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

Michel Desmurget^{a,b}, Nathalie Richard^{a,b}, Sylvain Harquel^{a,b}, Pierre Baraduc^{a,b}, Alexandru Szathmari^{a,c}, Carmine Mottolese^{a,c}, and Angela Sirigu^{a,b,1}

^aCentre de Neurosciences Cognitives, Centre National de la Recherche Scientifique/Unité Mixte de Recherche 5229, 69500 Bron, France; ^bUniversité Claude Bernard Lyon 1, 69100 Villeurbanne, France; and ^cDepartment of Pediatric Neurosurgery, Neurological Hospital Pierre Wertheimer, 69500 Bron, France

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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.

motor cortex | motor synergies | brain mapping | cortical stimulation

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-motoneuronal 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-motoneuronal 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 phylogenesis of motor functions in primates.

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¹To whom correspondence should be addressed. E-mail: sirigu@isc.cnrs.fr.

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Hand/Mouth Motor Synergies

Fig. 2. (A) Cortical sites evoking hand/mouth motor synergies in which the arm flexes and the closing hand moves toward the opening mouth. In children (red squares) all sites were found in different subjects. In adults (blue squares) two sites were found in the same individual (identified by small black dots within the blue square symbols). (B) Mean EMG latencies and SDs for the muscles involved in hand/mouth motor synergies. ADM, abductor digiti minimi; BI, biceps; FCR, flexor carpi radialis; OO, orbicularis oris; OP, opponens pollicis. (C) Individual example of a hand/mouth motor synergy. A nonresponsive muscle is shown to illustrate the specificity of the evoked response (extensor digitorum communis, EDC). nc, latency could not be computed reliably; ns, not significant. Same conventions as Fig. 1 for all panels.

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

Hand/Mouth Motor-Sensory Synergies

Fig. 3. (A) Cortical representations of hand/mouth motor-sensory synergies that integrate upper limb efferences and oral efferences. All sites were found in different subjects. (B) Nature and mean latencies of the independent responses evoked by the stimulation (extension, ext; flexion, flx; SEP, somatosensory evoked potential). (C) Individual example of a hand/mouth motor-sensory synergy. ADM, abductor digiti minimi; FCR, flexor carpi radialis. SEP is the mean signal for 200 stimulations. Same conventions as Fig. 1 for all panels.

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 synergic, functionally 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 palmo-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 clumsiness of the motor 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's original view, stating that the sensorimotor cortex represents single muscles rather than movement synergies. Both views, however, may be reconciled around the idea that two levels of representation, local and distributed, do coexist in this region (31–34).

A potential criticism can be raised regarding the existence of these responses in only a subset of subjects tested in the present study. The constraints of peroperative neural recording must be, however, kept in mind. Indeed, to minimize the risk of seizure and because functional mapping must be limited in duration, PrG can never be mapped exhaustively in surgical procedures. Here, we recorded 144 sites in 26 subjects. This means that only six points were tested, on average, in each patient (they were chosen by the surgeon for their clinical relevance). This is not enough to identify all types of expected responses in all subjects. In agreement with this view, additional analyses presented in *SI Text, Individual Factors* show that none of the following factors could account for the presence/absence of integrated responses in our subjects: nature (neoplastic versus malformation), location

(center of mass), absolute and relative volume of the brain injury, age of the patient, and spatial distribution of the stimulation sites. As shown in a now large number of peroperative studies, motor responses that are clearly present at the population level cannot be easily evidenced, in most cases, at the individual level (5, 9, 35, 36). This was clearly emphasized by Penfield and Boldrey in their pioneering 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 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 nonconsecutively 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 contralesional hemibody, 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 neuromonitoring system (ISIS-IOM, 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

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 relinearization inverts 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 $M + 2 \times SD$ threshold.

SEPs were recorded with the ISIS IOM Inomed neuromonitoring system. Standards Ag/AgCl (Viasys) surface electrodes were used to provoke contractions in the contralateral hemibody in six muscles of the mouth (orbicularis oris) and upper limb (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 μ s 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 way 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 neuronavigation system, and reconstructed offline (see *SI Methods* for details).

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