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24. *Macaca nemestrina* PBMCs were purified from a Ficoll gradient, and 2×10^7 cells were PHA-stimulated in culture for 72 hours. The cells were then infected with HIV-1. Three or 7 days after infection, the cells were pelleted, resuspended in 1 ml of stock virus, and inoculated intravenously into the autologous animals.
25. The positions of the oligonucleotide primers are numbered relative to the HIV-1 HXB2, HIV-2_{ROD}, and SIV_{mne} isolates in the Human Retroviruses and AIDS Database. Primer SK38-SK39 and probe SK-19, primer SK145-SK431 and probe SK102, primer SK68-SK69 and probe SK-70, and primer AA55-M667 and probe KG1 [P. Gupta, L. Kingsly, R. Anderson *et al.*, *AIDS* **6**, 143 (1992)] were the two gag, env, and LTR HIV-1 specific primers, respectively [C.-Y. Ou *et al.*, *Science* **239**, 295 (1988)]. VB312 [gag nucleotides (nt) 539 to 566 = 5′-GTGGGAGATGGGCGCGAGAAACTC-CGCT-3′ and gag nt 837 to 810 = 5′-CACGCA-GAAGAGAAAGTGAAAGATACT-3′] and VB306-VB310 (gag nt 603 to 630 = 5′-AGGTTACGGC-CCGGCGGAAAGAAAAAGT-3′ and gag nt 780 to 753 = 5′-ACAGGTTCAGAAAATTTAAAAAGCC-TTT-3′) were the outer and inner sets of HIV-2 gag gene primers, respectively. VB308 (gag nt 684 to 714 = 5′-AACCTTCTTTTGACTCCAACAGGCTC-TCTG-3′) was the HIV-2 gag gene probe [C.-Y. Ou, personal communication]. The HIV-2 nested primer pairs are homologous to and cross-hybridize with SIV gag sequences but not with HIV-1 (*26*). SIVgag1-SIVgag2 (gag nt 587 to 619 = 5′-ATTAGGCTACGACCCGGCGGGAAGAAAAAG-TAC-3′ and gag nt 1537 to 1505 = 5′-CAGCAC-TAGCTTGCAATGTGGGTTAGCATTTTG-3′) and SIVgagGP (5′-CTGTCAGAAGGCTGCACCCCCTA-TGACATTAATCAGATGT-3′) were the SIV gag gene primers and probe. Primers flanking the HLA-DQ α locus were used to assess the ability of the sample to be amplified and served as an internal calibration. PCR was performed as described (*35*) with an automated thermal cycler programmed for 30 cycles at 94°C for 50 s, 55°C for 50 s, and 72°C for 90 s. Nested PCR was performed as described [M. R. Furtado, B. Balachandran, P. Gupta, S. M. Wolinsky, *Virology* **185**, 258 (1991)] with an automated thermal cycler programmed for 35 cycles at 95°C for 60 s and 60°C for 3 min. Negative cell DNA and reagent controls were run in parallel. Specific product DNAs were detected by a radioisotopic and two nonisotopic (Roche, Fair Lawn, NJ, and Genprobe, San Diego, CA) assays (*35*). All experiments were performed at least in duplicate.
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28. R values are defined as the ratio of the absorbance units of the tested animal serum to the absorbance units of the cutoff value. The cutoff value is the mean absorbance value of three negative controls sera plus 0.250 absorbance units.
29. Neutralizing antibody titers were determined in twofold serial dilutions of heat-inactivated sera. Duplicate samples were reacted with 10 TCID HIV-1_{LAI} for 1 hour at 37°C, and the serum-virus mixture was incubated on 2×10^5 CEM cells in complete RPMI medium for 7 days. Evidence for viral replication was determined by antigen capture ELISA. The neutralizing titer equaled the highest dilution that blocked 100% of viral replication.
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36. All animals assigned to this study were housed in the BSL/3 containment facility at the University of Washington Regional Primate Research Center. This study was an approved project of the University Animal Care and Use Committee. The University of Washington is an accredited American Association for the Accreditation of Laboratory Animal Care institution. Animal monitoring and invasive procedures, including injection of virus inocula and blood collection, were performed under ketamine-HCl sedation administered at 10 mg per kilogram of body weight.
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Distributed Neural Network Underlying Musical Sight-Reading and Keyboard Performance

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Music, like other forms of expression, requires specific skills for its production, and the organization and representation of these skills in the human brain are not well understood. With the use of positron emission tomography and magnetic resonance imaging, the functional neuroanatomy of musical sight-reading and keyboard performance was studied in ten professional pianists. Reading musical notations and translating these notations into movement patterns on a keyboard resulted in activation of cortical areas distinct from, but adjacent to, those underlying similar verbal operations. These findings help explain why brain damage in musicians may or may not affect both verbal and musical functions depending on the size and location of the damaged area.

Music is a message comprising combinatory rhythmic patterns of discrete pitches communicated by a composer to a listener, often through an interpreter. Music and speech have certain aspects in common: Both are used expressively and receptively; both involve fine sequential motor activity for their production; both are constructed of perceptually discrete sounds that can be represented in a writing system. Like speech, music is governed by culture-dependent combinatorial rules; that is, one can speak of a musical grammar in the mind of the composer, performer, and listener that in many respects parallels the grammar

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of language (*1*). Accordingly, conjoint impairment of verbal (aphasia) and musical (amusia) abilities is a frequent outcome of damage to the left cerebral hemisphere in musicians (*2*). However, speech and music also differ in important aspects: A musical phrase does not convey the same sort of information that a verbal sentence does; it evokes feelings or emotions—patterns of body tension and release—rather than referring to specific ideas or objects. Its grammar is organized in terms of harmony and counterpoint rather than patterns of grammatical categories such as noun and verb. Musical notation is graphically, symbolically, and functionally different from the alphabetic writing system (*3*, *4*). Consistent with these distinctions, aphasia is not necessarily associated with impaired musical abilities in musicians (*5*).

The existence of a dissociation between verbal and musical disturbances suggests a relative functional independence of the neurobiological substrates of each ability (*6*). Whereas much is known about the cerebral representations of verbal functions through neuropsychological studies of aphasics (*7*) and positron emission tomography (PET) imaging of normal subjects performing verbal tasks (*8*), the neural organization of musical skills and performance has been more difficult to uncover, mainly because of the rarity of brain-damaged musicians. We thus used PET measurement of regional cerebral blood flow (rCBF) in ten professional pianists (*9*) to study the neurobiological substrates of two particular skills unique to musicians: their ability to sight-read a score and to translate the notations into movement patterns on a keyboard to produce a musical performance.

To functionally isolate the component operations underlying sight-reading and piano performance, we used subtractive PET methodology (*8*). We also applied a technique that combines the functional information derived from PET with the anatomical information of the subjects' brains obtained by magnetic resonance imaging (MRI), a procedure that increases the precision of functional localizations (*10*).

The subjects participated in seven task activation conditions, in a counterbalanced order (*11*). The main experimental condition consisted of the presentation, on a TV monitor located above the subject's head, of the score of a little known partita written by J. S. Bach, which each subject played on a keyboard with the right hand while listening to the performance (*12*). Each of the other conditions served as control to isolate the component operations of the main task and they consisted of (i) visual fixation of the lit screen, (ii) listening to ascending and descending musical scales played on a piano, (iii) playing ascending and descending scales on the keyboard with the right hand while listening to what was played, (iv) presentation of a single dot in one of four quadrants of the screen and manual responses as a function of dot location, (v) reading a musical score presented on a screen, and (vi) reading a musical score presented on the screen and listening to its performance played on a piano (*13*).

We analyzed the data by comparing state activation in paired tasks after stereotaxic image-averaging across subjects to increase the signal-to-noise ratio in the subtraction images (*14*). The significant foci of activation resulting from CBF changes related to task differences are presented in Table 1 in terms of cerebral stereotaxic coordinates.

Each of the three components of the main experimental task (playing, listening, and reading) engaged specific cortical areas that were initially isolated through analysis of the control tasks (Fig. 1). Playing the scales with the right hand (task iii) activated the left motor cortex (area 4), and the right cerebellum corresponding to the motor representation of the right hand, and of the left premotor cortex (area 6). Activation related to listening to musical scales was detected in the secondary auditory cortex of both hemispheres (area 42) and in the superior temporal gyrus of the left hemisphere (area 22), and this obtained whether the scales were played to the subject (task ii) or by the subject (task iii). Listening to a musical piece activated the same cortical areas but also engaged the right superior temporal gyrus, indicating a bilateral involvement of the temporal cortex that was not detected in the scale-listening task.

When the subjects read a musical score (task v) without listening or playing, there was bilateral activation of the extrastriate visual areas, as expected by requirements of processing visual information. However, the areas in the left lingual and fusiform gyri normally engaged in the visual processing of words (*6*) were not activated by the musical notations. Instead, the left occipitoparietal junction was recruited, consistent with the participation of the dorsal visual system in spatial processing (*15*, *16*). In contrast to word reading, the relevant information contained in musical notations is derived not through feature analysis of the notes but through analysis of the spatial location of the notes and of their relative height separation on the staff which is directly related to pitch intervals (*4*, *17*).

The addition of listening to score reading (task vi) produced further activation

Table 1. Significant foci of activation derived by paired activation subtraction. Coordinates of peak activation are expressed in millimeters (*14*): *X* represents the medial-lateral axis (negative, left), *Y* the antero-posterior axis (negative, posterior), and *Z* the dorsoventral axis (negative, ventral). The Brodmann's and cortical area corresponding to the coordinates are also shown.

X	*Y*	*Z*	Brodmann's area	Cortical area
		Listening to scales minus visual fixation		
54	−13	6	Right 42	Secondary auditory
−50	−25	9	Left 42	Secondary auditory
−56	−4	2	Left 22	Superior temporal
		Playing and listening to scales minus listening to scales		
−35	−26	54	Left 4	Primary motor
15	−62	−20	Right cerebellum	Cerebellum
−4	−7	57	Left 6	Superior frontal gyrus
		Reading score minus presentation of visual dots		
20	−95	2	Right 18	Secondary visual
3	−92	11	Right 18	Secondary visual
−23	−95	−3	Left 18	Secondary visual
−24	−66	38	Left 19	Occipito-pariet. sulcus
		Reading score and listening minus reading score		
−50	−23	9	Left 42	Secondary auditory
55	−16	6	Right 42	Secondary auditory
58	−9	5	Right 22	Superior temporal
−50	−33	12	Left 22	Superior temporal
−46	−38	49	Left 40	Supramarginal gyrus
		Sight-reading, playing, and listening minus reading score and listening		
−40	−19	53	Left 4	Primary motor
15	−59	−17	Right cerebellum	Cerebellum
−48	10	29	Left 44	Inferior frontal gyrus
−51	6	36	Left 6	Premotor cortex
−16	6	53	Left 6	Premotor cortex
−28	−64	56	Left 7	Superior parietal lob.
20	−66	57	Right 7	Superior parietal lob.

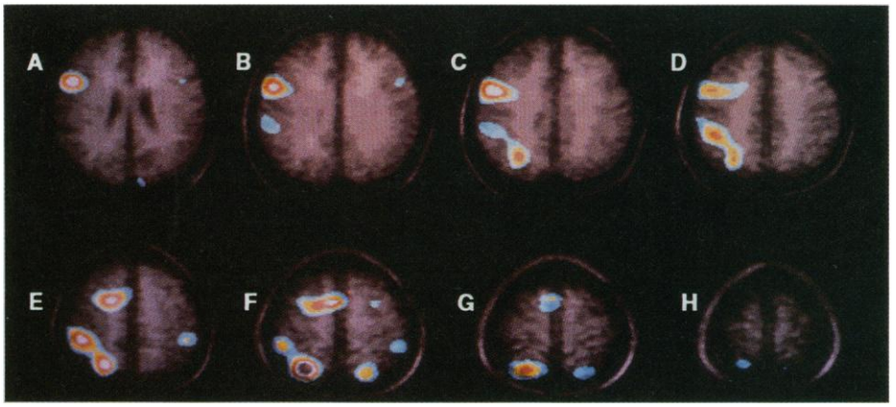

Fig. 1. Cortical activation during sight-reading and piano performance. The images were obtained after averaging from ten subjects and subtracting the musical scale-playing condition. The PET foci of activation are superimposed over MRI horizontal slices of the subjects' brains. Slice A is at +29 on the ventrodorsal axis, and the slices (**A** to **H**) are 6 mm apart. Activation in the anterior left hemisphere corresponds to the involvement of area 44 (A and B) and area 6 (C to F), recruited for the patterning of the motor sequences required for the right manual execution of the piece. Activation in the posterior part of the left hemisphere corresponds to the involvement of area 40 or supramarginal gyrus (D and E) and reflects the mapping of visual and auditory representations of the melody; symmetrical, but less intense ($P < 0.05$), activation of the right area 40 is indicated in slice E. The foci of activation in the most posterior region of the cortex is located in the left occipitoparietal sulcus (C and D) and in the superior parietal lobule (area 7) of both hemispheres (E, F, and G); the latter activation can be attributed to the sensorimotor transformation inherent in visually guided finger positioning. The activation of the motor area 4 was canceled out by subtracting the scale-playing condition, and it is not shown here as it was merging with the other foci on slice E. The present technique does not allow inference about the cerebral organization of individual subjects. However, the variance was of the same order of magnitude in this study as it was in PET studies examining face recognition, object categorization, and letter reading (*21*), suggesting that individual differences were not more pronounced in this musical performance task than in tasks calling for more universal capabilities.

that neither reading nor listening alone had produced, and this activation was located in the superior and posterior part of the supramarginal gyrus (area 40), in the inferior parietal lobule of both hemispheres. The recruitment of these areas only when both reading and listening were conjointly involved suggests that they perform a mapping between musical notation and its corresponding sounds or melody. The visual-to-sound mapping function of the inferior parietal lobule is well established in the verbal domain, and the destruction of this area results in alexia with agraphia (*7*). However, the foci of activation in the present musical task were located in the superior part of the supramarginal gyrus, the destruction of which does not affect reading and writing (*18*). This indicates that the mapping of printed musical notation and its auditory representation takes place in areas distinct from, yet adjacent to, the structures underlying the mapping of visual and auditory representations of words.

Two additional areas that were not implicated by playing, reading, or listening alone were recruited when the subjects performed the main experimental task that required the conjunction of these three components. One involved the superior parietal lobule (area 7) of both hemispheres and may reflect the generation of spatial information derived from the location of the notes on the staff for the actual motor performance required in the manual execution of the musical piece. Consistent with this suggestion is evidence (*16, 19*) that this area of the parietal cortex is strategically placed to mediate the sensorimotor transformations for visually guided skilled actions and finger positioning. The other area of activation specific to the main experimental task involved the left premotor cortex (area 6) and the left inferior frontal gyrus (area 44), immediately above Broca's area, which plays a critical role in organizing the motor sequencing underlying speech production; the activation of the dorsal region of area 44 in the present task may thus reflect a similar role in the organization of the motor sequences inherent in keyboard performance.

Our results suggest that sight-reading and piano performance entail processing demands that are realized by a cerebral network distributed over the four cortical lobes and the cerebellum. This network parallels the neural substrates of verbal processing but is distinct from it, and the spatial nature of musical notation requires for its reading the participation of the superior parietal lobe, which is not normally involved in verbal performance. The cerebral areas used during the execution of these musical skills are therefore relatively functionally independent from the areas used for verbal tasks, which explains why some aphasic musicians can pursue their musical activities with little disruption (*6*). Nonetheless, the proximity of the critical cerebral structures underlying both verbal and musical performance makes a conjoint disruption of both domains a likely occurrence when brain damage is either extensive or diffuse (*20*). The organization of the neural substrates of musical performance is thus a function of the specific processing demands of these skills, consistent both with a distributed representation made necessary by the multiplicity of operations required for musical performance and with a modular representation reflecting the processing competences of the cerebral structures involved. However, sight-reading and playing are only a fraction of musical experience, and we are still far from understanding the pleasure and emotions elicited by music, as well as the composer's mind.

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11. The subjects were in a supine position, the head firmly held in a customized frame, and with an earphone in each ear. An intravenous catheter was placed into the left brachial vein for injection of [^{15}O]H_2O (34 mCi per injection), which served as CBF tracer [M. E. Raichle *et al.*, *J. Nucl. Med.* **24**, 790 (1983)]. In each activation condition, the task started conjointly with the injection of the radioactive solution, and the PET measurement of CBF began 15 s later and lasted for 60 s. The PET scanner was a Scanditronix PC-2048 camera, which produces 15 image slices at a three-dimensional resolution of 5 by 5 by 7 mm [A. C. Evans *et al.*, *IEEE Trans. Med. Imaging* **10**, 90 (1991)]. A rotating ^{68}Ge source was used to correct the images for attenuation of the gamma rays in the skull and brain tissue. For each subject, a high-resolution magnetic resonance image was obtained (63 slices, 2 mm thick) with a Philips Gyroscan (1.5 T). The image planes were chosen parallel to the subject's glabella-inion line, which was aligned with the tomograph's laser reference line and transcribed onto the head-holder as a marker for the correlation of PET imaging and MRI.
12. Each subject played on a Roland electronic keyboard, located above the abdomen and individually adjusted for convenient positioning of the right hand on the keys. The keyboard was interfaced with a Yamaha MIDI selector, set on "Grand Piano." The output of the selector was forwarded to a digital audio tape recorder, which served as an amplifier to which the subject's earphones were connected and which also recorded on tape the subject's performance. The whole musical score was presented on a high-resolution Mitsubishi TV monitor located 60 cm from the subject's eyes and perpendicular to eye gaze. The score consisted of the soprano part of the 4th Variation of Partita BWV 767 by J. S. Bach, which none of the subjects had ever seen or heard. Before the task, the subject was told the key signature of the piece as well as the range of notes so that he could adjust the keyboard accordingly, but he was not shown the score. Performance was nearly flawless except for the odd false notes.
13. The musical score in the reading task (v) was the soprano part of J. S. Bach's choral BWV 694 and in the reading and listening task (vi) was the soprano part of J. S. Bach's choral BWV 717, both of which are harmonically and rhythmically similar to the partita used in the main experimental task and which were also unknown to the subjects.
14. The PET activation functional images were mapped onto the magnetic resonance structural images with a PIXAR three-dimensional (3-D) imaging system (*10*). This interactive 3-D image software was used to establish an orthogonal coordinate frame based on the anterior commissure–posterior commissure (AC-PC) line as identified in the MRI volume. These coordinates were used to apply a linear resampling of each matched pair of MRI and PET data sets into a standardized stereotaxic coordinate system [J. Talairach and P. Tournoux, *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, New York, 1988)]. We reconstructed the PET images using a 20-mm Hanning filter to overcome residual anatomical variability, normalized for global CBF; the difference between control and experimental conditions was determined for each subject. We obtained the image volume of the mean state-dependent change by averaging across subjects [P. T. Fox *et al.*, *J. Comput. Assist. Tomogr.* **9**, 141 (1985)] and then converted it to a t-statistic by dividing the mean state-dependent change by the mean standard deviation in normalized CBF for all intracerebral voxels and by multiplying this quotient by the square root of n (number of subjects). Anatomical and functional images were merged to allow direct localization on the magnetic resonance images of t-statistic peaks identified by an automatic peak-detection algorithm [M. A. Mintun *et al.*, *J. Cereb. Blood Flow Metab.* **9**, 96 (1989)] and for the anatomical correlation of extended zones of activation not expressible in terms of isolated peaks. The peak distribution was then searched for significant signals with change-distribution analysis [P. T. Fox *et al.*, *ibid.* **8**, 642 (1988)] and z score thresholding. No correction for the number of comparisons was performed [P. T. Fox, *ibid.* **11**, A79 (1991)], and peaks with significance levels of $z > 2.81$, $P < 0.005$, are reported.
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19. M. Taira *et al.*, *Exp. Brain Res.* **83**, 29 (1990).
20. An illustration is provided by the French composer Maurice Ravel who suffered a progressive cerebral disease of unknown origin. His first symptoms were an agraphia and an ideomotor apraxia, but his musical faculties were not initially affected and he continued playing the piano and composing for about one more year before he became unable to read and play music and to compose. He was able to play scales and to appreciate musical performance throughout his illness [M. Rosenthal, *Monde Musique* **103**, 114 (1987); M. Marnat, *Ravel* (Fayard, Paris, 1986)].
21. J. Sergent *et al.*, *Brain* **115**, 15 (1992); J. Sergent *et al.*, *Cereb. Cortex* **2**, 68 (1992).
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