.1126/science.1115807

VIEWPOINT

Language Acquisition and Brain Development

Kuniyoshi L. Sakai

Language acquisition is one of the most fundamental human traits, and it is obviously the brain that undergoes the developmental changes. During the years of language acquisition, the brain not only stores linguistic information but also adapts to the grammatical regularities of language. Recent advances in functional neuroimaging have substantially contributed to systems-level analyses of brain development. In this Viewpoint, I review the current understanding of how the "final state" of language acquisition is represented in the mature brain and summarize new findings on cortical plasticity for second language acquisition, focusing particularly on the function of the grammar center.

A child acquires any natural languages within a few years, without the aid of analytical thinking and without explicit "grammar" instruction as usually taught in school. The origin of grammatical rules should thus be ascribed to an innate system in the human brain (*1*). The knowledge of and competence for human language is acquired through various means and modality types. Linguists regard speaking, signing, and language comprehension as primary faculties of language, i.e., innate or inherent and biologically determined, whereas they regard reading and writing as secondary abilities. Indeed, the native or first language (L1) is acquired during the first years of life through such primary faculties while children are rapidly expanding their linguistic knowledge (*2*). In contrast, reading and writing are learned with much conscious

effort and repetition, usually at school. This ability may be influenced by cultural rather than biological factors. However, the existence of developmental dyslexics indicates that reading ability requires specific neural mechanisms (*3*), and a link between poor reading and impaired auditory resolution has been suggested (*4*). It is therefore crucial to understand how distinct linguistic faculties develop in the brain throughout various ages. Figure 1 illustrates the typical development of L1 faculties. This correlates with a massive increase in brain volume during the first years. Speech in infants develops from babbling at around 6 to 8 months of age, to the one-word stage at 10 to 12 months, and then to the two-word stage around 2 years. Note that sign systems are spontaneously acquired by both deaf and hearing infants in a similar developmental course (*5*), starting from manual silent "babbling" (*6*). However, these obvious developmental changes refer to language output. Speech perception and even grammatical knowledge develops much earlier, within the first months after birth (*7*, *8*).

A clear contrast among linguistic factors exists between L1 and a second language (L2). The L2 ability does not seem to take any determined steps of development, and it shows enormous individual variation. Whether L2 relies on the same dedicated mechanism of L1 is thus a matter of debate (*9*). An L2 can be mastered at any time in life, though the L2 ability rarely becomes comparable to that of L1 if it is acquired beyond the hypothesized "sensitive period" from early infancy until puberty (~12 years old). The notion of a sensitive period for language acquisition comes from the loss of flexibility for cerebral reorganization due to acquired aphasia after puberty (*10*). The concept of the sensitive period has been extended to L2 acquisition in that English proficiency declines after the age of 7 years when Chinese or Korean speakers move to the United States (*11*). This hypothesis has recently been challenged by an event-related brain potential (ERP) study. Adults who learned a miniature artificial language showed a similar ERP response to a syntactic anomaly as native speakers do (*12*). It may also be possible that different linguistic abilities are acquired in their own developmental courses and that the timing and duration of their sensitive periods differ. In this viewpoint, I will first clarify the fundamental linguistic factors and their possible representation in the mature brain as revealed by brain mapping techniques. The major linguistic factors are phonology and lexico-semantics at the word level and sentence comprehension and syntax at the sentence and discourse level, which certainly interact with each other (Fig. 2A). A critical question is whether these factors correspond to distinct regions of the brain. I will then focus on advances in functional imaging studies of L2 acquisition, indicating activation changes in particular regions of the brain during the course of language development.

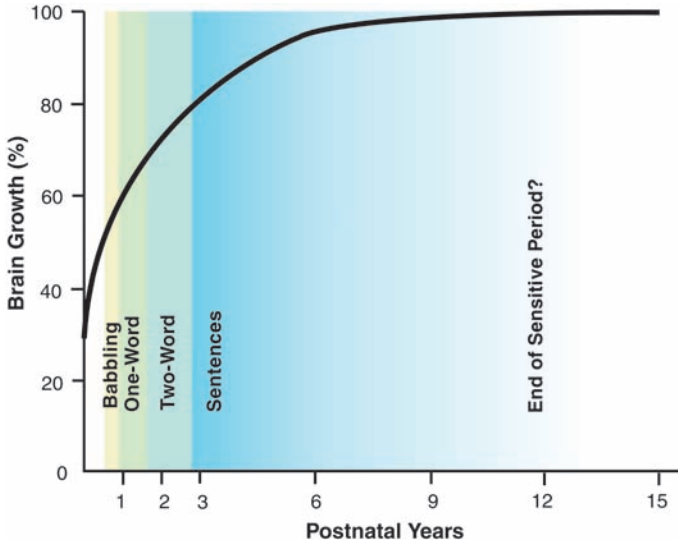


Fig. 1. Brain growth and first language (L1) acquisition. Human brain weight is presented as a function of age, where 100 in the ordinate corresponds to the mean adult value (*10*). Approximate times of milestones in normal speech development are also indicated.

Phonology and Lexico-Semantics

Recent functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have indicated that auditory phonological processing is associated with activation in the posterior superior temporal gyrus (STG) [Brodmann's area (BA) 22], whereas lexico-semantic processing is typically associated with activation in the left extra-sylvian temporoparietal regions, including the angular gyrus and supramarginal gyrus (AG/SMG) (Fig. 2A) (*13*). However, studies on phonological versus lexico-semantics have reported many additional regions, including the inferior frontal regions, and phonological processing may have varied levels of abstraction within distinct subregions (*14*). We have shown that bilateral STG activation is more enhanced in phonological decision and voice-pitch comparison tasks than in syntactic and semantic decision tasks even when the same speech stimuli are used (*15*). On the other hand, activations in the left AG/SMG and frontal regions are less consistent among the lexico-semantic tasks tested by a number of functional imaging studies. Lexico-semantic tasks may involve various cognitive factors other than semantic processing, and thus different cortical regions might be recruited depending on the particular strategy used by the participants.

Sentence Comprehension

Sentences convey not only lexico-semantic information for each word but sentence meaning based on syntactic structures. Semantic processing at the sentence level differs from a simple summation of lexico-semantic processing for each word. For example, the meaning of "John thinks that David praises his son" clearly differs from that of "John thinks that his son praises David," although the lexical items involved in each of these sentences are identical. Therefore, the processing of syntactic structures plays a critical role in the selective integration of lexico-semantic information into sentence meaning. We proposed that the left inferior frontal gyrus (IFG) region extending from the triangular part (F3t or BA 45) to the orbital part (F3O or BA 47) is the putative region for the selection and integration of semantic information, which are separable from simple lexico-semantic processing (*16*) (Fig. 2B, green region). We directly compared cortical activations in tasks involving comprehension of sentences with those in lexical decision tasks and found discourse-level selective activation in the left F3t/F3O under both auditory and visual conditions. We also clarified that the functional connectivity between the left F3t/F3O and a region in the left precentral sulcus is significantly enhanced during the sentence task but not during the lexico-semantic task (*17*). In the neuroimaging field, there is a growing emphasis on structural and functional connectivity to clarify how distributed but interacting populations of neurons work in a coordinated fashion during language processing.

A recent fMRI study showed that the processing of American Sign Language (ASL) recruited the bilateral cortical areas of both deaf native signers and hearing native signers, whereas the processing of written English was left-lateralized (*18*). Note that for the deaf signers, ASL is the L1 and written English the L2. Another fMRI study reported

Department of Basic Science, Graduate School of Arts and Sciences, University of Tokyo, Komaba, Tokyo 153-8902, Japan. Core Research of Evolutional Science and Technology (CREST), Japan Science and Technology Agency, Kawaguchi-shi 332-0012, Japan. E-mail: sakai@mind.c.u-tokyo.ac.jp

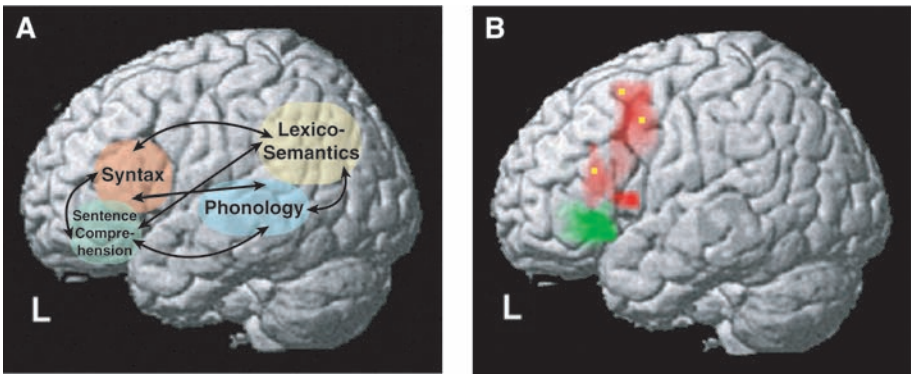


Fig. 2. (**A**) Possible network of fundamental linguistic functions in the brain. The exact correspondences between the left (L) brain regions and linguistic factors are still under study. (**B**) The grammar center and other left frontal regions critically involved in sentence processing. The green region (the left F3t/F3O) is selectively activated in the comprehension of sentences (*16*, *17*), whereas the red regions (the left lateral premotor cortex, the left dorsal IFG, and the left F3op/F3t) are specifically involved in syntactic processing (*15*, *26*) and can be regarded as the grammar center.

bilateral cortical activation for the processing of British Sign Language (BSL), but without evidence of enhanced right-hemisphere recruitments in sign language when compared with an audio-visual speech condition (*19*). It is, therefore, a considerable challenge to clarify ''what's right and what's left.'' Because sign-language aphasia is due primarily to left-hemisphere lesions (*20*), it should be clarified whether comprehension of sentences is functionally lateralized in sign and speech. By using tasks involving comprehension of sentences and sentential nonword detection, we compared different groups and stimulus conditions (*21*). Under the sign condition with sentence stimuli in Japanese Sign Language (JSL), we tested two groups of participants: deaf signers of JSL and hearing bilinguals of JSL and Japanese. Under the speech condition, we tested hearing monolinguals of Japanese with auditory Japanese stimuli alone or with an audio-visual presentation of Japanese and JSL stimuli. Across all four conditions, there were consistently left-dominant activations involving frontal and temporo-parietal regions. Furthermore, irrespective of the modalities of sign and speech, activations selective to the comprehension of sentences were found primarily in the left regions, including the left F3t/F3O; only the left F3t/F3O showed no main effects of modality condition. These results indicate amodal commonality in the functional dominance of the left cortical regions for comprehension of sentences as well as the essential and universal role of the left F3t/F3O in processing linguistic information from both signed and spoken sentences.

Syntax: The Grammar Center

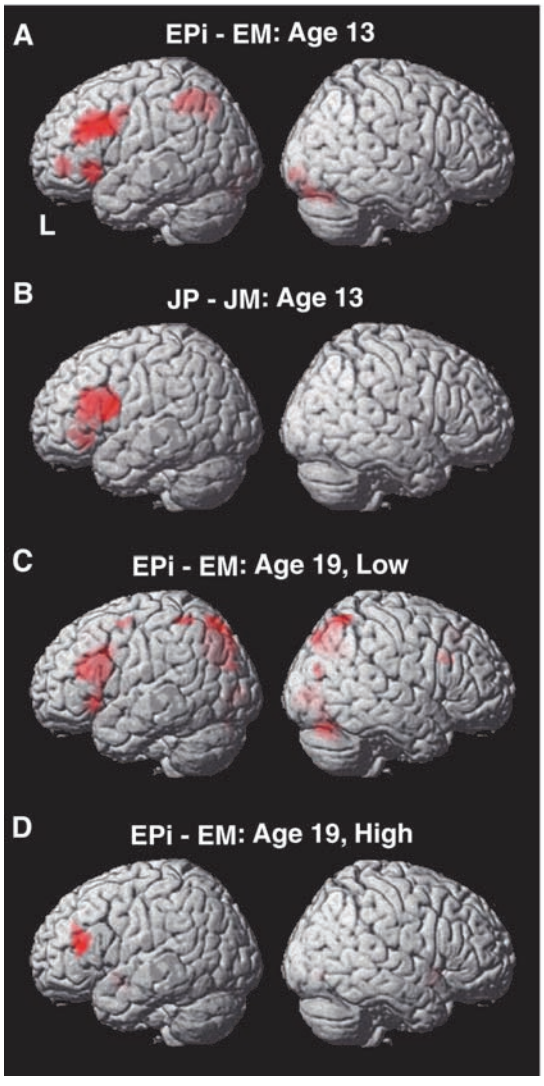
Although there has been much speculation concerning subdivisions for various aspects of sentence processing and consensus is still lacking, there is accumulating evidence that the opercular and triangular parts (F3op/F3t or BAs 44 and 45) of the left IFG and the left lateral premotor cortex (BAs 6, 8, and 9; mainly in BA 8) are selectively related to grammatical processing (*15*, *22*–*26*). The left lateral premotor cortex is located at the junction of the precentral sulcus and the inferior frontal sulcus and is just dorsal to the left F3op/F3t. I propose that these left frontal regions can be regarded as the ''grammar center,'' reflecting the universal nature of grammatical processing. Is there a specialized (domain-special) neural system for grammatical processing that is separable from other domain-general cognitive systems? We examined cortical activation by directly comparing brain activations in syntactic decision tasks with those in verbal short-term memory tasks (*26*). The left dorsal IFG (a part of F3op/F3t) as well as the left lateral premotor cortex showed selective activation for syntactic decision tasks when they were directly compared with a verbal short-term memory task (Fig. 2B, red regions). The activation of these regions is related to processes of analyzing syntactic structures, and it cannot be explained either by task difficulty or by verbal short-term memory components. The human left frontal cortex is thus uniquely specialized in the syntactic processes of sentence comprehension, without any counterparts in other animals.

There is great controversy regarding the limits of noninvasive imaging techniques as a tool for human studies; for example, such correlation methods are insufficient to show causal relationships between cortical activations and linguistic functions. To establish a causal link between the grammar center and syntactic processing, we used transcranial magnetic stimulation (TMS) and a minimal-pair paradigm in which either a syntactic or semantic factor differed between stimulus pairs (*27*). Event-related paired TMS pulses over the left F3op/F3t selectively reduced reaction times in explicit syntactic decisions but not in explicit semantic decisions, suggesting the selective physiological effects of facilitation or priming. This effect was observed during syntactic decisions regarding both normal and anomalous sentences and when magnetic stimulation was administered to the left F3op/F3t at a specific time (150 ms from a verb stimulus). Even if the ''normal'' sentences were physically identical stimuli, TMS showed the differential effects on the normal sentences that paralleled the effects on anomalous sentences, depending on the types of explicit linguistic decisions being made. These results indicate that the left F3op/F3t plays an essential role as the grammar center of human sentence processing.

Functional Changes of the Grammar Center During L2 Acquisition

How can the function of the grammar center be modified during the acquisition of new languages? There are at least two major factors that may affect the cortical activation change: the proficiency level (PL) of L2 and the age of acquisition (AOA). It has been reported that L1 (AOA before about 6 years) and L2 (AOA after about 7 years) are represented differentially in cortical areas (*28*), whereas other studies have reported that they have common neural substrates during sentence comprehension tasks (*29*). An fMRI study supports the AOA effect on cortical activations, showing that the left IFG activation for grammatical processing in L2 is greater than that in L1 (*30*). However, another fMRI study claims that the degree of exposure to language affects the left IFG activation, even if the AOA is matched (*31*). It has also been pointed out that the left frontal and extrastriate regions are differentially modulated, either by age or task performance among children (aged 7 to 10) and adults (*32*). However, the age and PL effects on cortical activations are often confounded with the demands required in each language task and the resultant task performance, and it remains unknown whether these factors are actually separable from each other.

Given these uncertainties, we tried to clarify the relative contributions of age, PL, language task demands, and task performance to modulating activations in the left IFG. We examined whether learning of English past-tense verbs as L2 knowledge altered the brain activations of 13-year-old students (native Japanese speakers) studying English for the first time (*33*). We targeted twins as participants (six monozygotic and one dizygotic twin pairs), because it is intriguing to ask whether the shared factors of twins actually influence their language abil-



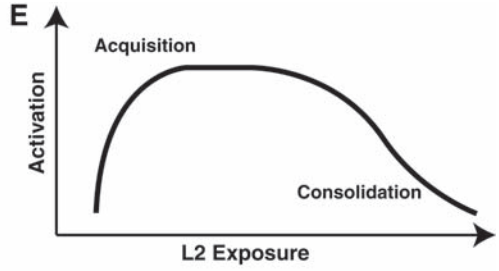


Fig. 3. Functional changes of the grammar center during second language (L2) acquisition. (**A**) Past-tense task-selective activation in L2 (EPi, the English past-tense task with irregular verbs) after classroom training for participants age 13 years (*33*). (**B**) Past-tense task-selective activation in L1 (JP, the Japanese past-tense task) for participants age 13 years. (**C**) Past-tense task-selective activation in L2 (EPi) for the lower PL subgroup of participants age 19 years (*34*). (**D**) Past-tense task-selective activation in L2 (EPi) for the higher PL subgroup of participants age 19 years. (**E**) Possible activation changes in the brain during L2 acquisition and consolidation.

ities and neural substrates. For 2 months, the students participated in intensive training in English verbs as part of their standard classroom education. The twins completed two sets of fMRI sessions, one before (day 1) and one after (day 2) training. When an English past-tense (EP) task was contrasted with an English verb-matching (EM) task for day 2, activations were found primarily in the left IFG (Fig. 3A); these activations had been absent in the same contrast for day 1. The contrast between Japanese past-tense (JP) and Japanese verb-matching (JM) tasks resulted in the same left IFG activation (Fig. 3B), which is in agreement with the universal nature of grammatical processing. These results suggest that cortical plasticity for L2 acquisition is guided toward L1 specialization of the left IFG, at least at the age of 13, despite notable differences between L1 and L2 in the students' linguistic knowledge and in their performance in making past-tense forms. The activation increases of the left dorsal IFG across days 1 and 2 showed a highly significant correlation within each pair of twins. This suggests that the functional changes specifically observed in the left IFG were susceptible to shared genetic and environmental factors for each twin in a surprisingly predictive manner. The activation increases in the left IFG predicted the extent to which the individual participants improved their knowledge of the past tense. In a subsequent fMRI study, we tested participants aged 19 who had studied English for 6 years, thereby comparing the cortical activations involved in the above-mentioned EP and EM tasks (*34*). The activation in the left dorsal IFG was lower, corresponding to a higher PL (Fig. 3, C and D), suggesting that the PL plays a major role in the activation of this region. On the other hand, the left F3t/F3O activation in Japanese (L1) of participants aged 13 was significantly greater than that for those aged 19, despite the matched performances in L1. We conclude that the grammar center subserves specific linguistic functions that are critically required when mastering any language.

Combining these task-selective activation changes, left dorsal IFG activation increases with PL improvements at the early stages of L2 acquisition and becomes lower when a higher proficiency in L2 is attained. These results may reflect a more general law of activation changes during language development. Cortical activations increase initially at the onset of acquisition, followed by the maintenance of the activations and then a fall in activations during consolidation of linguistic competence (Fig. 3E). On the other hand, the developmental changes in regional cerebral blood flow and cerebral metabolic rates are known to manifest initially as an increase and later, after about the age of 9, as a decrease (*35*). Because such metabolic differences between children and adults might affect the acquisition, analysis, and interpretation of fMRI data in group analyses, an appropriate task control is necessary to compensate for the global physiological changes in the brain. Moreover, if the general law stated above is applicable, a brain region may show higher, lower, or comparable activation, depending on which developmental stages are compared.

Outlook

Noninvasive imaging techniques have already been applied to study the "initial state" of brain activations reflecting speech perception in infants (*36*, *37*). In the future, participants at various developmental stages will be systematically tested by functional imaging studies with language and/or general cognitive tasks. Regional cerebral volume and tissue concentration differences have also been characterized by voxel-based morphometry, and this technique may elucidate structural development of the brain in a larger population, extending the study of adult human brains (*38*). Indeed, twin studies have contributed to reveal genetic factors for brain structure, more significantly those influencing language areas in the left hemisphere (*39*). Longitudinal studies of both structure and function of brains may further reveal their developmental tendencies in general, as well as individual differences. Moreover, the observation of functional changes during recovery from neurological conditions, such as dyslexia and aphasia, will help facilitate remediation and rehabilitation in both children and adults. As to the normal development of the brain, further research is still

necessary to determine whether the left IFG activation depends on exposure to L1 and L2 at a particular stage, thus clarifying the existence of a sensitive period. Future studies will investigate how individual subregions of the left frontal cortex, as well as other cortical regions, work in concert and subserve human-unique language acquisition. This promising approach to evaluating developmental changes in terms of not only indirect behavioral changes but direct brain changes is taking a first step toward a new era in the systems neuroscience of human language.

References and Notes

1. N. Chomsky, *On Nature and Language* (Cambridge Univ. Press, Cambridge, UK, 2002).
2. M. T. Guasti, *Language Acquisition: The Growth of Grammar* [Massachusetts Institute of Technology (MIT) Press, Cambridge, MA, 2002].
3. A. A. Beaton, *Dyslexia, Reading, and the Brain: A Sourcebook of Psychological and Biological Research* (Psychology Press, Hove, UK, 2004).
4. M. Ahissar, A. Protopapas, M. Reid, M. M. Merzenich, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 6832 (2000).
5. G. Morgan, B. Woll, Eds., *Direction in Sign Language Acquisition* (Benjamins, Amsterdam, 2002).
6. L. A. Petitto, S. Holowka, L. E. Sergio, D. Ostry, *Nature* **413**, 35 (2001).
7. P. K. Kuhl, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11850 (2000).
8. K. Hirsh-Pasek, R. M. Golinkoff, *The Origins of Grammar: Evidence from Early Language Comprehension* (MIT Press, Cambridge, MA, 1996).
9. S. D. Epstein, S. Flynn, G. Martohardjono, *Behav. Brain Sci.* **19**, 677 (1996).
10. E. H. Lenneberg, *Biological Foundations of Language* (Wiley, New York, 1967).
11. J. S. Johnson, E. L. Newport, *Cognit. Psychol.* **21**, 60 (1989).
12. A. D. Friederici, K. Steinhauer, E. Pfeifer, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 529 (2002).
13. C. J. Price, *J. Anat.* **197**, 335 (2000).
14. A. Boemio, S. Fromm, A. Braun, D. Poeppel, *Nat. Neurosci.* **8**, 389 (2005).
15. K. Suzuki, K. L. Sakai, *Cereb. Cortex* **13**, 517 (2003).
16. F. Homae, R. Hashimoto, K. Nakajima, Y. Miyashita, K. L. Sakai, *Neuroimage* **16**, 883 (2002).
17. F. Homae, N. Yahata, K. L. Sakai, *Neuroimage* **20**, 578 (2003).
18. H. J. Neville *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 922 (1998).
19. M. MacSweeney *et al.*, *Brain* **125**, 1583 (2002).
20. G. Hickok, U. Bellugi, E. S. Klima, *Sci. Am.* **284**, 58 (2001).
21. K. L. Sakai, Y. Tatsuno, K. Suzuki, H. Kimura, Y. Ichida, *Brain* **128**, 1407 (2005).
22. K. Stromswold, D. Caplan, N. Alpert, S. Rauch, *Brain Lang.* **52**, 452 (1996).
23. M. Dapretto, S. Y. Bookheimer, *Neuron* **24**, 427 (1999).
24. D. Embick, A. Marantz, Y. Miyashita, W. O'Neil, K. L. Sakai, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 6150 (2000).
25. A. D. Friederici, B. Opitz, D. Y. von Cramon, *Cereb. Cortex* **10**, 698 (2000).
26. R. Hashimoto, K. L. Sakai, *Neuron* **35**, 589 (2002).
27. K. L. Sakai, Y. Noguchi, T. Takeuchi, E. Watanabe, *Neuron* **35**, 1177 (2002).
28. K. H. S. Kim, N. R. Relkin, K. M. Lee, J. Hirsch, *Nature* **388**, 171 (1997).
29. M. W. L. Chee *et al.*, *Neuron* **23**, 127 (1999).
30. I. Wartenburger *et al.*, *Neuron* **37**, 159 (2003).
31. D. Perani *et al.*, *Hum. Brain Mapp.* **19**, 170 (2003).
32. B. L. Schlaggar *et al.*, *Science* **296**, 1476 (2002).
33. K. L. Sakai, K. Miura, N. Narafu, M. Muraishi, *Cereb. Cortex* **14**, 1233 (2004).
34. Y. Tatsuno, K. L. Sakai, *J. Neurosci.* **25**, 1637 (2005).
35. H. T. Chugani, M. E. Phelps, J. C. Mazziotta, *Ann. Neurol.* **22**, 487 (1987).
36. G. Dehaene-Lambertz, S. Dehaene, L. Hertz-Pannier, *Science* **298**, 2013 (2002).
37. M. Peña *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 11702 (2003).
38. C. D. Good *et al.*, *Neuroimage* **14**, 21 (2001).
39. P. M. Thompson *et al.*, *Nat. Neurosci.* **4**, 1253 (2001).

40. I thank Y. Miyashita for encouragement. This work was supported by a Core Research of Evolutional Science and Technology (CREST) grant from the Japan Science and Technology Agency and by Grants-in-Aid for Scientific Research on Priority Areas ("Higher-Order Brain Functions," 17022013) and for the 21st Century COE (Center of Excellence) Program ("Research Center for Integrated Science") from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

10.1126/science.1113530

VIEWPOINT

Sex Differences in the Brain: Implications for Explaining Autism

Simon Baron-Cohen,* Rebecca C. Knickmeyer, Matthew K. Belmonte

Empathizing is the capacity to predict and to respond to the behavior of agents (usually people) by inferring their mental states and responding to these with an appropriate emotion. Systemizing is the capacity to predict and to respond to the behavior of nonagentive deterministic systems by analyzing input-operation-output relations and inferring the rules that govern such systems. At a population level, females are stronger empathizers and males are stronger systemizers. The "extreme male brain" theory posits that autism represents an extreme of the male pattern (impaired empathizing and enhanced systemizing). Here we suggest that specific aspects of autistic neuroanatomy may also be extremes of typical male neuroanatomy.

Leaving aside political correctness, there is compelling evidence for sexual dimorphism in the brain, cognition, and behavior (*1*). In this Viewpoint, we review the evidence at all three levels. Classic autism and Asperger syndrome (AS) are the two clearest subgroups on the autistic spectrum of conditions, and both affect males more often than females. We conjecture that understanding sex differences in the general population has implications for understanding the causes of autism-spectrum conditions.

The E-S Theory of Psychological Sex Differences

Although males and females do not differ in general intelligence, specific cognitive tasks reveal sex differences. Differences favoring males are seen on the mental rotation test (*2*), spatial navigation including map reading (*3*), targeting (*4*), and the embedded figures test (*5*), although there are conflicting studies regarding the latter (*6*). Males are also more likely to play with mechanical toys as children (*7*), and as adults, they score higher on engineering and physics problems (*8*). In contrast, females score higher on tests of emotion recognition (*9*), social sensitivity (*10*), and verbal fluency (*11*). They start to talk earlier than boys do (*12*) and are more likely to play with dolls as children (*7*). Effect sizes range from small (Cohen's $d = 0.2$ for emotion recognition) to large (Cohen's $d = 1.3$ to 1.9 for targeting), with a substantial degree of overlap between male and female distributions, even for effects considered large by the conventions of psychology. All of these differences exist at the level of populations, not individuals; from such population differences, no inferences can or should be made about individuals.

Although these population differences partially arise from experiential factors, experiments in animals suggest a biological foundation. Male rats perform significantly better than females do on the radial arm and Morris water maze (*13*). This sex difference is eliminated by castrating males or by treating females with testosterone neonatally (*14*).

Autism Research Centre, Cambridge University, Department of Psychiatry, Douglas House, 18b Trumpington Road, Cambridge CB2 2AH, UK.

*To whom correspondence should be addressed. E-mail: sb205@cam.ac.uk