Neural representations of ethologically relevant hand/mouth synergies in the human precentral gyrus

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Complex motor responses are often thought to result from the combination of elemental movements represented at different neural sites. However, in monkeys, evidence indicates that some behaviors with critical ethological value, such as self-feeding, are represented as motor primitives in the precentral gyrus (PrG). In humans, such primitives have not yet been described. This could reflect well-known interspecies differences in the organization of sensorimotor regions (including PrG) or the difficulty of identifying complex neural representations in peroperative settings. To settle this alternative, we focused on the neural bases of hand/mouth synergies, a prominent example of human behavior with high ethological value. By recording motor- and somatosensory-evoked potentials in the PrG of patients undergoing brain surgery (2–60 y), we show that two complex nested neural representations can mediate hand/mouth actions within this structure: (i) a motor representation, resembling self-feeding, where electrical stimulation causes the closing hand to approach the opening mouth, and (ii) a motor–sensory representation, likely associated with perioral exploration, where cross-signal integration is accomplished at a cortical site that generates hand/arm actions while receiving mouth sensory inputs. The first finding extends to humans’ previous observations in monkeys. The second provides evidence that complex neural representations also exist for perioral exploration, a finely tuned skill requiring the combination of motor and sensory signals within a common control loop. These representations likely underlie the ability of human children and newborns to accurately produce coordinated hand/mouth movements, in an otherwise general context of motor immaturity.

Since Penfield’s original work, it is commonly assumed that complex motor responses are produced by combining elemental movements that are independently represented at different neural sites (1). However, the generality of this model was recently challenged in nonhuman primates, where reaching, grasping, defensive, and hand/mouth movements have been found to be represented as complex motor primitives in independent circumscribed territories of the precentral gyrus (PrG) (2–4). To account for this observation, it was suggested that complex motor primitives have emerged during primate evolution to optimize the production of ethologically relevant behaviors (4). However, to date, direct evidence is lacking that such integrated representations of ethologically relevant movements also exist in humans. This may have two different origins.

First, it could be that complex ethologically relevant representations exist in human PrG but have not yet been described, due to the difficulty of identifying neural representations associated with the expression of elaborate sensorimotor behaviors in peroperative contexts. With respect to this point, Penfield and other researchers have clearly reported complex multijoint motor responses following cortical stimulation (5–8), including concurrent movements of the hand and mouth (9). Nevertheless, these movements were not investigated systematically in several subjects, described in detail, or related to the existence of integrated neural representations for ethologically relevant behaviors. An obstacle to the investigation of these representations could have been the tendency to stop the stimulation following movement onset. This was explicitly acknowledged by Penfield in the following terms: “the stimulating electrode has frequently been removed at the first evidence of response, and thus the opportunity of producing more of the elaborate synergic responses may have been missed” (6).

At a second level, it could be that the PrG does not contain functional representations of complex ethologically relevant behaviors in humans. This possibility is consistent with the existence of substantial dissimilarities in sensorimotor organization between human and nonhuman primates (10, 11). Interestingly, these dissimilarities are well documented for the precentral region mediating ethological synergies in monkeys. In this species, electrical stimulation in the rostral part of PrG evokes coordinated hand-to-mouth movements (12). These movements are part of the behavioral repertoire of the primate newborns (13), which is consistent with the observation that the rostral (phylogenetically oldest) part of PrG lacks cortico-motoneural cells and generates movements by recruiting the integrative mechanisms of the spinal cord through descending projections that are mature at birth (14). However, in human infants, the difficulty of evoking motor responses through electrical stimulation of the rostral PrG does not seem consistent with the existence of early mature descending projections (15, 16). Also, in adults, transcranial magnetic stimulation studies have suggested, in apparent contrast with monkey data, that late-maturing cortico-motoneural cells are present in the human rostral PrG (17, 18).

The main aim of this study was to determine whether integrated neural representations of complex actions can be found in the human PrG. We investigated this possibility by studying the neural bases of hand/mouth synergies, a salient example of

Significance

The motor repertoire of infants is narrow. Yet newborns can accurately bring their hands toward their mouth for self-feeding, thumb-sucking, or perioral exploration, thus showing fine coordinated movement synergies between the hand and mouth. Here, we show that these gestures of high ethological value are selectively encoded in the human brain and represented as integrated primitives within the precentral gyrus, a key region for sensorimotor processing. These findings have major implications for our understanding of the organization and phylogensis of motor functions in primates.

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early and elaborate human behavior with high ethological value (19–21). To this end, motor and somatosensory mapping were combined in children and adult patients undergoing brain surgeries.

Results

Twenty-six patients (12 females) whose surgery required uncovering the PrG were involved in the study (SI Text, Patients). The age of the patients ranged from 2 to 60 y old (mean, 29 ± 20). Seven subjects were younger than 10 y old, including four younger than 4 y old. Brain mapping was carried out in three consecutive steps using well-defined procedures commonly known to minimize the risk of postoperative sequelae in patients (Methods). First, direct electrical stimulation of the cortex was used to identify eloquent motor regions. Second, for all the sites that evoked upper limb motor responses, we recorded the somatosensory-evoked potentials (SEPs) induced by passive movements of the mouth (i.e., movements evoked through electrical stimulation of the orbicularis oris muscle). The aim was to determine whether specific sites could embody a closed hand/mouth sensorimotor loop. When one such site was identified, additional data were collected to determine whether this site of interest also received sensory afferences from the upper limb muscles of the contralateral hemibody. Collecting upper limb SEPs in a systematic way was not possible, considering that the duration of the mapping protocol had to be limited to 15 to 20 min. Third, SEPs related to upper limb stimulations were collected for all the sites that evoked mouth motor responses. The aim was then to determine whether such sites that were motor for the mouth could be sensory for the hand. No such site was identified.

Independent Motor Responses. Electrical stimulation was delivered at 144 sites distributed over the surface of PrG (see SI Text, Summary of Results for details and additional figures). Forty-seven of these sites produced isolated motor responses of the upper limb (n = 35) or the mouth (n = 12) (Fig. 1). Among upper limb responses, seven involved the whole limb, three involved the proximal arm, and 25 involved the distal hand and wrist segments. As shown in Fig. 1A, we found upper limb movements to be represented more dorsally than mouth movements, which clustered ventrally, in both adults and children, in agreement with the typical somatotopic organization originally identified by Penfield and Boldrey (5) (see SI Text, Somatotopy of Independent Responses for quantitative evidence and additional figures). Although some level of overlap was observed between upper limb and mouth representations at the interindividual level, we did not find any subject for whom independent motor sites for the mouth were located dorsally next to the independent motor sites for the upper limb.

Hand/Mouth Motor Synergies. We identified 10 sites evoking hand/mouth motor synergies in nine different subjects, including two of the youngest patients of our sample (3 y old). As shown in Fig. 2, these sites were not located in a specific portion of the PrG but interleaved with the sites evoking independent movements of the upper limb and mouth, for both adults and children (see SI Text, Motor Synergies for quantitative evidence and additional figures). During stimulation of these sites, the mouth gradually started to open while the closing hand moved toward the face through contraction of upper limb flexor muscles (Fig. 2 B and C), as if wanting to bring something to the mouth. These synergies were the only intersegmental synergies found in this study. Functionally, they were unlikely to result from the incidental recruitment of adjacent upper limb and mouth motor sites (22). Indeed, they could not be broken down into independent mouth or upper limb movements when the intensity of the stimulation was reduced up to the point that no response was observed. Also, the mean intensity at which hand/mouth motor synergies (4.6 mA) and independent responses (4.2 mA) were triggered was not statistically different [t(55) = –0.49, P > 0.60]. Finally, hand/mouth motor synergies never recruited extensor muscles of the upper limb (triceps, extensor digitorum communis) while the mouth was opening, despite the fact that extension movements represented more than 30% of all of the responses recorded for the upper limb along the central sulcus (the hypothesis that only flexion movements were recruited by chance in the 10 hand/mouth motor synergies identified in this study is unlikely; P < 0.023).

Hand/Mouth Motor–Sensory Synergies. Following motor stimulations, SEPs were recorded from the orbicularis oris at only the sites that were found to evoke motor responses of the upper limb (including sites representing hand/mouth motor synergies). Ten sites were then identified in 10 subjects, including two of the youngest patients of our sample (2- and 4-y-olds) (Fig. 3A). Functionally, these neural sites were thus concurrently sensorial for the mouth and motor for the hand/wrist (Fig. 3 B and C). Notably, none of the sites where hand/mouth motor synergies

![Fig. 1](image_url)
were evoked received sensory afferences from the mouth. In 80% of the cases, sensory responses were recorded from motor sites triggering flexion movements. As shown in Fig. 3A, these sites were not evenly distributed over the precentral surface. For both adults and children, they were clustered in the dorsal sector of the PrG, where hand/arm movements are typically represented (see SI Text, Motor–Sensory Synergies for quantitative evidence and additional figures).

Following the recording of mouth SEPs, additional data were gathered to determine whether the sites mediating hand/mouth motor–sensory synergies also received sensory afferences from the upper limb. To this end, we collected SEPs from five muscles (opponens pollicis, abductor digiti minimi, flexor carpi radialis, extensor digitorum communis, and biceps). For all tested sites, none of these responses were found. This negative result was not due to a technical limitation in the stimulation procedure as shown by our ability to record upper limb SEPs in the same region (SI Text, Upper Limb SEPs).

Finally, SEPs related to upper limb movements (same muscles as above) were collected for the sites that evoked motor responses of the mouth (including the sites mediating hand/mouth motor synergies). Again, no sensory responses were found, suggesting that sensory afferences related to the hand and wrist do not converge with their counterpart mouth motor representation along the precentral region.

Discussion

These results show that hand/mouth movements, a typical, ethologically relevant human behavior, are represented as integrated synergies within the PrG. We found two types of these representations.

The first, a hand/mouth motor representation, coordinates upper limb and oral commands to produce synergistic movements in which the closing hand is brought toward the opening mouth. A similar type of representation has been previously observed in monkeys within the PrG where electrical stimulation evoked movements in which the hand of the animal closes into a grip posture and moves toward the opening mouth (2). Our findings show that such hand/mouth motor synergies also do exist in the human PrG. However, in contrast to monkey data, which reveal a rather clustered organization (2), we found hand/mouth motor representations to be distributed over the surface of PrG. Two main hypotheses may explain this difference. First, PrG could be differently organized in humans and monkeys (see Introduction). Second, previous data in monkeys could be biased toward intraindividual variability (multiple replications in two animals), whereas our data in humans could be rather slanted toward interindividual variability (few replications in nine subjects). In agreement with this second hypothesis, it appears that interindividual variability of motor representations is large in the human PrG (9) and that the degree of clustering in monkey PrG...
can be quite variable from study to study for multijoint manipulative synergies (2, 3).

The second, a motor–sensory representation, integrates oral somesthesia with motor information from the upper limb. We speculate that such sensorimotor representation, not yet described in the literature, may constitute a hardwired feedback loop suited to bind oral sensory inputs with upper limb motor commands, for guiding hand movements according to mouth sensations. In monkeys, cutaneous and proprioceptive inputs from the upper limb to the primary motor cortex (M1) corticospinal cells have been shown to originate from the muscles to which these cells send motor projections or, for proximal regions of the arm, from the distal muscles of the hand (23, 24). However, no sensory projections from the mouth muscles to the cellular populations of M1-generating motor responses of the upper limb have been described. Our data indicate that this type of heterogeneous intersegmental organization does exist in the human PrG. This region contains neural populations that integrate sensory and motor signals from distinct body segments required to work together to produce syndromically functional relevant behaviors.

Interestingly, we did not identify a reciprocal sensorimotor representation that would combine motor projections to the mouth and sensory afferences from the upper limb. Indirect evidence suggesting that such a loop might exist is the palmar mental reflex, whereby a brisk sensory stimulation of the hand palm elicits a twitch in the mentalis muscle of the chin (25). Nevertheless, this reflex is different in nature from the hand/mouth motor–sensory loop described here: it has no obvious functional meaning, it tends to disappear during childhood, and it is thought to be controlled at the subcortical level by the facial motor nuclei (26). Thus, our inability to evidence a neural population that would integrate sensory afferences from the hand and motor efference to the mouth may indeed reflect the observation that mouth sensory signals guide hand movements and usually not the reverse.

Functionally, our findings mirror the existence of two basic behaviors of the human motor repertoire: hand-to-mouth goal-directed movements and hand-to-mouth perioral/haptic exploration. Interestingly, these behaviors have been reported to occur independently of each other in newborns and fetuses (19–21, 27, 28), with a level of accuracy that strongly contrasts with the early childhood overuse of this exploratory system. In other words, although human infants have poor motor skills (29, 30), they can easily bring their thumb (or a hand-held object) within the opening mouth and maintain it around the oral cavity for the purpose of sucking (or haptic exploration) (19–21). It is therefore tempting to speculate that the neural representations we identified in the present study in children and adults mediate the expression of these behaviors in newborns and fetuses. The existence of such supramodal representations in PrG diverges from Penfield and Boldrey’s pionering study (5). Interestingly, in addition to an inevitable undersampling, these authors also suggested that some patients fail to exhibit commonly expected motor responses because “the pattern of response may depend upon which spots are first stimulated on the day of operation.” In other words, it is possible that prior stimulation induces temporary changes in the excitatory state of neighboring areas, through local recruitment of GABAergic interneurons (37). This could temporarily increase the threshold required for motor responses beyond the maximal stimulation threshold (8 mA).

Finally, in apparent contrast with previous observations in monkey (2–4), in the present study, we did not identify complex natural neural representations for other ethologically relevant behaviors (e.g., defensive, manipulative) besides hand/mouth synergies. This could be taken as an indication that such representations do not exist in the human PrG, at least in the region we stimulated, but this hypothesis is unlikely. Indeed, we clearly found multijoint movements that resemble some of the defensive and manipulative synergies identified in monkey studies (2–4) (see SI Text, Other Synergies for details and discussion). However, these movements were uncommon, and because of the temporal and clinical constraints inherent in surgical studies, they could not be investigated in sufficient depth to be formally categorized as “functional synergies.” Further studies will have to determine whether complex representations also exist for coordinated behaviors other than hand/mouth behaviors.

To summarize, the present study shows that complex hand/mouth behaviors can be represented as integrated synergies within PrG. One may speculate that these representations, identified in the youngest children of our sample (2 y), are present earlier in infancy and constitute the neural bases of the remarkable capacity shown by human newborns to accurately perform synchronous and coordinated hand/mouth movements, in a general context of motor clumsiness and physiological immaturity. The existence of these integrated representations could reflect the ethological value of these behaviors and the existence of an evolutionary pressure to maximize their efficiency (4).

Methods

A standard protocol in brain surgery was used to collect motor-evoked potentials (MEPs) (7, 38, 39). Electrical stimulation was delivered through a bipolar electrode placed on the cortical surface. The probe was made out of two spherical steel tips located 5 mm apart. A constant voltage stimulator (Nimbus Cortical Stimulator, Newmedic) was used to produce a train of low-frequency biphasic pulses: pulse frequency, 60 Hz; single-pulse phase duration, 1 ms; amplitude, 2–8 mA. The duration of the stimulation varied from 1 to 3 s. Initial stimulus intensity was set to 2 mA and was then increased to 4 mA and 8 mA. If no motor response was observed at the highest intensity, the site was classified as “silent” (or nonresponsive). Up to three replications were performed for each responsive site. To avoid seizures, these stimulations were delivered consecutively at the minimal intensity that was initially found to trigger a response. During the preoperative phase of the surgery, the patients were prepared for electromyographic (EMG) recordings. Disposable surface Ag/AgCl electrodes (Viasys) were placed over the contralateral hombexid, in 12 muscles covering the face (zygomaticus, orbicularis oris), upper limb (deltoid, biceps, triceps, extensor digitorum communis, flexor carpi radialis, opponens pollicis, abductor digiti minimi), and lower limb (vastus medialis, tibialis anterior, gastrocnemius). Only responses involving the mouth and upper limb are considered in this report. EMG signals were collected continuously throughout stimulation sequences with a dedicated electromonitoring system (555-IDM, Inomed Medizintechnik). The collected signals were differentially amplified with a gain of 1,000–10,000 to fall within a ±5 V range, sampled at 10 kHz, filtered in a 30–300 Hz frequency band, and stored. For the purpose of computing motor latencies, EMG signals

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were further processed offline, as described in a previous paper (40). In brief, the envelope of the surface EMG was estimated by a scheme of demodulation, smoothing, and relinearization (41). In this process, demodulation rectifies the EMG and then raises the result to the power of 2, smoothing filters the signal (averaging filter, 50 points window), and relinearizes inert the power law applied during the demodulation stage and returns the signal to units of EMG amplitude. Baseline signal (mean -M and SD -SD-) was then determined from the 1,000 ms period preceding stimulation onset. EMG onset was defined as the first point of the poststimulation envelope located above the M + 2 SD threshold.

SEPs were recorded with the SIS IOM Inomed neuronomonitoring system. Standards Ag/AgCl (Viasys) surface electrodes were used to provoke contractions in the contralencesial hemibody in six muscles of the mouth (ori- cularis oris) and upper lip (biceps, extensor digitorum communis, flexor carpi radialis, opponens pollicis, abductor digiti minimi). In this protocol, commonly used in rehabilitation and research settings to mimic voluntary movements (42), the afferent signals collected in the sensorimotor regions reflect the recruitment of cutaneous and proprioceptive afferent fibers (groups I and II) (43, 44). Stimulation consisted of standard electrical trains (nine pulses, 500 μs wide, 10 ms interpulse interval) delivered at a 2.7 Hz frequency. Stimulation intensity varied from 5 to 20 mA, depending on patients, target muscle, and measured impedances. SEPs were recorded on the cerebral cortex in a bipolar array using cortex strip electrodes (four or six contacts; Dixi Medical). The signal was stored at a 10 kHz sampling rate and filtered in a 0.5–300 Hz frequency band. A period of 120 ms was considered after each stimulus onset to allow signal averaging in real time across stimuli (n = 200). After averaging, the resulting curves were saved for offline processing. Significance of evoked activities was assessed using standard procedures (45, 46). In brief, a baseline signal was first defined for each grid location by averaging all individual signals. For each time sample, a t test was then computed between the SEPs and the baseline curves, using a 95% significance level. To correct for multiple comparisons and dependences between successive tests, a time correction was applied. Periods showing more than 100 consecutive significant t tests (corresponding to a 10 ms period) were considered as significant. In a last step, SEP activities were filtered with a 100 Hz low-pass filter for display purposes.

For both MEPs and SEPs, cortical sites were localized with high resolution on individual MRIs, using a peroperative neuronomavigation system, and reconstructed offline (see SI Methods for details).

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