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Effective connectivity of functional brain regions through concurrent intracerebral electrical stimulation and frequency-tagged visual presentation

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Direct Electrical Stimulation (DES) is a powerful method for establishing the critical function(s) of brain regions. Yet, behavioral effects elicited by DES, especially in the human association cortex, can be caused by disturbance of connected brain regions beyond the stimulation site [1]. Assessing the spatial distribution and the extent of these remote effects is therefore fundamental for understanding cortical networks underlying brain function and behavior. This question has generally been addressed either through spontaneous intracranial EEG (iEEG) recordings during DES, or brain connectivity measures (cortico-cortical evoked potentials or CCEP, functional/structural connectivity) collected independently [2]. However, the relationship between these measures and brain function is still undefined, as neural changes specifically associated with behavioral effects are unclear. Here we introduce an original effective connectivity approach - concurrent intracerebral electrical stimulation and frequency-tagged visual presentation - to objectively quantify DES effects within a specific neurofunctional network. We apply this approach to the fusiform face area (FFA) in the lateral portion of the middle fusiform gyrus (FG) [3], a key region of the face-selective cortical network [4] underlying a critical human brain function: face identity recognition (FIR).

Subject CJ was recently reported as the first case of transient FIR impairment induced by DES to the right FFA, providing original support for the critical role of this region in FIR [5]. Here we show that DES to the right FFA of CJ reduces or abolishes concurrently recorded functional brain responses to faces at neighboring and remote locations of the cortical face network (Fig. 1C). While recording neural activity to natural familiar faces with frequency-tagging (faces at 6Hz for 70 seconds, Fig. 1A [6]), DES was applied to bipolar contacts (F1–F2, F2–F3, F3–F4; 1.2mA, 55Hz; Fig. 1B) for 10 seconds inside the patient's right FFA as defined by independent functional magnetic resonance imaging (fMRI) [5]. Although CJ was unaware of DES onset and duration, she raised her hand (as asked before the procedure) during stimulation to signal changes in visual experience, reporting afterwards being unable to recognize the face identities for a few seconds. She often stated that people shown during stimulation had the same face, in line with DES effects observed without FPVS [5]: "*They all had the same face*", "*they were unrecognizable*", "*I don't know who they were*", "*for 5s they were like strangers*", "*I couldn't recognize them; the rest of the time, I had no problem*" (occurring on 3/3 stimulations for F2–F3, 1/3 for F3–F4, but 0/2 for F1-2 in the medial FG, outside the FFA). Faces were not perceived as distorted (see **Video**). Neural modulations across sampled intracerebral contacts (N = 121) evoked by FFA stimulation were assessed by quantifying the face response amplitude at 6Hz among all contacts of interest (i.e., contacts with a 6Hz face response outside stimulation: 35 minus the 2 stimulated contacts, i.e., 33 contacts) and across time (6 epochs of 10s: Pre1, Pre2, Stimulation, Post1, Post2, and Post3, Fig. 1B, see supplementary methods). Importantly, frequency-tagging allows us to objectively identify and quantify high signal-to-noise ratio neural activity with a high frequency resolution (0.1Hz) [7], independently of DES-evoked artifacts that are objectively distinguishable in the frequency spectrum (Supplementary Fig. 1). DES induced a strong decrease or complete disappearance of the 6Hz face response compared to pre-stimulation periods on both stimulated and distant contacts (Fig. 1C). To quantify the number of contacts showing amplitude decrease, iEEG spectra of Pre2 and Stimulation periods were subtracted from one another (stimulation amplitude effect), and Z-score transformed ($Z > 2.32$, $p < 0.01$ for significance). Across the 3 stimulation sites (F1–F2, F2–F3, F3–F4), 20 contacts showed a significant reduction, located close to the stimulated site in the right middle FG, remotely in the ipsilateral and even in the contralateral anterior temporal lobe (ATL) (10 contacts during F2–F3 stimulation, Fig. 1C, see Supplementary Fig. 2 for F1–F2 and F3–F4 stimulations). Importantly, all but one contacts were face-selective as defined independently [5]. Across contacts of interest, iEEG amplitude was specifically reduced during the stimulation period for all stimulation sites (Fig. 1D), albeit weaker for F1–F2. Compared to corresponding time windows without stimulation, the stimulation amplitude reduction (Pre2 minus Stimulation) was significant for F2–F3 and F3–F4 stimulations, but not F1–F2 ($p=0.01$, $p=0.01$; $p=0.17$; respectively, 2-tailed paired permutation tests; Fig. 1D). Finally, we found significant correlations between the amplitude of the stimulation effect and independent amplitude measures (face-selective response [5]; 6Hz face response without stimulation) or an independent functional connectivity measure computed using the 6Hz face response (amplitude envelope correlation) for F2–F3 and F3–F4 stimulations ($p < 0.05$, Pearson correlation, outliers with z-score>3 removed, uncorrected; Fig. 1E), but not for F1–F2. This suggests that the two sites evoking

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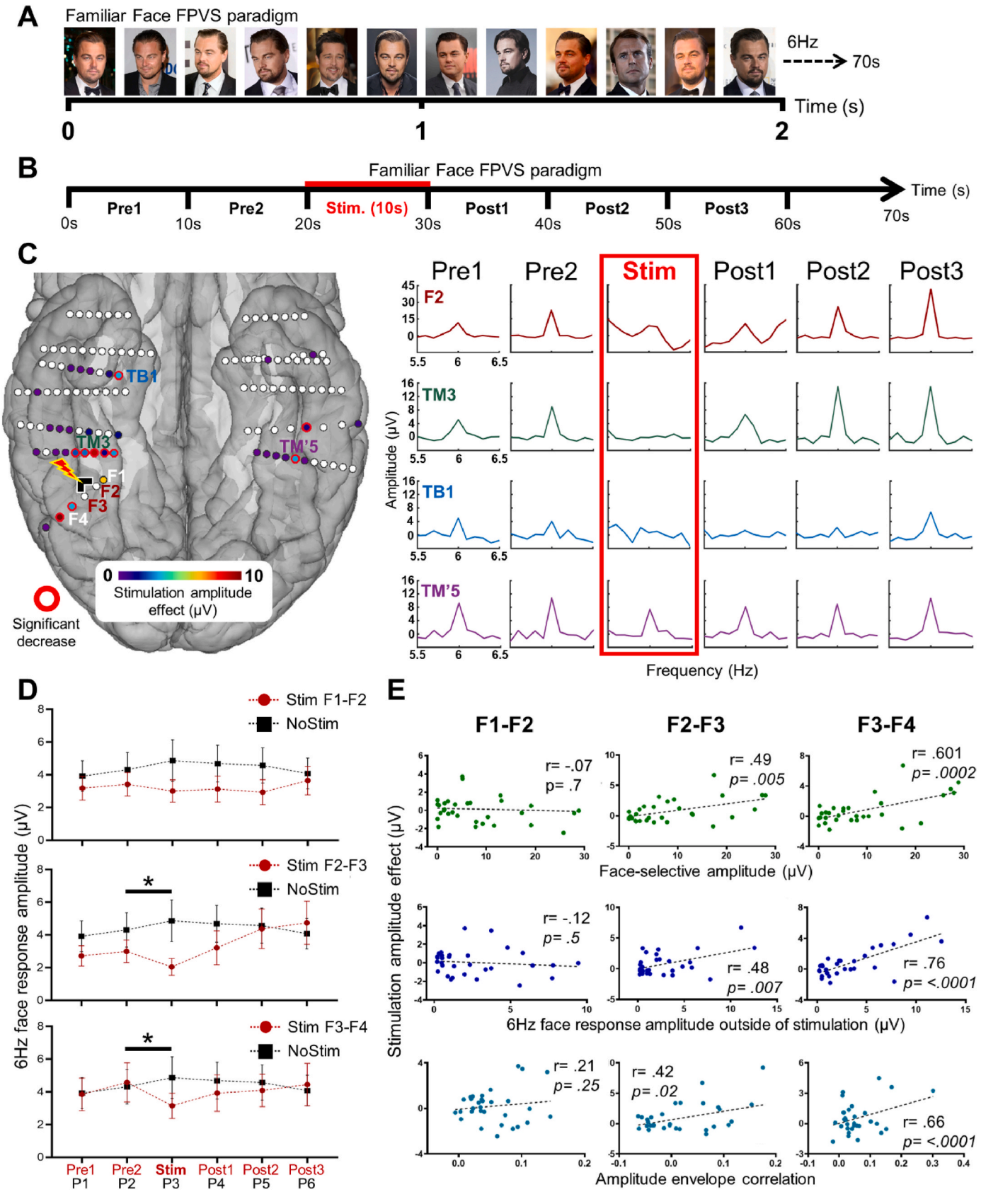

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Fig. 1. A. Familiar face FPVS paradigm, administered outside stimulation and during the stimulation sessions, composed of natural images of familiar faces presented periodically at 6Hz for 70s [6] (note that this paradigm is generally designed to record responses reflecting the discrimination between different familiar face identities every 5 images, but the most robust response was used here, i.e., the face response at 6Hz). **B. Stimulation session procedure.** Subject CJ was lying in her hospital bed facing the monitor. After about 20s of periodic visual presentation, a 10s electrical stimulation of the right FFA (3 stimulated sites) was administered. Portions of SEEG recordings corresponding to the FPVS sequence were then divided into 10s epochs: 2 epochs before stimulation (Pre1, Pre2), 1 during stimulation (Stim) and 3 after stimulation (Post1, Post2, Post3). Neurophysiological activity was recorded during the whole FPVS sequence, and the face response at 6Hz was identified and quantified in the frequency domain for each epoch and contact. **C. Example of one stimulation site (F2–F3) and the corresponding local and remote changes of the 6Hz face response (average of 3 stimulations sessions).** The stimulated site is displayed on a reconstructed cortical surface of subject CJ's brain (along with the other sites, F1–F2 and F3–F4). Contacts of interest (contacts with a 6Hz response outside stimulation, 33 contacts) are color-coded according to the amplitude difference between Pre2 and the stimulation periods (stimulation amplitude effect). Contacts with a significant difference are circled in red ($p < 0.01$). For some contacts, the right panel shows the amplitude variation across time of the 6Hz response in the frequency domain. The stimulated contacts (F2) and remote contacts (TM3, TB1, and TM'5) showed a decrease or even suppression of the 6Hz face response during stimulation. **D. Global variation of the 6Hz face response across contacts.** Average amplitudes of the 6Hz response throughout the FPVS sequence across the pool of contacts of interest during stimulated (Stim F1–F2, F2–F3, F3–F4) and non-stimulated sequences (NoStim). The non-stimulated sequences were divided into 6 time windows as for the stimulated sequences (P1 to P6). * indicate significant differences between the stimulation amplitude effect (Pre2 minus Stim) and the corresponding time windows for non-stimulated sequences (P2–P3) (2-tailed paired permutation tests: F1–F2: p = 00.17; F2–F3: p = 00.01; F3–F4: p = 00.01; Nperm: 40,000). **E. Correlation plots between the stimulation amplitude effect (Pre2 minus stimulation periods) and either independent face responses (face-selective and 6Hz face amplitudes outside stimulation) or an independent measure of functional connectivity computed using the 6Hz face response (amplitude envelope correlation) across the contacts of interest.** Outliers with values higher than Z = 3 were removed. ThePearson correlation coefficients and the p-values are indicated for each correlation.

perceptual changes (F2–F3 and F3–F4) specifically affected the cortical face network. Importantly, there was no correlation between the stimulation effect and the Euclidean distance from the stimulation site or the amplitude of the stimulation artifact for all stimulation sites (Supplementary Fig. 3).

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2024.05.016.

Overall, these observations go beyond CCEP evidence that middle FG stimulation evokes distributed cortical face network activity and independently alters face detection [8], showing that DES to the right FFA disrupts concurrently activated bilateral face-selective regions, causing FIR impairment. Thanks to a dense electrode sampling, we found that this effect concerns the bilateral ATL and more specifically the right anterior FG (contact TM3 and adjacent contacts, Fig. 1C), an underestimated portion of the cortical face network critical for FIR [9]. The present study therefore provides original evidence of effective connectivity - likely to be monosynaptic - between two main components of the human face network, the (right) middle and anterior FG (for CCEP evidence of connectivity between the middle FG and posterior regions, see Ref. [10]). Overall, the original approach introduced here offers great promise to assess the effective connectivity of cortical networks of visual function, including their debated hierarchical organization [4,8,9], and to better understand the causal relationship between specific neural responses, network structure and behavior. Future studies could use this approach with multiple stimulated regions in several individual brains to provide a comprehensive view of functional cortical networks including strength and directionality measures.

Data sharing

The original data of this study will be made publicly available upon acceptance of the paper.

CRediT authorship contribution statement

Luna Angelini: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Angélique Volfart:** Conceptualization, Data curation, Writing – original draft. **Corentin Jacques:** Data curation, Formal analysis, Writing – original draft. **Sophie Colnat-Coulbois:** Data curation, Resources. **Louis Maillard:** Conceptualization, Methodology, Resources. **Bruno Rossion:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Jacques Jonas:** Conceptualization, Data curation, Investigation, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.05.016.

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