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Keywords: NIRS, Hemispheric lateralization, Primate, Motor perception, Auditory perception

Abstract

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1. Introduction

Lateralization is often presented as a key characteristic of the human brain, which separates it from other animal brains [1,2]; yet, an increasing number of studies, particularly in non-human primates (from here onward, primates), dispute this claim in a broad array of topics ranging from object manipulation, gestural communication to produc...
available studies in primates have focused on the lateralization of perception of synthesized sinusoidal or more complex vocal signals, and reported inconsistent results. For instance, in rhesus macaques (Macaca mulatta), the processing of species-specific and/or heterospecific calls as well as non-vocal sounds, elicited various patterns of lateralized activations within the Superior Temporal Gyrus (STG) such as in the left lateral parabelt, either toward the right or the left hemisphere depending on the study [17-20]. In chimpanzees (Pan troglodytes), a similar PET study reported a rightward activation within STG for processing conspecific calls [21]. In general, such a variability of direction of hemispheric lateralization for processing calls appears similar to the hemispheric lateralization variability described in humans for language processing, depending on the type of auditory information and of language functions that are processed [22-24].

Compared to the leftward bias suggested for language, research investigating emotion perception in primates has strengthened the idea of a right bias in lateralization specific to emotion processing [3]. For example, Farr and Hopkins [25] found that right ear temperature increased in captive chimpanzees when they were watching emotional videos, consistent with a greater right hemisphere involvement [25]. The rightward hemisphere bias documented in chimpanzees is also found in other primate species such as olive baboons (Papio anubis) during natural interactions, as evidenced by studies investigating the perception of visual emotional stimuli [26-29]. Yet, while the right hemisphere has understandably received much focus, the left hemisphere is also involved in emotion processing. For example, Schirmer and Kotz have suggested that the left hemisphere is particularly involved in the processing of short segmental information during emotional prosody decoding [24]. Whether this functional differentiation, essential for speech perception in humans [30], is also present in non-humans is unclear. Baboons appear in this respect a particularly interesting animal model to study for lateralization, with several recent studies underlining the similarities in manual and brain asymmetries with humans [5,14,31]. Furthermore, the baboon brain is on average twice as large as the macaque brain [32], which may facilitate the specific investigation of sensory regions. Indeed, this species displays all the primary cortical structures found in humans [33]. Finally, olive baboons were also successfully investigated as an animal model for epilepsy in studies of cerebral blood flow changes occurring in altered cortico-cortical interactions [34].

However, a major drawback in current studies lies in the complexity with which brain asymmetry can be investigated comparatively in primates. Here, we used functional Near-Infrared Spectroscopy (fNIRS) to test whether the blood oxygen level dependent (BOLD) response in baboon brains differed accordingly between the two hemispheres following left- versus right-asymmetrical auditory and sensorimotor stimulations. fNIRS is a non-invasive optical imaging technique that has been developed to investigate brain processes in potentially at-risk populations such as human premature newborns, but which is now widely used with adult human participants. fNIRS is a relatively young imaging technique, with around two decades of use for functional research [35]. Considering its portability and its lessened sensitivity to motion artefacts [36] compared to other non-invasive techniques, it might be an excellent methodology to study brain activations in primates under more ecologically relevant testing conditions, for example with a wireless and wearable device. As a first step, the present study tested fNIRS in baboons immobilized under light anesthesia monitoring. In relation with each of the stimulation types, we targeted relevant, corresponding brain regions of interest – the motor cortex within the central sulcus and the auditory cortex regions in the temporal lobe respectively – by positioning the two sets of fNIRS channels in both hemispheres (one by hemisphere for a given region). We predicted that, if fNIRS was suitable to record brain signal in baboons, it would reflect contralateral hemispheric asymmetries in signals for each stimulation type within their corresponding brain region of interest (ROI), namely the motor cortex, associated with right- versus left-arm movements, and the temporal cortex, associated with the right- versus left- versus stereo ear auditory presentations. Our latter prediction was modulated by the knowledge that auditory regions are less lateralized, with about fifty percent of fibers projecting in bilateral regions [37,38], compared to cortical motor regions.

2. Material & methods

2.1. Subjects

We tested three healthy female baboons (Talma, Rubis and Chet, mean age = 14.6 years, SD ± 3.5 years). The subjects had normal hearing abilities and did not present a neurological impairment (confirmed with respective T1w anatomical brain images – 0.7 × 0.7 × 0.7 resolution – collected in vivo under anesthesia in a 3 T MRI Bruker machine). Although pre-existing hearing or sensorimotor asymmetric disabilities were not specifically assessed for the present study, they were very unlikely in our selected subjects as no related atypical social, manual, postural, and locomotion behaviors were detected either during the annual health assessment of each baboon by the vet staff and by the staff in charge of animal welfare, and/or during daily survey of the behaviors of each baboon in their respective social group. All animal procedures were approved by the “C2EA-71 Ethical Committee of neurosciences” (INT Marseille) under the application number APAFIS#13553-20180215S147729. They were conducted at the Station de Primatologie CNRS (UPS 846, Rousset-Sur-Arc, France) within the agreement number C130877 for conducting experiments on vertebrate animals. All methods were performed in accordance with the relevant French law, CNRS guidelines and the European Union regulations (Directive 2010/63/EU). All monkeys were born in captivity from 1 (F1) or 2 generations (F2), and are housed in social groups at the Station de Primatologie in which they have free access to both outdoor and indoor areas. All enclosures are enriched by wooden and metallic climbing structures as well as substrate on the group to favour foraging behaviours. Water is available ad libitum and monkey pellets, seeds, fresh fruits and vegetables were given every day.

2.1.1. Subject’s hand preference in communicative gesture and bi-manual task

The impacts of subjects’ handedness on cerebral lateralization of language, motor and visual functions are well known in human neuroscience [39]. While baboons are generally right-handed at group-level when communicating with manual gestures [31], or when performing bimanual coordinated action [4], direction of hand preference (left-, right- or ambiguously handed) may vary at the individual level depending on the type of manual task (e.g. communicative gesture versus bimanual manipulative action). For that purpose, we report here the hand preference of each baboon during manual communicative gesturing (CG - snapping one hand repetitively on the ground in the direction of a conspecific to threaten it) and during a bimanual tube task (BM - holding a PVC tube with one hand while removing the food inside the tube with the fingers of the other hand). In both contexts, Talma was left-handed (CG: n = 27, HI = -0.56, z-score = -2.89; BM: n = 31, HI = -0.42, z-score = -2.33) whereas Rubis showed a preference toward the right hand (CG: n = 16, HI = 0.25, z-score = 1; BM: n = 79, HI = 1, z-score = 8.88). Conversely, Chet was left-handed in communicative gesture (n = 25, HI = -0.44, z-score = -2.2) but right-handed in the bimanual tube task (n = 11, HI = 0.45, z-score = 1.51).

2.2. Recordings

We selected one of the most wearable, wireless and light fNIRS devices available on the market (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands) to measure the brain activations in baboons during the sensorimotor and auditory stimulations. The data were obtained at 50 Hz using six channels (three by hemisphere with ch1, ch2,
ch3), three inter-distance probes (3–3.5–4 cm) investigating three different cortical depths (1.5–1.7–2 cm respectively) and two wavelengths (760 and 850 nm). To localize our ROIs, the motor and auditory cortices, the fNIRS probes were placed using T1 MRI scanner images previously acquired by the LPC group on baboons (see Fig. 1).

Each fNIRS session was planned during a routine health inspection undergone by the baboons at the Station de Primatologie. As part of the health check, subjects were isolated from their social group and anesthetized with an intramuscular injection of ketamine (5 mg/kg - Ketamine 1000®) and medetomidine (50 μg/kg - Antisedan®). Then Sevoflurane (Sevotek®) at 3–5 % and atipamezole (250 μg/kg - Antisedan®) were administered before recordings. The area of interest on the scalp was shaved. Each baboon was placed in ventral decubitus position on the table and the head of the individual was maintained using foam positioners, cushions and Velcro strips to remain straight and to reduce potential motion occurrences. Vital functions were monitored (SpO2, Respiratory rate, ECG, EtCO2, T°) and a drip of NaCl was put in place during the entire anaesthesia. Just before recording brain activations, sevoflurane inhalation was stopped and the focal subject was further sedated with a minimal amount of intravenous injection of Propofol (Propovet®) with a bolus of around 2 mg/kg every 10–15 min or by infusion rate of 0.1 – 0.4 mg/kg/min. According to the literature in humans, while propofol proportionally decreases cortical blood flow and cerebral metabolic rate of oxygen, normal cerebral circulation and metabolism are maintained [40]. After the recovery period, baboons were put back in their social group at the Station de Primatologie and monitored by the veterinary staff.

2.3. Sensorimotor stimulations

The sensorimotor stimulations consisted of 20 successive extensions of the same arm, alternatively right and left repeated three times according to the same set plan (L-R-R-L-L-R) for all baboons, resulting in a total of 120 arm movements. One experimenter on each side of the baboon extended slowly their respective arm while stimulating the interior side of the hand (gentle rhythmic tapping) with their fingers throughout the duration of the extension (about 5 s) upon a brief vocal command triggered by another experimenter. There was a 10 s lag between each block.

2.4. Auditory stimulations

The auditory stimuli consisted of 20s-long series of agonistic vocalizations of baboons and of chimpanzees recorded in social settings (in captivity in an outside enclosure for baboons; and in the wild for chimpanzees). Equivalent white noise stimuli matched for the energy dynamics (i.e. the sound envelopes) were produced and used for comparison to control for the sound energy dynamic differences. In the present study and analysis, we only examine the effect of the lateralization of auditory stimulations (i.e., left ear versus right ear versus stereo) as a whole on hemispheric asymmetry and thus do not distinguish between auditory signal types or species (e.g. white noise and vocalizations). The auditory stimuli were broadcast pseudo-randomly, alternating voiced and white noise stimuli and separated by 15 s silences, either binaurally (stereo), only on the left side, or only on the right side. Due to signal artefacts and anaesthesia shortfalls, the number of stimuli between the three baboons differs slightly. For Talma, the total sequence consisted of 37 stimuli; for Rubis, the total sequence consisted of 47 stimuli; and for Chet, the total sequence consisted of 25 stimuli.

2.5. fNIRS signal

We performed the first level analysis with MatLab 2018b (Mathworks, Natick, MA) using the SPM_fNIRS toolbox [41, https://www.nitrc.org/projects/spm_fnirs/] and homemade scripts. Hemoglobin conversion and temporal preprocessing of O2Hb and HHb were made using the following procedure:

Fig. 1. Schematic representation of fNIRS channel locations on ROIs according to T1 MRI template from 89 baboons [60] for (a) the sensorimotor and (b) the auditory stimulations. Red and blue dots indicate the positions of the receivers and transmitters respectively. Yellow dots indicate channel numbers.
1. Hemoglobin concentration changes were calculated with the modified Beer-Lambert law [42];

2. Motion artifacts were removed manually in each individual and each channel for the auditory stimulations. Thus, 10 s in total (1.3%) were removed from the O₂Hb and HHb signals of Rubis and 35 s (4.8%) for Talma and Chet fNIRS data;

3. A low-pass filter based on the hemodynamic response function (HRF) [43] was applied to reduce physiological confounds.

4. A baseline correction was used for both the sensorimotor and auditory stimulations by subtracting respectively (i) the average of 10 s intervals preceding each block; (ii) the average of the 15 s of silence preceding each sound.

The O₂Hb concentration was averaged according to the temporal properties of the BOLD response for each baboon: for Talma in a window of 4–12 s post stimulus onset for each trial; and for Rubis and Chet in a window of 2–8 s post stimulus onset. This was done to select the range of maximum concentration changes (μM). The difference of concentration ranges is explained by the presence of some tachycardiac episodes for both Rubis and Chet during the experiment, involving an HRF almost twice as fast as the one found for Talma.

2.6. AQ score calculation

Asymmetry Quotients (AQ) were derived for each subject and each experimental condition (i.e.: stimulation of the right arm and of the left arm for the sensorimotor experiment; right, left and stereo audio stimulation for the auditory blocks) by first calculating the difference between the right hemisphere (RH) and the left hemisphere (LH) values, to which we subsequently subtracted the same difference during the preceding baseline block for the same subject to normalize across trials. In particular, for motor stimuli, the baseline represented the 10 s block without motor activity immediately before a passive stimulation block of the right or left arm. For auditory stimuli, the baseline was calculated on the 15 s silence block that immediately preceded the auditory stimuli. In this analysis, all auditory stimuli (baboon and chimpanzee calls, and corresponding white noises) were analysed together. We excluded one block ‘chimpanzee white noise audio stereo’ (2.7 % of O₂Hb signal) for Rubis, and two blocks ‘chimpanzee white noise audio stereo’ and ‘baboon white noise audio stereo’ (8.3 %) for Talma as the recorded data revealed themselves artefactual beyond repair. Positive AQ values indicate a rightward asymmetry and negative values indicate a leftward asymmetry. In addition, for both sensorimotor and auditory stimulations, one-sample t-tests were performed with R studio comparing each condition to zero to investigate a bias in terms of brain activation. Finally, to study the lateralization patterns in each individual, we performed two-way ANOVAs on the AQ of all trials in the different stimulation conditions in individual baboons with channels (ch1, ch2, ch3) and sides (right versus left motor stimulation; right versus left versus stereo auditory stimulation) as fixed factors, using the aov function of R studio. Note that the degrees of freedom (dfs) in ANOVAs for auditory stimulations varied across the three subjects due to blocks removal because of fNIRS acquisition issues.

3. Results

3.1. Sensorimotor stimulations

To the exception of left arm stimulations in channels 1 and 2 for Rubis and right arm stimulations in all channels for Chet, one-sample t-tests showed that all mean AQ values were significantly different from zero (see Fig. 2 and Table 1 in supplementary material). Furthermore, two-way Anova analyses revealed significant differences at p < 0.001 between the left and right arm stimulations across the three channels and baboons. Hence, we observed an effect of lateralization for Rubis (F1,356 = 141.876), Chet (F1,356 = 80.771), and Talma (F1,356 = 22.600). In addition, there was a significant effect of channel for Talma (F2,356 = 13.950, p < 0.001), a trend for Chet (F2,356 = 2.973, p = 0.052), and no effect for Rubis (F2,356 = 0.114, p = 0.89). For Talma, Ch2 differed from others; while for Chet, the trend could be explained by more activity recorded from Ch3 to Ch2 to Ch1. Overall, the difference of AQ between left- versus right-arm stimulations were consistently contralateral across the subjects for all 3 channels, with, in each baboon, relatively more rightward activities for left arm stimulations in comparison to right arm stimulation, and relatively more leftward activities for right arm stimulations in comparison to left arm stimulation (Fig. 2. See Table 2 in supplementary material for the mean AQ values).

3.2. Auditory stimulations

Mean AQ values were found significantly different from zero for subjects Rubis and Chet in all channels for right ear stimulations exclusively (see Fig. 3 and Table 3 in supplementary material). For both baboons, right ear stimulation hence led to significantly more activations in the left hemisphere.

Following this, two-way Anovas only revealed significant side effects...
for the baboon Chet ($F_{2,28} = 19.547$, $p < 0.001$), with no effect of channel ($F_{2,28} = 0.562$, $p = 0.58$). In other words, for Chet, the bias was relatively more leftward for right ear stimulation compared to left and stereo stimulations for all channels. No side difference was found for Talma and Rubis, despite the latter having right ear stimulations leading to more significant activations in the left hemisphere (Fig. 3. See Table 4 in supplementary material for the mean AQ values).

4. Discussion

The results of the present study show that non-invasive fNIRS is a valid imaging technique to investigate functional lateralization paradigms in a nonhuman primate species, which warrants more work to explore its potential in a comparative context.

Our most potent results were found with the sensorimotor stimulation. Results for Talma in channel 2 were most in line with our original prediction, namely a clear mirror pattern of contralateral asymmetries between the two arms, with right arm movements eliciting left hemisphere asymmetry and left arm movements eliciting right hemisphere asymmetry. Results were also clear-cut for Rubis and Chet, though interestingly opposed, with Rubis having a strong leftward asymmetry as a result of her right arm being stimulated, and Chet showing a strong rightward asymmetry for her left arm. Nevertheless, in Rubis and Chet, the direction of the difference of hemispheric asymmetry measures between left versus right arm stimulations in the motor cortex remained also contralateral and thus consistent with Talma and with our predictions. Specifically, in each of the 3 baboons, right arm movements elicited relatively more leftward hemispheric asymmetry than left arm movements, and left arm movements elicited relatively more rightward hemispheric asymmetry than right arm movements across all channels. Such a relative rather than absolute approach (compared to zero) has the critical advantage to normalize the effect of brain lateralization between stimulations regardless of any potential initial biases in the baseline (e.g., related either to direction of individual hand preference, to potential variations of degree of stimulation between the two arms, or to potential position deviance from the targeted cortical region of each of the two fNIRS optodes within their respective hemisphere). Our results are consistent with previous studies in primates: for arm/hand movements, 90% of the corticospinal pathway project to the contralateral spinal cord [44–48]. Hence, our study replicates these findings, with brain signals differences detected by non-invasive fNIRS.

Despite the robust consistency of findings across subjects concerning the direction of the effect between the left and the right arms, the reasons for inter-individual variabilities as well as the lack of mirror pattern of results between the two arms (channel 2 of Talma excepted) remains unclear. A first possibility is that these differences across channels could be explained by the difference of inter-distance probes (3–4 cm) resulting in a variation of the signal depth into our subjects’ cortices. This is possibly highlighted by the channel trend found in subject Chet. Second, if we consider that the dominant hand for bimanual coordinated action in baboons might induce more contralateral hemispheric activation asymmetry in the motor cortex than the non-preferred hand (see [5]), a possibility is that the direction of handedness of each baboon might have influenced the results. However, our overall results are not consistent with this hypothesis. While Rubis and Chet were both classified as right-handed for bimanual tube task, their respective stronger contralateral effect on brain asymmetry are related to oppose arm stimulations (i.e., the right arm for Rubis and the left for Chet) and while Talma was classified as left-handed, it is the non-preferred arm stimulation (i.e., the right arm), which elicited the strongest contralateral brain asymmetry pattern (channel 2 excepted). Finally, minor protocol variations may also explain the differences between baboons by affecting the individual baseline’s fNIRS measures such as potential subtle variation in the position of each fNIRS optode within their respective hemisphere, or potential involuntary differences in the degree of arm stimulation between the two experimenters involved in each of the subject’s arms manipulations. To address this latter point, a noticeable improvement to the protocol would be to use an automated vibrotactile device to provide an identical degree of sensorimotor stimulations between the two arms [49].

Our results regarding auditory stimulations were also consistent with predicted asymmetries but only for one subject: right ear stimulation led to a strong leftward brain activation lateralization for Chet in all three channels. Nevertheless, despite Rubis’ results mirroring Chet’s in the case of right ear stimulation (both leading to significant activity in the contralateral hemisphere), we did not find evidence of lateralization in auditory stimulation for Talma and Rubis. Indeed, for these two baboons the direction and degree of asymmetry varied irrelevantly of whether the sound was presented to the right or left ear, namely toward the left temporal areas for Rubis and toward the right temporal areas for Talma. These mixed results related to auditory stimulation might be interpreted with respect to some characteristics of the hemispheric organization of the brain. It is well-known that at least one third of the auditory fibres from the olivary complex project to ipsilateral brain regions inducing less lateralization compared to motor brain regions. Furthermore, it has been shown that receptive fields in some regions sensitive to somatosensory input from the auditory cortex are 50% contralateral and 50% bilateral [38,50]; and that temporal regions such as the belt, parabelt and STS receive strong ipsilateral connections in rhesus macaques [51,52], suggesting overall a less marked lateralization for auditory processing compared to motor regions. Interestingly, the subject’s handedness in communicative gesture could also explain these mixed results. In fact, our left-handed subject Talma showed a clear right hemisphere bias for most stimuli (to the exception of the right ear stimulation in channel 2); whereas Rubis, right-handed in communicative gesture, showed a stronger bias toward the left hemisphere for the sounds.

Fig. 3. Normalized averaged AQ (and corresponding SE) above the temporal cortex following auditory stimulations in three adult female baboons (see Fig. 1 for localization of the channels). All AQS were normalized using the scale function of R studio (R studio (2015) Inc., Boston, MA, url: http://www.rstudio.com/). In an absolute perspective, positive values correspond to right hemisphere activation. In a relative perspective, more positive values correspond to more rightward differences in activation. Mu $\neq 0$ at $p < 0.05^{*}$ and $p < 0.01^{**}$.
broadcast in right and left ears. These preliminary findings may thus highlight the impact of hand preference in communicative contexts on contralateral brain organization in baboons during auditory processing but would need further investigations in a larger cohort of subjects.

Overall, given the lack of statistical power related to low sample size, we cannot draw any conclusion regarding the direction of hemispheric lateralization at a population-level for sound processing in baboons, or their relation to hand preference for communicative gesturing. Yet, despite these caveats, the fact that we once again recorded activity in the direction of our original predictions, at least with respect to right ear stimulations, suggests that more work is needed before ruling out fNIRS as a valid tool to functionally approach vocal perception in a phylogenetic perspective.

In conclusion, our study shows that fNIRS is a valid methodology to access brain signals in primates non-invasively, particularly for investigating neurocorrelates of movements. We have replicated findings in the literature about brain contralateral hemispheric activation in two different modalities showing that fNIRS is able to capture such functional differences even in a context in which baboons were anesthetized. However, we have also uncovered large variation between individuals. This may be due to interindividual differences leading to the inability to precisely record in the same spot for all baboons. Indeed, while we based our placing of optodes on our subjects based on an averaged structural MRI pattern to which all tested individuals contributed, we cannot exclude small variation across cortices. In the future, fNIRS should thus be coupled with structural imaging techniques such as MRI to allow the precise positioning of the optodes for each individual. In addition, despite various advantages such as a low sensitivity to motion artefacts [53], fNIRS has also inherent limitations such as a poor temporal resolution compared to EEG and poor spatial resolution in comparison to fMRI [54]. The former can be a problem while investigating emotional vocalizations that crucially depend on temporality [24, 30]. Regarding the latter, despite analogous measurements of the BOLD signal [55], the optical pathway relied upon by fNIRS cannot reach the depth of brain areas below 2–2.5 cm [56], limiting its overall use.

Yet, these limitations or the need to couple fNIRS with existing techniques does not deny a more widespread use of fNIRS in the future. To the contrary, we believe that our study opens new avenues for brain investigation in nonhuman primates using fNIRS for two main reasons. First, fNIRS has been used in a multitude of contexts when other brain imaging techniques could not be used, for example in the field with greater ecological conditions [57]. We acknowledge that a drawback of our study is that our data have been recorded in anesthetized baboons. While the literature suggests that propofol, a GABAA-agonist, leaves intact the cortical response, particularly for auditory inputs [58,59], and generally offers possible answers on the limited asymmetry recorded in our baboons in auditory contexts, a logical next step is to train and habituate baboons to accept wearing a fNIRS device. Our experimental paradigms could then be extended in awake monkeys with more sophisticated design involving behavioural contingencies related to different kinds of stimulation. Second, our study stresses that fNIRS could in the future become a valuable method to explore brain activations in lateral regions in a non-invasive way in nonhuman animals without attempting the physical integrity of the subjects, which would ultimately make investigation of brain mechanisms in animal much more accessible and flexible.

CRediT authorship contribution statement

Coralie Debracque: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. Thibaud Gruber: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Writing - original draft, Writing - review & editing. Romain Lacoste: Investigation, Methodology, Resources, Writing - review & editing. Didier Grandjean: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Writing - review & editing. Adrien Meguerditchian: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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References


