

# Nurture versus Nature: Long-Term Impact of Forced Right-Handedness on Structure of Pericentral Cortex and Basal Ganglia

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Does a conflict between inborn motor preferences and educational standards during childhood impact the structure of the adult human brain? To examine this issue, we acquired high-resolution T1-weighted magnetic resonance scans of the whole brain in adult “converted” left-handers who had been forced as children to become dextral writers. Analysis of sulcal surfaces revealed that consistent right- and left-handers showed an interhemispheric asymmetry in the surface area of the central sulcus with a greater surface contralateral to the dominant hand. This pattern was reversed in the converted group who showed a larger surface of the central sulcus in their left, nondominant hemisphere, indicating plasticity of the primary sensorimotor cortex caused by forced use of the nondominant hand. Voxel-based morphometry showed a reduction of gray matter volume in the middle part of the left putamen in converted left-handers relative to both consistently handed groups. A similar trend was found in the right putamen. Converted subjects with at least one left-handed first-degree relative showed a correlation between the acquired right-hand advantage for writing and the structural changes in putamen and pericentral cortex. Our results show that a specific environmental challenge during childhood can shape the macroscopic structure of the human basal ganglia. The smaller than normal putaminal volume differs markedly from previously reported enlargement of cortical gray matter associated with skill acquisition. This indicates a differential response of the basal ganglia to early environmental challenges, possibly related to processes of pruning during motor development.

## Introduction

A compelling question permeating discussions of brain plasticity relates to the interplay between inborn traits and their environmental modulation. Although genes can shape brain structure (Pezawas et al., 2004), it can also be modified by environmental factors such as training (Maguire et al., 2000; Gaser and Schlaug, 2003b; Draganski et al., 2004). Long-term structural effects of skills acquired during childhood are difficult to study. Individuals will need to be well motivated to continuously practice the new skill over months and years. We approached this issue in humans using the model of switched handwriting because of its forced nature and stability.

A predominance of right-handedness is an inborn trait that can be found in ~90% of humans independently of cultural

background (Corballis, 2003). Although structural and functional differences in brain organization have been found with handedness (Serrien et al., 2006; Sun and Walsh, 2006), the role of genetic and environmental factors is unclear. Although social expectancies result in switched or “converted” left-handedness for writing, such people usually retain left-handedness for many other skilled manual activities. Using functional brain imaging in adult converted left-handers and age-matched subjects with consistent handedness, we found that an attempt to switch handedness impacts on the cerebral motor control of writing (Siebner et al., 2002) and simple finger movements independently of the executing hand (Klöppel et al., 2007). Although the acquisition of a new skill (i.e., handwriting) was limited to the right hand, we found consistent changes affecting apparently unrelated movements such as single finger button presses with both left and right hands. Rather than rendering converted left-handers more “normal” (i.e., similar to consistent right-handers), our previous work indicated the opposite. Their functional organization is less similar to that of right-handers than is that of consistent left-handers (Klöppel et al., 2007).

Expanding on our functional imaging work, we set out to see whether the task-related changes in motor activation of adult converted left-handers have a structural correlate to indicate plastic reorganization by training (i.e., through environmental factors). In addition to the well established method of whole-

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brain voxel-based morphometry (VBM), a complementary approach was also used to study changes in cortical folding patterns associated with handedness (Amunts et al., 2000) and attempts to switch handedness for writing. Based on previous work (Maguire et al., 2000; Gaser and Schlaug, 2003b; Draganski et al., 2004), we expected an increase in the relative volume of gray matter of structures involved in the planning and execution of skilled manual movements.

## Materials and Methods

We examined 34 converted left-handers (mean age, 40; range, 24–56 years; 22 males, 12 females) and compared them with 23 consistent age- and sex-matched right-handed (mean age, 34; range, 22–59 years; 17 males, 6 females) and 18 similar left-handed subjects (mean age, 36; range, 25–56 years; 12 males, 6 females). Participants gave written informed consent and the local Ethics Committee approved the experimental procedures. Inclusion as a converted left-hander depended on a clear recollection by parents or subjects of writing commenced with the left hand at school, followed by a switch to the right. Subjects with a history of neurological disease or prolonged impairment of hand function were excluded. Sixteen subjects from each group were previously included in a functional imaging study (Klöppel et al., 2007) that is complementary to this structural one. The Edinburgh Handedness Inventory (Oldfield, 1971) was used in which a score of  $-100$  reflects extreme left-handedness and  $+100$  extreme right-handedness. Results ranged in right-handers from 60 to 100 (median, 100), left-handers from  $-100$  to  $-60$  (median,  $-95$ ), and converted left-handers from  $-80$  to  $+50$  (median,  $-42.5$ ) (supplemental Figs. 1, 2, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material). Questionnaires were used to identify those converted left-handers with at least one left-handed first-degree family member.

The frequency of upstrokes and downstrokes while continuously writing pairs of lowercase “l” letters (“ll”) with the right and left hand was measured and analyzed with an electronic writing tablet, as described previously (Klöppel et al., 2007). To objectively assess individual side-to-side relative handwriting dexterity, a writing quotient was derived to reflect the degree of right-to-left lateralization (“frequency of with right hand/frequency with left hand”). Usable data from both hands were acquired from 20 right-handers and 18 consistent and 32 converted left-handers. *F* tests with *post hoc* Scheffé testing were used to compare the absolute frequencies as well as the writing quotient between groups.

**Data acquisition.** Magnetic resonance imaging (MRI) was performed on a 3T system (TRIO; Siemens) with a T1-weighted FLASH three-dimensional sequence (repetition time, 15 ms; echo time, 4.92 ms; flip angle, 25°; 192 slices; slice thickness, 1 mm; matrix,  $256 \times 256$  mm).

**Data analysis.** VBM was performed using SPM5 ([www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)). Images were segmented into gray matter, white matter, and normalized to Montreal Neurological Institute (MNI) space using a unified approach (Ashburner and Friston, 2005). Parameters for bias correction, tissue classification, and spatial normalization into a standard space of the MNI are iteratively estimated from the same generative model. An additional step, usually referred to as modulation, is included to compensate for the effect of spatial normalization. This step involves multiplying the spatially normalized segmented images by the relative change of volume with spatial normalization (Ashburner and Friston, 2000). After this step, the values of each voxel represent a measure of the relative local volume of that tissue class. Finally, we smoothed the gray matter segment using an isotropic Gaussian smoothing kernel of 10 mm (full width at half-maximum). Correction for multiple comparisons was performed using a family-wise error (FWE) correction across the whole brain volume scanned. Groups differing in handedness were compared on a voxel-by-voxel basis using an ANOVA design. Pearson’s correlation was used to test for an association between significant voxels and the degree of lateralized handwriting, its absolute frequencies, and the Edinburgh score.

Given that the cortical folding pattern is highly variable, forcing individual anatomy to match a common template as used in VBM is not always optimal. As a complementary method to VBM, we studied cortical structure using a validated, automated, and hence equally unbiased structure recognition software package (<http://brainvisa.info/>) to deter-

mine the surface area of the left and right central sulcus (Jouvent et al., 2008). This three-dimensional surface-based method extracts gyrus- and sulcus-specific information for comparison between groups and has been found sensitive to handedness-related differences (Mangin et al., 2004).

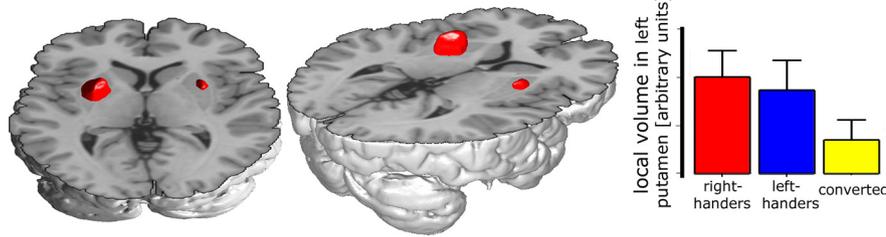
Each cortical fold is detected first as a simple dark ridge of the three-dimensional T1-weighted image. Then standard sulci, made up of groups of such folds, are identified by a set of 500 artificial neural networks that have been trained on a database of 26 manually labeled brains. Each identified sulcus is finally meshed to compute its surface as a sum of triangular areas. We restricted the analysis to the surface of the central sulcus ( $AREA_{CS}$ ) because  $AREA_{CS}$  is closely related to the sulcal depth studied in related neuroanatomical work (Amunts et al., 1996, 2000) and is the least variable structure among sensory-motor areas (supplemental Figs. 4, 5, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material). To assure accuracy, final labeling of the central sulcus was inspected and corrected or removed when required by a user blind to subject handedness. We computed a lateralization index of right-to-left differences in the surface area of the central sulcus [ $2 \times (AREA_{LEFT\ CS} - AREA_{RIGHT\ CS}) / (AREA_{LEFT\ CS} + AREA_{RIGHT\ CS})$ ] (Mangin et al., 2004). Based on previous reports (Amunts et al., 1996, 2000; Mangin et al., 2004), we expected that, in individuals with consistent handedness, the surface of the central sulcus would be larger in the hemisphere contralateral to the dominant hand. Therefore, we applied one-tailed statistical tests when comparing consistent right- and left-handers. Two-tailed tests were used when comparing the converted group with the groups of consistent right- and left-handers.

## Results

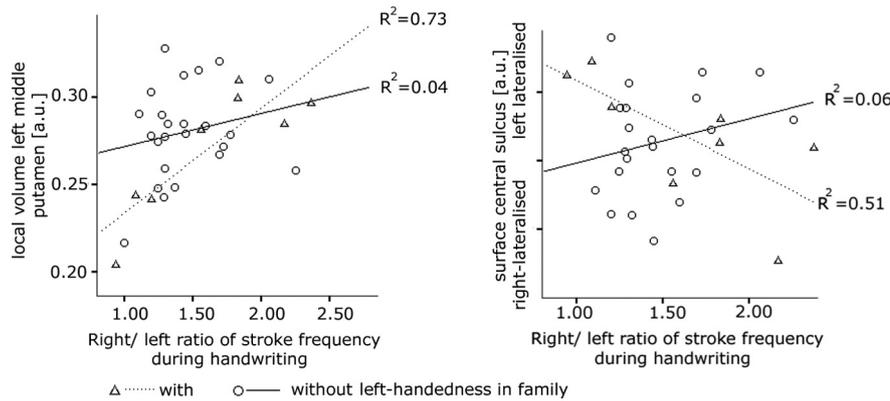
No differences were observed in writing kinematics between right- and converted left-handers (supplemental Fig. 3, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material). The writing quotient in right-handers ranged from 0.87 to 2.79 (mean, 1.87; SD,  $\pm 0.42$ ) and from 0.31 to 1.47 (mean, 0.53; SD,  $\pm 0.25$ ) in the left-handers. In the converted group, the writing quotient was comparable with right-handers, ranging from 0.94 to 2.91 (mean, 1.51; SD,  $\pm 0.41$ ). No correlation between individual writing quotients and Edinburgh scores was observed in any group, indicating that they reflect different aspects of handedness.

The ANOVA revealed that the volume of gray matter in the middle part of the left putamen significantly differed between groups ( $F = 16.53$ ;  $p_{corrected} = 0.027$  at  $x, y, z = -28, 2, 6$  in MNI space). To follow up on this finding, we tested for changes with handedness in the putamen of both hemispheres. *Post hoc* *t* tests indicate that the group effect in the ANOVA was caused by a smaller middle section of the putamen in converted left-handers relative to consistent right-handers ( $t = 5.58$ ;  $p < 0.001$ , at  $x, y, z = -28, 0, 6$ ) and consistent left-handers ( $t = 3.44$ ;  $p < 0.001$ , at  $x, y, z = -26, 4, 6$ ) (Fig. 1). There is a suggestion of a subtle reduction in local volume of left putamen in consistent left-handers compared with right-handers ( $t = 2.02$ ;  $p = 0.023$ ). The *post hoc* analysis revealed similar handedness-related changes in the same subregion of right putamen ( $F = 9.85$ ;  $p_{uncorrected} < 0.001$  at  $x, y, z = 28, 10, 2$ ) again driven by a relative reduction in putaminal gray matter volume in the converted group. However, this finding did not survive correction for multiple comparisons. The local volume of left putamen did not differ between converted subjects from left-handed families compared with those without ( $p > 0.4$ ).

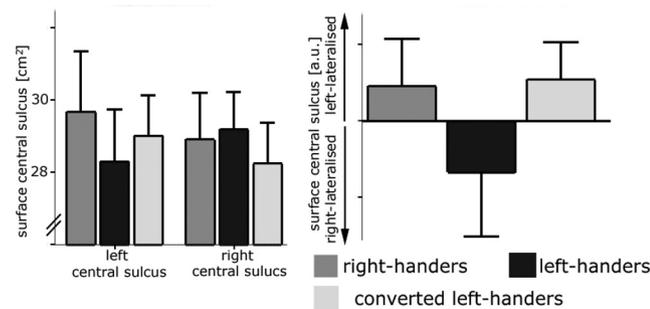
Only converted left-handers showed a linear relationship between the writing laterality quotient and left putaminal gray matter volume for voxels surviving FWE correction in the categorical comparisons reported above. A relatively smaller middle putamen was associated with greater left-handedness in writing ( $r = 0.433$ ;  $p = 0.013$ , two-tailed) (Fig. 2) that remained significant after controlling for effects of age ( $r = 0.39$ ;  $p = 0.03$ , two-tailed) or mean stroke frequency ( $r = 0.4$ ;  $p = 0.03$ , two-tailed). An



**Figure 1.** Areas showing significant changes related to handedness (image threshold for display purposes:  $p < 0.001$ , uncorrected). Results overlaid on a single subject T1-weighted MRI scan in MNI-space. Right panel, Local gray matter volume in left putamen (at  $x, y, z = -28, 2, 6$ ). Error bars represent 90% confidence intervals of the mean.



**Figure 2.** Scatter plot revealing that a greater right-hand lateralization of writing significantly correlates with a relatively larger volume of the left middle putamen (left panel) and the right-lateralization of cortical surface area size in the central sulcus (right panel) in converted left-handers with a first-degree left-handed family member. a.u., Arbitrary units.



**Figure 3.** Left panel, Central sulcus surface area for each group, separately for each hemisphere. Right panel, Illustration of lateralization of the central sulcus surface area. Error bars represent 90% confidence intervals of the mean. a.u., Arbitrary units.

interesting pattern emerged on splitting the converted left-handers into those with and without a history of left-handedness in at least one first-degree relative (Fig. 2). The correlation between “local” volume in left middle putamen and the laterality quotient was driven by the eight converted individuals with a positive family history of left-handedness. These individuals showed greater midputaminal volume the more right-lateralized their writing ( $r = 0.85$ ;  $p < 0.01$ ). No consistent relationship was found in the 24 converted left-handers without left-handed first-degree relatives ( $r = 0.21$ ;  $p > 0.5$ ).

No correlation was found between the relative local putamen volume and individual variations in writing performance with the contralateral hand as indexed by mean stroke frequency. There was also no correlation with individual Edinburgh scores in the converted group as a whole or in subgroups differing in familial left-handedness.

Although standard voxel-based morphometric analysis showed no consistent differences between groups in sensorimotor cortex, the analysis of  $AREA_{CS}$  revealed differential lateralization between the two consistently handed groups ( $t = 1.92$ ;  $p = 0.032$ , one-tailed). This difference was caused by a larger  $AREA_{CS}$  contralateral to the dominant hand in both groups with consistent handedness. The lateralization pattern in the converted group was significantly different to that in consistent left-handers ( $t = 2.32$ ;  $p = 0.02$ , two-tailed) with a larger  $AREA_{CS}$  in the left nondominant hemisphere, corresponding to the pattern found in consistent right-handers (Fig. 3). We found no correlation between individual variations in the degree of handedness (based on either the Edinburgh questionnaire or lateralization of handwriting) and  $AREA_{CS}$  or its lateralization index in the converted group as a whole. However, when including only the eight converted individuals with left-handed first-degree family members,  $AREA_{CS}$  was more right-lateralized the more right-lateralized was handwriting ( $r = -0.72$ ;  $p = 0.045$ , two-tailed) (Fig. 2, right panel). In this subgroup, converted individuals showing a stronger right-hand advantage for writing had a smaller  $AREA_{CS}$  in the left nondominant hemisphere ( $r = -0.33$ ) but a larger

$AREA_{CS}$  in the right dominant hemisphere ( $r = 0.2$ ).

Both consistently handed groups showed a strong positive correlation between relative putaminal volume and ipsilateral  $AREA_{CS}$  ( $p < 0.001$ , two-tailed;  $r = 0.57$  and  $r = 0.62$  for the left and right hemisphere, respectively). Such a correlation was present only in those converted subjects with a family history ( $p < 0.05$ , two-tailed;  $r = 0.47$  and  $r = 0.42$  for the left and right hemisphere, respectively), but no such correlation was evident in those without a family history ( $p > 0.5$ ).

### Discussion

We found two structural signatures of forced right-handedness in the adult human brain. First, surface-based structural analyses showed a reversal of left–right asymmetry of  $AREA_{CS}$  in the converted group, with a larger central sulcus surface area in the left, nondominant hemisphere. Second, VBM identified a relative reduction in gray matter volume of the middle part of the left putamen, with a similar trend in the homologous part of the right putamen.

### Changes in structural asymmetry of pericentral cortex

Ample evidence from morphometric MRI studies indicates that experience shapes brain structure (Maguire et al., 2000; Gaser and Schlaug, 2003b; Draganski et al., 2004). In our study, both consistently handed groups showed a larger  $AREA_{CS}$  in the dominant relative to the nondominant hemisphere in line with previous studies on hand preference (Kim et al., 1993; Amunts et al., 1996; Dassonville et al., 1997; Volkmann et al., 1998). Although structural asymmetries in pericentral cortex appear to be a consistent feature of handedness, it is unclear whether they are a secondary marker of handedness (i.e., reflecting use-dependent plasticity) or constitute a causative feature that drives human handedness.

The morphometric results in converted left-handers strongly support the first hypothesis. Left-handers who switched handedness for handwriting displayed a more left-lateralized  $AREA_{CS}$  with a relative expansion of  $AREA_{CS}$  in the nondominant hemisphere (Fig. 3). This is in line with our study on simple finger movements. Here, the degree of acquired right-handedness correlates with the magnitude of functional activation in the left primary motor cortex of converted left-handers (Klöppel et al., 2007). Standard VBM did not pick up these cortical changes, which speaks to a greater sensitivity of cortical surface-based morphometric methods in certain circumstances.

### Structural changes in the basal ganglia

Adult converted left-handers showed a relatively smaller middle part of the left putamen compared with both consistently handed groups. Since the middle part of the right putamen showed a similar trend, we infer that forced right-handedness had a similar effect on putaminal structure in both hemispheres. This contrasts with the change in pericentral sulcal surface area in converted left-handers, which is asymmetrically expressed with a shift in surface area asymmetry from the right to the left hemisphere. Figure 1 illustrates that relative putaminal volume in the converted group does not fall between that of the two groups with consistent handedness. This is similar to findings from our functional MRI study (Klöppel et al., 2007).

Rather than looking at changes in anatomically defined regions, VBM allowed us to pinpoint subregions wherever they occurred in the brain. Converging evidence from functional and structural brain imaging shows that the middle part of the putamen represents a transition zone between the caudal “executive” and the rostral “associative” territory of the putamen that is implicated in higher order aspects of manual motor control (Scholz et al., 2000; Taniwaki et al., 2003; Gerardin et al., 2004; Lehericy et al., 2006; Vaillancourt et al., 2007; Jaffard et al., 2008). Tractographic MRI studies have shown that the midputamen receives inputs mainly from premotor and prefrontal cortex (Lehericy et al., 2004; Draganski et al., 2008). The middle part of the putamen represents the striatal territory where executive and associative cortico-basal ganglia-thalamo-cortical loops overlap. Several functional imaging studies have shown a gradual shift in task-related activity from the caudal to rostral parts of the putamen as individuals learn a new manual skill (Lehericy et al., 2005; Poldrack et al., 2005) or when they plan rather than execute novel and over-learned movements (Jankowski et al., 2009). The location found in our study suggests that forced preference for right-hand writing had greatest impact on the striatal territory that provides an interface between executive and cognitive control of skilled movements.

We argue that a forced switch of handedness represents an early and persistent environmental modulator of maturation of the basal ganglia, which itself is genetically determined and only complete in the third decade of life (Steen et al., 1997; Sowell et al., 1999; Snook et al., 2005). Morphometric studies in children aged 7–16 have described a substantial loss of striatal and pallidal volume during normal development (Sowell et al., 1999; Thompson et al., 2000), likely because of pruning processes. Studies in genetically caused disorders found a relative size increase of these structures compared with controls (Binkofski et al., 2007; Gothelf et al., 2008). We hypothesize that the environmental challenge posed by forced right-handed writing enhances normal pruning in the territory of the putamen that integrates executive and cognitive aspects of motor control.

In converted left-handers, individual variations in the volume of the left midputamen correlate with the acquired dexterity of handwriting. Those individuals in whom conversion was least

effective in establishing right-lateralized handwriting showed the smallest putaminal volumes. This finding supports the notion that structural changes found in the putamen are related to switching handedness. Interestingly, this correlation was found only in the subgroup with at least one left-handed family member. Given the lack of correlation with the absolute frequency of writing, as well as with the Edinburgh score, this relative change of putaminal volume is related to the degree of conversion of handwriting rather than to proficiency or handedness per se. A “more normal” relative volume of the putamen correlates with handwriting in those with a greater degree of conversion. A possible explanation is that strongly right-lateralized converted subjects are incorrectly characterized and were, in fact, consistent right-handers. This explanation is unlikely given that the 10 converted left-handers who were most right-lateralized when writing were still clearly left-lateralized by Edinburgh scores (mean score,  $-38$ ). More likely, converted subjects with a more normal putaminal volume were able to better adapt to the environmental challenge of conversion, so that the interaction had a lesser effect on their brain structure. It is noteworthy that the degree of lateralized handwriting also correlates with neuronal activation in the anatomically connected left premotor cortex during simple button presses, independently of the executing hand (Klöppel et al., 2007).

Previously, studies of morphometric changes associated with long-term skilled movements often focused on musicians. Such studies report volume increases in appropriate critical brain regions (Schlaug, 2001; Gaser and Schlaug, 2003a). We suggest a switch of handedness, viewed as a perturbation of normal development, is a fundamentally different process from that associated with improving and constantly honing normally acquired motor skills, as in musicians who may themselves have genetically “primed” brain organization. It has been suggested that motor learning is normally associated with a switch from subcortical to cortical control during brain maturation (Thomas et al., 2004). Such a mechanism would explain differential learning-associated effects at different ages, or when learning is restricted to a certain time of life.

### Effect of family history

Prompted by one of the reviewers, we explored whether a positive family history of left-handedness was associated with distinct structural changes in the context of forced dextral writing. Only the eight converted subjects with at least one left-handed first-degree relative showed a correlation between the acquired right-hand advantage for writing and structural changes at the cortical and subcortical levels. The more that “familial” left-handers acquired a right-hand advantage for writing, the more the central sulcal area volumetric change was lateralized to the right dominant hemisphere and the greater the volume of the left middle putamen. No such correlations were found in the remaining 24 converted subjects without family history of left-handedness. The correlation patterns suggest that, in the context of familial left-handedness, the motor system deals more efficiently with forced dextral writing if there is little left-to-right shift of the inborn left-hemispheric dominance in the pericentral executive cortex. The difference between converted subjects with or without a family history of left-handedness underscores the relevance of genetic factors to the individual manifestations of left-handedness (Annett, 1978, 1999; Medland et al., 2009), but it may also reflect differences in social attitudes to left-handedness if a parent or sibling is also left-handed. Whatever the cause, these findings also provide evidence for subgroups in populations of people with converted handedness and most likely also in consistent left-handers, which are prominently

influenced by genetic factors. Such factors need to be taken into account in future work.

## Summary

Morphometry using high-resolution structural magnetic resonance scans has identified two distinct structural correlates of forced right-handedness in the adult human brain. Both consistently handed groups (right and left) showed a strong positive correlation between midputamen volume and  $AREA_{CS}$  of the ipsilateral hemisphere. This finding suggests that the development of both could be linked during normal maturation. A different pattern in the converted left-handed group speaks to a disruption of normal structural development that involves a putaminal territory that functionally integrates executive and cognitive control of skilled movements.

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