keys on one search array, we created a condition in which FEF cells express a visual stimulus selectivity they would not otherwise have[7,12,13]. Overtraining also led to an apparent increase in the distribution of visual response latencies of FEF neurons. Further work is needed to establish whether the latencies of individual neurons change, or whether different populations of neurons have been recorded in the control and experimental monkeys.

Our finding is probably related to the enhancement of the visual responses of neurons in visuomotor structures including FEF observed specifically when the stimulus in a neuron's receptive field is used as the target for a gaze shift[13,14]. However, unlike earlier studies that presented one or two stimuli in blocks of trials, in our experiment distractors were always present, and target location was much less predictable. Therefore, the early visual selectivity we observed in the experimental monkeys is unlikely to be due only to directed attention or motor planning specific for a particular visual field location.

Discrimination of a target from distractors based on visual salience or the subject's instructed preference has been observed in visual cortex[15–19]. This discrimination occurs typically 140–150 ms after stimulus presentation, a time which coincides with the time of visual target discrimination by FEF neurons measured in control monkeys[20]. The latency of the colour based discrimination observed in FEF of the experimental monkeys was markedly shorter than the attention-related modulations observed in extrastriate visual cortex. Indeed, the timecourse of the early visual discrimination in FEF coincides with or shortly follows the latency of activation of colour-selective cells in macaque primary visual cortex, having estimated mean values ranging from 45 ms (ref. 21) to 80 ms (ref. 22). If there is insufficient time for attentional modulation based on stimulus evaluation, it is possible that the attenuated response of FEF neurons to the distractors is mediated by a reduction in the synaptic efficacy of neurons representing the constant distractor feature. The present data do not show whether the hypothetical synaptic plasticity occurs in FEF or in visual areas that register the colour of the search stimuli.

If plasticity underlies the FEF visual selectivity observed here, then this finding contrasts with previous work, because it demonstrates a change in neural selectivity due to selective experience that was not localized in a topographic map. Previous reports of neural plasticity based on experience in adult primates have described expansions of representations within topographic maps that are associated with perceptual or motor skill acquisition[23]. The experience-dependent, early visual selectivity we observed in FEF was not due to a topographically limited pattern of sensory stimulation or motor output, but rather was contingent on a particular stimulus–response mapping. This finding may indicate another form of adaptation of the mature brain that is associated with the establishment of a habit, if not a skill. □

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CORRESPONDENCE and requests for materials should be addressed to J.D.S. (e-mail: schalljd@ctrvax.vanderbilt.edu).

The neurobiology of sign language and its implications for the neural basis of language

Gregory Hickok*, Ursula Bellugi* & Edward S. Klima*†

* The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, USA
† The University of California, San Diego, California 92186, USA

The left cerebral hemisphere is dominant for language, and many aspects of language use are more impaired by damage to the left than the right hemisphere. The basis for this asymmetry, however, is a matter of debate; the left hemisphere may be specialized for processing linguistic information[1–3] or for some more general function on which language depends, such as the processing of rapidly changing temporal information[4] or execution of complex motor patterns[5]. To investigate these possibilities, we examined the linguistic abilities of 23 sign-language users with unilateral brain lesions. Despite the fact that sign language relies on visuospatial rather than rapid temporal information, the same left-hemispheric dominance emerged. Correlation analyses of the production of sign language versus non-linguistic hand gestures suggest that these processes are largely independent. Our findings support the view that the left-hemisphere dominance for language is not reducible solely to more general sensory or motor processes.

Like spoken languages, sign languages used by the deaf are highly structured linguistic systems, with a rigid developmental course, including a critical period for acquisition[6]. There is no universal sign language, nor are they manual forms of surrounding spoken languages: American sign language (ASL) and British sign language, for example, are mutually incomprehensible. Signed languages have linguistic structure at phonological, morphological and syntactic levels. At the phonological level, signs are fractionated into sublexical elements, including recurring hand shapes, articulation locations, and limb/hand movements[7,8]. There are even systematic 'phonetic' differences between sign languages leading to an 'accent' when native users of one sign language learn another[3,9]. At the morphological level, ASL has developed grammatical markers that serve as inflectional and derivational morphemes[9]. At the syntactic level, ASL specifies relations between signs through, among other things, the manipulation of signs in space, where different spatial relations convey systematic differences in meaning[10–12] (Fig. 1).

Thus, although sign language has linguistic structuring at the same levels as spoken language, the surface form is radically different, with spatial contrasts prominent at every level. The time course between the shortest linguistically relevant transitions during a sign, such as a change in hand shape, is approximately 200 ms (ref. 13), significantly longer than the time course of the shortest transitions within a spoken word (~40 ms) that have been

TABLE 1 Biographical and medical data of subjects

	Age at sign exposure (years)	Age at onset of deafness (years)	Sex	Handedness	Age at testing (years)	Lesion size/location	Lesion aetiology
Left-lesioned							
LHD01	6	5	M	R	81	lg/front–par	Ischaemic infarct
LHD02	5	5	F	R	66	mod/inf par	Ischaemic infarct
LHD03	0	0	F	R	37	lg/front	Ischaemic infarct
LHD04	6	1	F	R	51	sm/inf–ant front	Aneurism rupture*
LHD05	13	0	M	R	45	lg/temp–par	Haematoma
LHD06	0	0	M	R	77	mod/front–temp–par	Ischaemic infarct
LHD07	0	0	M	R	86	sm/sup front–par	Ischaemic infarct
LHD08	6	2	F	R	64	mod/medial occ	Ischaemic infarct
LHD09	7	<1	M	R	29	mod/front–par	Ischaemic infarct
LHD10	0	2	F	R	79	mod/inf-post front	Ischaemic infarct
LHD11	9	<1	F	R	73	mod/front–par	Ischaemic infarct
LHD12	11	0	F	R	79	lg/front–temp-par	Ischaemic infarct
LHD13	4	0	M	R	71	mod/inf front–par	Haematoma
Right-lesioned							
RHD01	12	0	F	R	71	lg/front–temp–par	Ischaemic infarct
RHD02	9	5	M	R	82	mod/temp–par	Ischaemic infarct
RHD03	5	0	M	R	60	lg/front–temp–par	Ischaemic infarct
RHD04	0	0	F	R	61	mod/sup front–par	Tumour*
RHD05	0	n/a	F	R	38	mod/sup par–occ	Haematoma*
RHD06	0	0	M	R	74	lg/front–temp–par	Ischaemic infarct
RHD07	11	2	F	R	78	mod/front–par	Ischaemic infarct
RHD08	7	<1	M	R	74	lg/front–temp–par	Ischaemic infarct
RHD09	6	3	F	R	83	mod/temp-par	Ischaemic infarct
RHD10	0	0	F	R	78	mod/temp–par–occ	Ischaemic infarct

Ages are rounded to the nearest year. Lesions are grouped into three size categories based on visual inspection: lg, large; mod, moderate; sm, small. Lesion location is indicated by the lobe(s) involved: front, frontal; temp, temporal; par, parietal; occ, occipital; and by position within the lobe: sup, superior; inf, inferior; ant, anterior; post, posterior.

* Surgical intervention.

argued to underlie left-hemisphere dominance for language. Determining the lateralization of signed language therefore bears directly on the issue of the role of fast temporal processing in hemispheric dominance for language.

There have been only a few case studies investigating the role of the left cerebral hemisphere in processing sign language[3,14,15], and no quantitative group-level analyses comparing sign-language users with damaged left and right hemispheres. Here we report on a relatively large group of 13 left-hemisphere-damaged (LHD) signers and 10 right-hemisphere-damaged (RHD) signers (Table 1).

Using an ASL-adapted version of the Boston Diagnostic Aphasia Examination[16], we assessed each subject's competence in several aspects of language use: production, comprehension, naming and repetition. LHD signers performed significantly worse than RHD signers on all measures (Fig. 2*a*). The differences apply even if subjects with lesions outside the perisylvian region are excluded (subjects in analyses, 10 LHD, 7 RHD; for each measure, $P < 0.03$). Finally, the difference between LHD and RHD signers is not a function of sampling error due to group differences in age at test, age of onset of deafness, or age of exposure to ASL. Across the two groups, there is no correlation between the total score on Boston Diagnostic Aphasia Examination rating scales[16] and these three variables ($P = 0.99$, 0.52 and 0.91, respectively).

To ensure that deficits in sign-language processing were not simply a function of deficits in general spatial cognitive ability, standard measures of visuo-spatial cognition were administered. Figure 2*b* presents examples of the performance on these visuo-spatial tasks for four aphasic LHD signers, who nonetheless performed well on these visuo-spatial

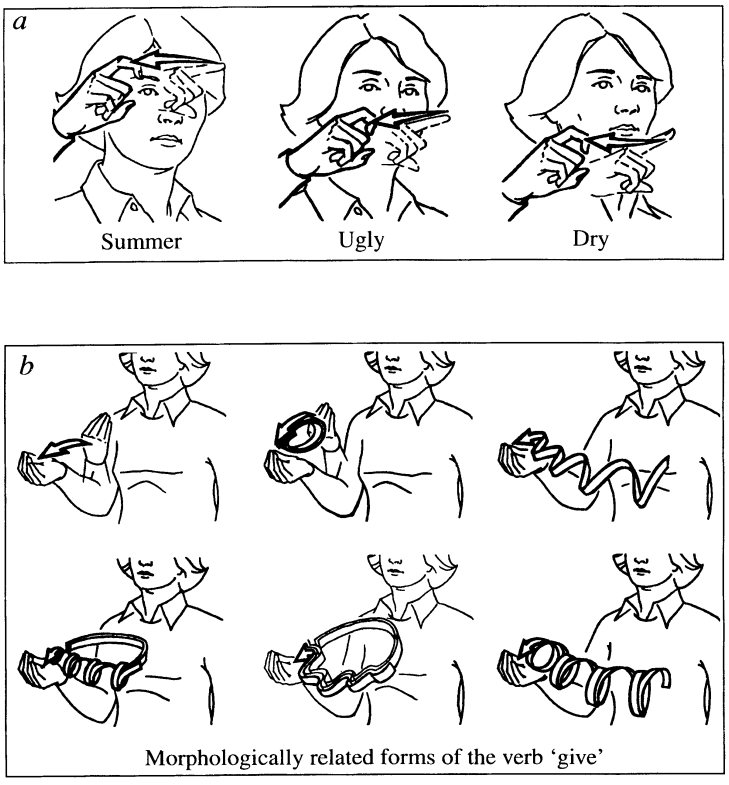

FIG. 1 *a*, Spatial contrasts at the lexical level. Articulation at different spatial locations relative to the body yields distinct signs. *b*, Spatial modulations in ASL morphology. Examples of how verb signs can be inflected through the modulation of movement, and how these inflections can be layered (embedded) within one another to derive subtle differences in meaning. Clockwise from top left: Give (uninflected); Give (continuous), 'give repeatedly'; Give (exhaustive), 'give to each in turn'; Give ((continuous) exhaustive), 'give repeatedly to each in turn'; Give ((exhaustive) continuous), 'give to each in turn again and again'; and Give (((continuous) exhaustive) continuous), 'give repeatedly to each in turn again and again'.

tasks, and four non-aphasic RHD signers, who performed poorly on these visuo-spatial tasks. This double dissociation between visuo-spatial abilities and sign language abilities indicates that these two domains of cognition are largely independent in deaf signers.

These data indicate that at the hemipheric level the neural organization of sign language is indistinguishable from that of spoken language. Given that sign language relies largely on spatial information rather than rapidly changing temporal information to encode linguistic distinctions, our findings demonstrate that

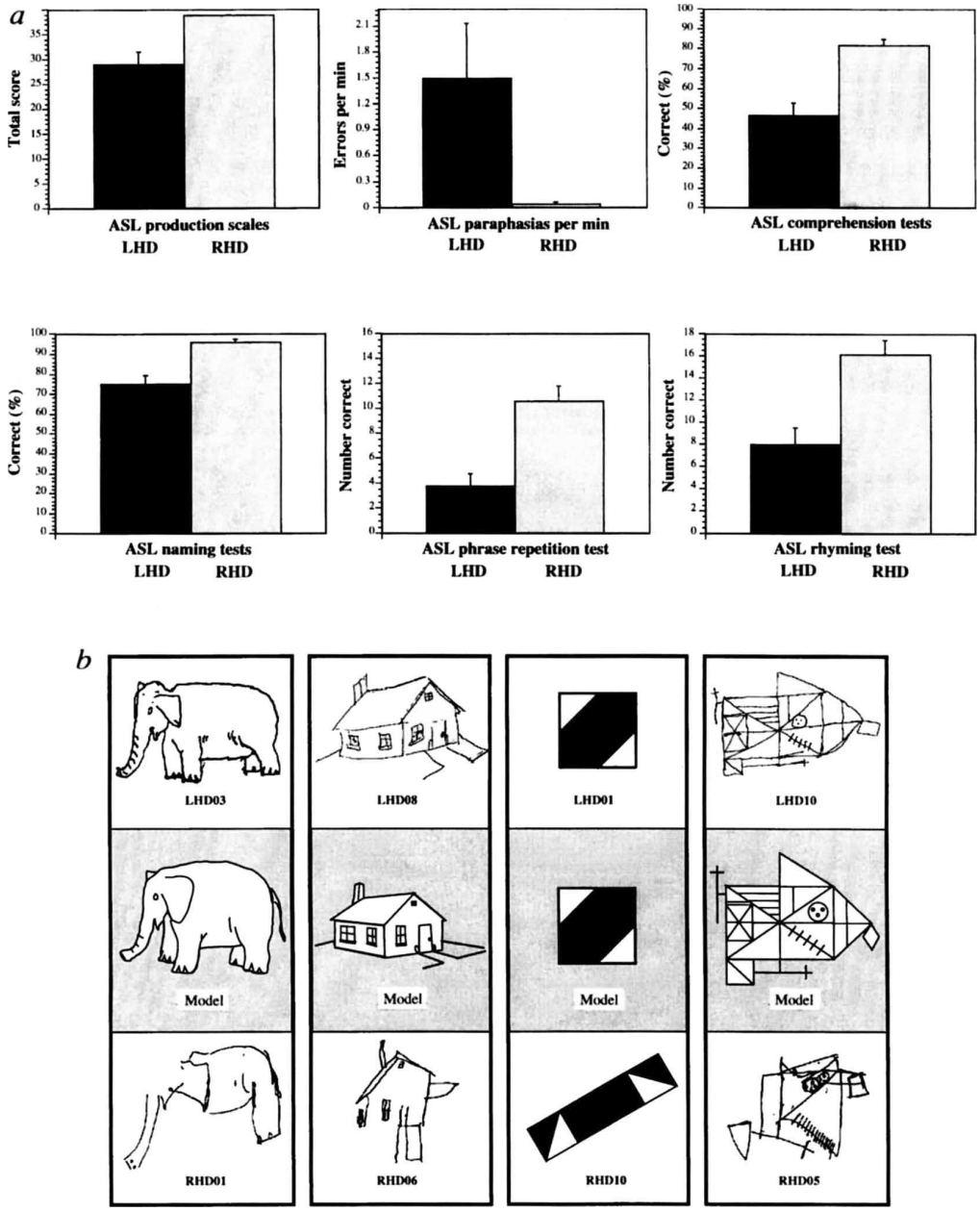

FIG. 2 *a*, Six measures of ASL ability for LHD versus RHD signers. All LHD signers and 9 of 10 RHD signers are deaf and use ASL as their primary means of communication; one RHD signer is a hearing ASL interpreter. Subjects with bilateral lesions or small lacunar infarcts were excluded. Subjects were tested at least three months after the stroke. Deaf, native ASL signers administered and scored all tests. Significance levels corrected for the number of tests, two-tailed: $P = 0.0002$. The production scales measure used the sum score on our ASL-adapted version of the Boston Diagnostic Aphasia Examination (BDAE) profile of speech characteristics[16]. Paraphasias per minute is the total number of sign errors in a sign sample elicited according to the BDAE protocol; $P = 0.02$ (excludes one LHD outlier, who produced errors at a rate 3 s.d. above the LHD mean). Comprehension tests were the BDAE commands subtest and our ASL-adapted version of the token test[18]; two subjects (1 LHD, 1 RHD) did not take these tests; $P = 0.016$. Naming tests are the BDAE visual confrontation and responsive naming tests; $P = 0.017$. The phrase repetition test was an ASL version of the BDAE phrase repetition test; $P = 0.001$. The rhyming test was a 'rhyme' judgement test in which subjects choose (out of an array of four) the two pictured objects whose signs were most similar in terms of sign-phonological features[3]; $P = 0.009$; 10 LHD and 7 RHD subjects took this test. *b*, Examples of performance on visuo-spatial tasks by LHD signers (top) and RHD signers (bottom), along with the target stimulus (middle). Tests include the BDAE drawing to copy subtest[16], the Weschler adult intelligence scale-revised block design test, and the Rey Osterrieth complex figure[19].

left-hemisphere dominance for language is not solely determined by a general proclivity for processing fast temporal information.

To investigate whether sign-language disruption can be reduced to disruptions of domain-general motor control[5], we administered an abbreviated version[3] of Kimura's movement copy test[5,17] to 11 of the LHD subjects; they were asked to copy non-representational manual movements using the arm ipsilateral to the lesion. We found varying degrees of disruption in the ability to perform this task; however, scores did not correlate significantly with measures of sign production during connected sign, including number of paraphasias per minute ($r = 0.36$, $P = 0.27$), number of paraphasias when corrected for number of signs produced ($r = 0.32$, $P = 0.33$), or fluency as defined in the Boston Diagnostic Aphasia Examination phrase-length scale ($r = 0.21$, $P = 0.54$). Further, on each of the language measures, subjects could be identified who produced similar scores in terms of their sign production yet differed substantially in their apraxia score (Fig. 3), indicating the dissociability between the two domains. Although it is difficult to rule out fully the existence of a significant correlation between these variables because of the relatively small sample size, these data suggest that there is a significant amount of variability in at least some aspects of sign language disruption that cannot be accounted for solely by a disruption of motor control.

Taken together, these data suggest that left-hemisphere dominance for language is not driven by physical characteristics of the linguistic signal or motor aspects of its production, but rather stem from higher-order properties of the system. Whether these turn out to be domain-specific aspects of grammatical structure or other, less specific, organizational properties awaits further investigation. □

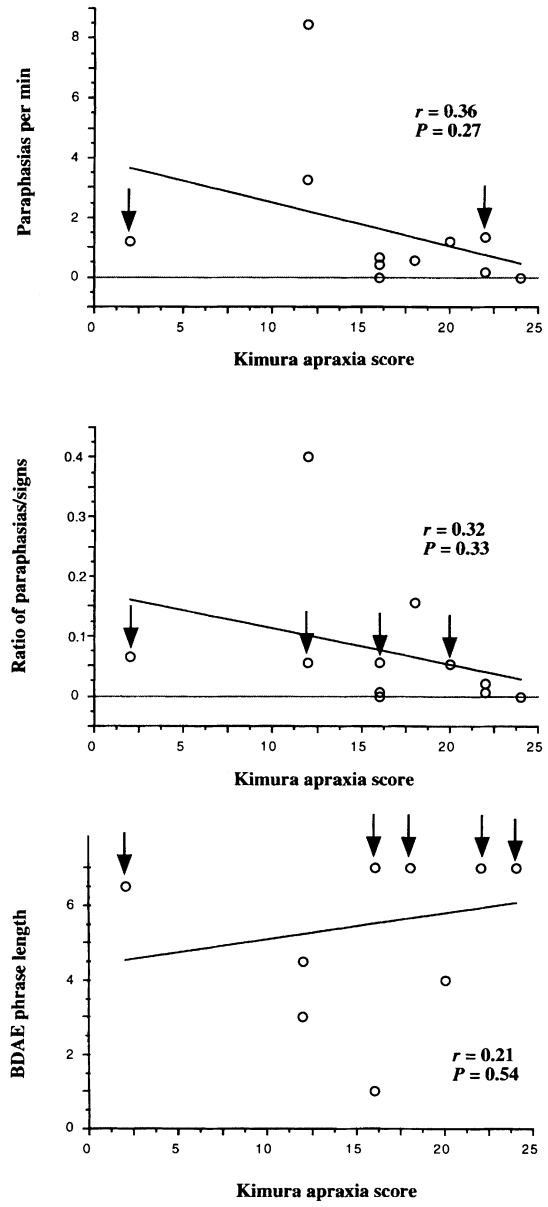

FIG. 3 Scatter plot and regression line for Kimura movement copy test score plotted against number of paraphasias (errors in sign) per minute of signing (top); ratio of paraphasias to total signs produced (middle); and BDAE phrase length scale (bottom). Note that significant variability in apraxia score does not necessarily predict variability in language measures (arrows).

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CORRESPONDENCE and requests for materials should be addressed to G.H. (e-mail: hickok@crl.ucsd.edu).

Rapid and opposite effects of BDNF and NGF on the functional organization of the adult cortex *in vivo*

Neal Prakash, Susana Cohen-Cory*† & Ron D. Frostig

Department of Psychobiology and the Center for Learning and Memory, University of California at Irvine, Irvine, California 92717, USA
* Division of Biology, Caltech, Pasadena, California 91125, USA

The adult cortex is thought to undergo plastic changes that are closely dependent on neuronal activity (reviewed in ref. 1), although it is not yet known what molecules are involved. Neurotrophins and their receptors have been implicated in several aspects of developmental plasticity[2–4], and their expression in the adult cortex suggests additional roles in adult plasticity[5–9]. To examine these potential roles *in vivo*, we used

† Present address: Mental Retardation Research Center, University of California Los Angeles, School of Medicine, Los Angeles, California 90024, USA.