Intracerebral electrical stimulation of a face-selective area in the right inferior occipital cortex impairs individual face discrimination

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Abstract

During intracerebral stimulation of the right inferior occipital cortex, a patient with refractory epilepsy was transiently impaired at discriminating two simultaneously presented photographs of unfamiliar faces. The critical electrode contact was located in the most posterior face-selective brain area of the human brain (right “occipital face area”, rOFA) as shown both by low- (ERP) and high-frequency (gamma) electrophysiological responses as well as a face localizer in fMRI. At this electrode contact, periodic visual presentation of 6 different faces by second evoked a larger electrophysiological periodic response at 6 Hz than when the same face identity was repeated at the same rate. This intracerebral EEG repetition suppression effect was markedly reduced when face stimuli were presented upside-down, a manipulation that impairs individual face discrimination. These findings provide original evidence for a causal relationship between the face-selective right inferior occipital cortex and individual face discrimination, independently of long-term memory representations. More generally, they support the functional value of electrophysiological repetition suppression effects, indicating that these effects can be used as an index of a necessary neural representation of the changing stimulus property.

Key Words: intracerebral recordings; individual face discrimination; repetition suppression; electrical brain stimulation; occipital face area; fast periodic visual stimulation.

1. Introduction

One of the most impressive functions of the human brain is its ability to differentiate complex visual forms (DiCarlo and Cox, 2007). The human face constitutes the most familiar, socially relevant, and complex visual form, so that discriminating individual faces requires elaborate and refined perceptual skills called for by few other categories of objects. Despite the high similarity among faces and their complex configuration of several parts (eyes, nose, mouth, etc.), adults attain a high degree of proficiency with these skills. Yet, to date, the neural basis of individual face discrimination in the human brain remains by and large a mystery.

In Humans, there is a large bilateral network of occipito-temporal areas responding preferentially to faces (i.e., face-selective areas), with right hemispheric dominance (e.g., Sergent et al., 1992; Allison et al., 1994; Haxby et al., 2000; Calder and Young, 2005; Weiner and Grill-Spector, 2010; Rossion et al., 2012a). To investigate sensitivity to individual faces of these areas, functional magnetic resonance imaging (fMRI) studies have taken advantage of the reduction of neural activity following repetition of the same stimulus (repetition suppression, also referred to fMR-adaptation or habituation; Grill-Spector and Malach, 2001; Grill-Spector et al., 2006). The rationale of this approach is that populations of neurons sensitive to differences between individual faces show a smaller response when the same face identity is repeated compared to the presentation of different face identities. Many fMRI studies have reported such decreases to individual face repetition in face-selective areas of the ventral occipito-temporal cortex (e.g., Gauthier et al., 2000; Grill-Spector and Malach, 2001; Andrews and Ewbank, 2004; Schiltz et al., 2006; Gilaie-Dotan and Malach, 2007; Davies-Thompson et al., 2009; 2013; Xu and Biederman, 2010; Ewbank et al., 2013). Multivariate pattern analyses of fMRI data have also identified various clusters of voxels in the ventral occipito-temporal cortex that are sensitive to individual faces (Kriegeskorte et al., 2007; Nestor et al., 2011; Goesaert and Op de Beeck, 2013). Taken together, the observations of these studies point to a distributed representation of individual face information in the ventral occipito-temporal cortex, with a right hemispheric advantage. However, the relationship between these effects – in particular the face identity repetition suppression effects in neuroimaging – and behavioral performance at individual face discrimination remains unknown. Moreover, these neuroimaging studies are not in a position to clarify the extent to which these identified brain regions encode *critical* information for individual face discrimination behavior.

This question can be tackled with other approaches. For instance, studies of neuropsychological patients with prosopagnosia – typically impairment in face recognition following brain damage – suggest that multiple regions of the right ventral occipito-temporal cortex play an important role in individual face discrimination (e.g., Sergent and Signoret, 1992; Rossion et al., 2003; Bouvier and Engel, 2006; Barton, 2008). However, patients with acquired prosopagnosia usually have large cortical lesions (e.g., Barton, 2008; Busigny et al., 2010a) preventing firm conclusions to be drawn about the critical role of a given cortical area in this process. Transcranial magnetic stimulation (TMS) on the scalp above a right face-selective area of the lateral occipital cortex (right “occipital face area”, “OFA”) may also impair individual face discrimination (Pitcher et al., 2007). Yet, it is fair to say that the TMS disruptive effects on individual face discrimination are relatively small (e.g., Solomon-Harris et al., 2013) and not always observed (Pitcher et al., 2008). More generally, these effects are of limited localizing value because TMS cannot be applied to other face-selective areas of the ventral visual stream, and the TMS effects are not necessarily limited to the cortical area directly under the coil (Sack and Linden, 2003).

In a recent study, we reported a transient inability to recognize photographs of famous faces during intracerebral electrical stimulation of the right occipital cortex in an epileptic patient implanted with depth electrodes (Jonas et al., 2012). Since the stimulated area was located in the right OFA, this study provided evidence for a causal link between this face-selective area and face recognition (Jonas et al., 2012; see also Vignal et al., 2000 and Parvizi et al., 2012 for reports of a distortion of the physician's face following electrical stimulation of the prefrontal cortex and fusiform gyrus respectively). Here we report the results of a second intracerebral exploration performed a year later in the same patient (KV, Jonas et al., 2012). Since this second exploration also involved intracerebral electrodes in the right inferior occipital cortex, it provided a unique opportunity to test the causal link between the right OFA and behavioral individual face discrimination. To do so, we designed an experimental paradigm with unfamiliar rather than familiar faces during intracerebral stimulation, testing individual face discrimination independently from memory factors. To test the relationship between repetition suppression/adaptation effects and individual face discrimination behavior, we measured repetition suppression by means of a fast periodic visual stimulation (FPVS) paradigm with trains of either identical faces or different faces (Rossion and Boremanse, 2011; Rossion et al., 2012b). This approach has the advantage of providing high signal-to-noise ratio repetition suppression effects for face identity within a few minutes of stimulation, a factor that is particularly important in a clinical context with limited testing time.

2. Materials and Methods

2.1 Case description

The patient is a 32-year-old right-handed female (KV) who has rare refractory right occipital epilepsy related to a focal cortical dysplasia involving the right inferior occipital gyrus. Her case was previously reported as evidence of a transient inability to recognize famous faces following intracerebral electrical stimulation of the right inferior occipital gyrus (Jonas et al., 2012). Because she was contraindicated to conventional resection based on this first stereo-electroencephalography (SEEG; Talairach and Bancaud, 1973), the patient underwent a second SEEG about a year later (December 2011) in order to perform radiofrequency-thermolesions of the epileptic focus (Catenoix et al., 2008). To date, the patient did not have surgery. All of the SEEG and behavioral data reported in the present paper study comes from this second electrode implantation and have never been reported.

The patient never reported face recognition difficulties, between and during seizures and had preserved memory and preserved visual perception (including faces and objects), as shown by neuropsychological evaluations (Jonas et al., 2012). She gave written informed consent for this study, which was approved by the ethical committee of the Nancy University Hospital.

2.2 Intracerebral electrode placement and SEEG recordings

Stereotactic placement of 3 intracerebral electrodes, consisting of 8-11 contiguous contacts of 2 mm in length, separated by 1.5 mm, was performed according to a well-defined and previously described procedure (Maillard et al., 2009). Intracerebral EEG was recorded at a 512 kHz sampling rate with a 128 channel amplifier (2 SD LTM 64 Headbox; Micromed, Italy). The reference electrode was a prefrontal midline surface electrode (FPz). All three electrodes were placed in the right ventral occipito-temporal cortex (see Figure 1). Electrodes D (8 contacts, D1 to D8) targeted the right ventral occipital cortex, from the lateral part of the inferior occipital gyrus to the posterior collateral sulcus. Electrode F (11 contacts, F1 to 11) was located more anteriorly in the ventral occipito-temporal junction, from the right inferior temporal gyrus to the lingual gyrus. Electrode L (8 contacts, L1 to L8) was located between electrodes D and F, also in the right occipital cortex but slightly above these electrodes. Note that this kind of electrode implantation is very rare in clinical practice, where most epileptic patients are implanted with more anterior electrodes to sample the temporal cortex.

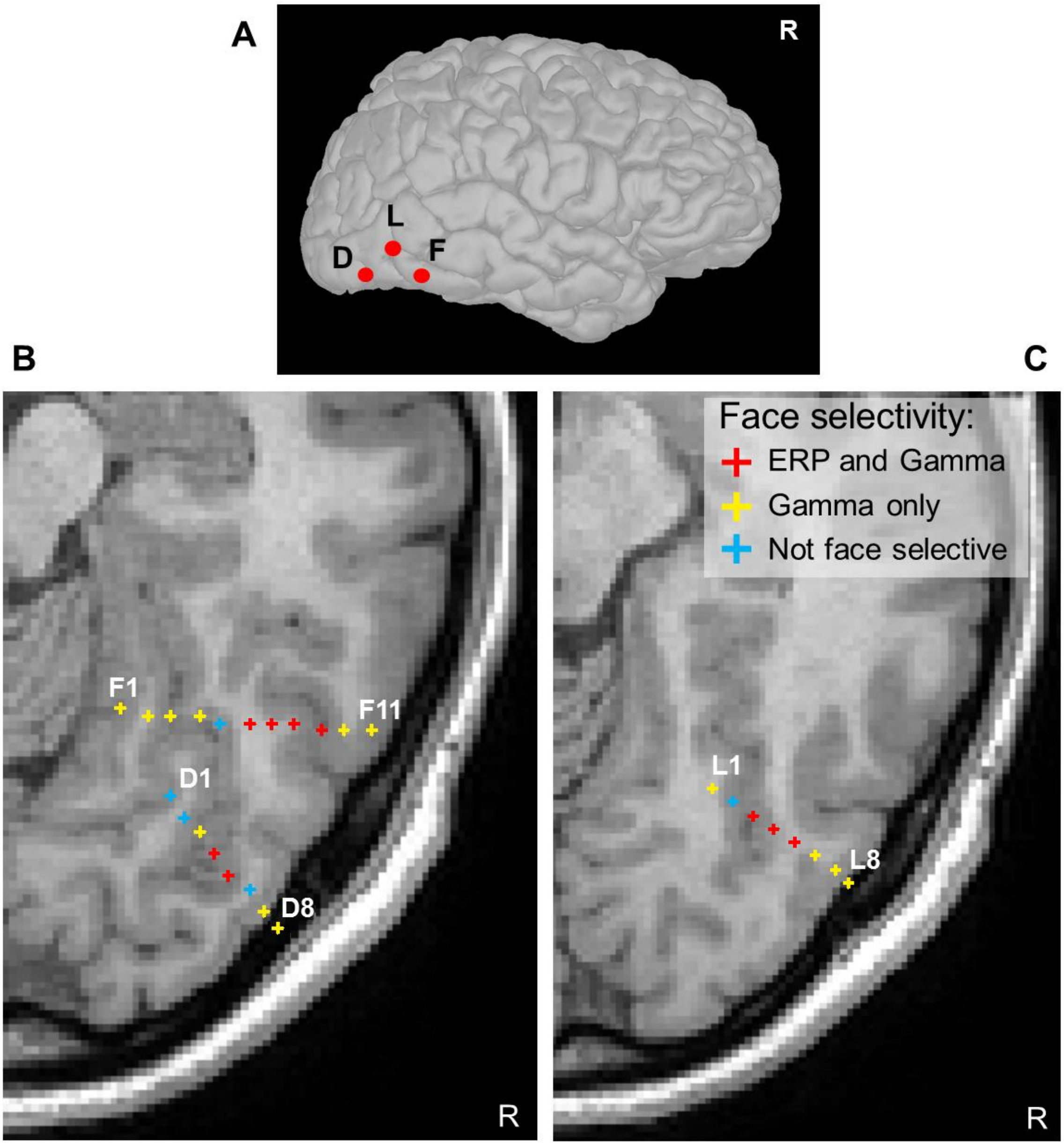

Figure 1. Anatomical locations of the 3 intracerebral electrodes implanted in the right inferior occipito-temporal cortex (electrodes, D, L and F) and face selectivity results on each contact. **A.** Schematic locations of enter points of the 3 electrodes shown on a segmented brain of patient KV. **B and C.** Schematic locations of the electrodes and all contacts along these electrodes on MRI axial slices. Each contact is represented by a cross. The color of the cross indicates face selectivity responses recorded on each contact. Only the most medial and the most lateral contacts of each electrode are named. Electrode L is located slightly above electrodes F and D. Contact D8 is the most lateral contact of electrode D and was not located inside the brain but sitting on the surface of the lateral occipital cortex.

2.3 Cortical stimulation: individual face discrimination task

Since typical clinical settings in SEEG do not allow performing a large number of electrical stimulations and the patient was only implanted with intracerebral electrodes during 3 days which were mainly dedicated to clinical investigations, we first identified the relevant electrode contacts for face processing, in order to test these contacts with a well-controlled individual discrimination task limited to the category of faces. Therefore, we first screened the effect of electrical stimulation on recognition of famous faces, scenes, and everyday objects, for most of the contacts (recognition task; Table 1). This allowed us to select relevant electrode contacts whose stimulation evoked perceptual or recognition disturbances specifically for faces (i.e., no recognition difficulties for visual scenes or object pictures). Then, we tested the effect of electrical stimulation on individual face discrimination only on these selected electrode contacts (individual face discrimination task; Table 1).

Table 1. Number of electrical stimulations performed at each stimulation site and type of stimulus sets used. For each stimulation, the patient was presented with a set of 5 successive images of the same category, 4 images without stimulation and 1 image during stimulation. In brackets are indicated the corresponding number of stimulations which evoked difficulties in recognizing visual objects for the recognition task and incorrect responses for the individual face discrimination task. Each stimulation location is defined by the name of the 2 contiguous contacts involved in the stimulation, by its anatomical location, and if possible by its functional location (OTS: occipito-temporal sulcus; CoS: collateral sulcus, rOFA: right occipital face area).

	Number of sets			
	Recognition task			Individual face discrimination task
Locations of stimulations	Famous faces	Objects	Famous scenes	Morphs of unknown faces
D2-D3 Right CoS	1 (0)			
D3-D4 Right CoS	1 (0)			
D4-D5 Right CoS, within rOFA	1 (0)	1 (0)		

D5-D6 Right CoS, within rOFA	2 (2)		1 (0)	6 (6)
D6-D7 Right lateral occipital cortex, within rOFA	2 (2)		1 (0)	1 (0)
L1-L2 Right CoS		1 (0)		
L2-L3 Right CoS	1 (0)			
L4-L5 Right CoS	2 (0)			
L6-L7 Right lateral occipital cortex	5 (3)		2 (0)	4 (2)
L7-L8 Right lateral occipital cortex	1 (0)			
F1-F2 Right lingual gyrus	1 (0)			
F2-F3 Right CoS		1 (0)		
F3-F4 Right CoS	2 (0)			
F4-F5 Right CoS	1 (0)	1 (0)		
F5-F6 Right CoS	1 (0)			
F6-F7 White matter	1 (0)			
F7-F8 Right OTS	1 (0)			
F9-F10 Right OTS		1 (0)		

2.3.1. Stimuli. Pictures of unfamiliar faces of 48 Caucasian undergraduate students were used. Faces were cropped along the face contour, so that no hair or external cues were visible. All images were obtained under identical conditions (distance, lighting, position). Photo Morpher v3.10 (Morpheus, Santa Barbara, CA, USA) was used to create 48 morph continua by morphing each face with two other faces of the same sex. For each face, 300 points were placed on the critical features (i.e., pupils, iris, eye bulbs, eyelids, eyebrows, mouth, nose, and overall facial contour) to allow smooth transitions between the 11 stimuli defining each morph continuum (two original faces representing the extremes, with consecutive increments of 10%). For each of the continua, two stimuli that differed from each of the two original faces (0% and 100%) by 40% (i.e., 30% and 70%) were selected. We constructed pairs of stimuli that consisted of two identical faces (two 30% or two 70%) or two different faces (one 30% and one 70%) presented next to each other (Figure 2). For each continuum, there were thus 3 kinds of trials (3 x 48 = 144). Then, we constructed 28 sets of 5 pairs of photographs. Out of the 28 potential sets, the patient was eventually shown 13 sets (65 pairs) in total. In the majority of sets (11/13), there were three pairs of different faces and two pairs of identical faces. The size of the presented faces was 8 cm in height x 6 cm in width (roughly 8 degrees x 6 degrees at a distance of 60 cm).

2.3.2. Procedure. Bipolar electrical intracerebral stimulations were applied between two contiguous contacts along a common electrode (50 Hz over 5 seconds at intensities ranging from 1 to 2 mA; Jonas et al., 2012). During the recognition task, the patient was shown with sets of 5 colored photographs of a same category (famous faces, famous scenes or objects that she correctly recognized before the stimulation procedure) presented one by one. The patient had to name each photograph in turn. For each set, the stimulation was triggered randomly during the presentation of one of the 5 photographs (1 s before the presentation). During the individual discrimination task, each face pair was presented one by one, with 5 pairs presented consecutively. Stimulations were triggered randomly during the presentation of only one pair of each set, beginning 1 s before the onset of that pair (Figure 2). Within a set (i.e., 5 pairs presented consecutively), each pair of faces was presented for 2000 ms, with an interstimulus interval varying randomly between 4100 ms and 4500 ms (black screen of 300 ms followed by a central fixation cross randomized between 3800 ms and 4200 ms). One face was located in the center of the screen and the other face on the right side, so that the patient's first fixation fell onto a face rather than between the two faces. For each pair of faces the patient was instructed to decide whether the faces were identical or different. A video camera and sound recorder recorded the patient’s performing the experiment and an experimenter sitting behind the patient in the room also recorded her oral response. Electrical stimulation was applied only on a pair of different faces because we hypothesized that the effect of stimulation would disrupt the perception of the information that differs between different faces rather than making identical faces look different. The patient was not aware of the stimulation onset, stimulation offset, or the localization of the stimulation site. The patient was seated in a chair in her hospital room, facing the computer screen placed 60 cm away from her face. Visual stimuli were presented on a computer screen using E-Prime v2.0. For two sets of 5 pairs, the patient was also asked to perform the matching task without any electrical stimulation.

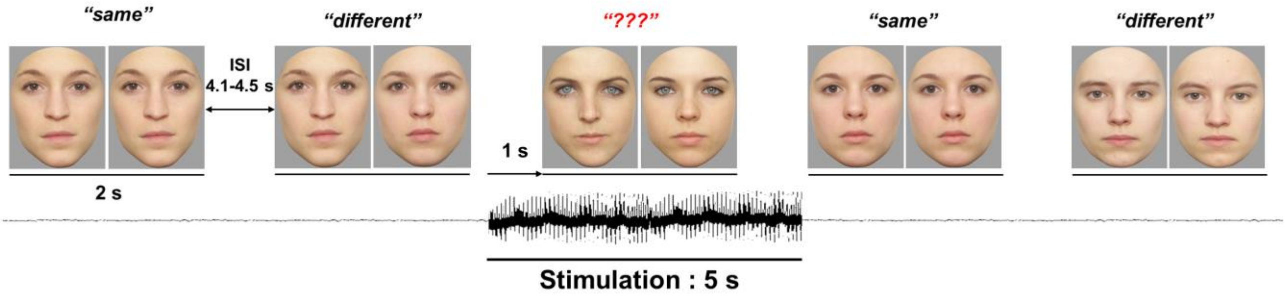

Figure 2. Schematic representation of the individual face discrimination task during electrical intracerebral stimulation in the right inferior occipital gyrus. The electrical stimulation was performed randomly on one of five consecutive trials, always on a pair showing two different faces.

2.4 Face-selectivity: fMRI face localizer

The comprehensive method used for this fMRI localizer study was previously reported in detail (Jonas et al., 2012) and will only be briefly summarized here. Nine epochs [duration 14.4 s; 4 repetition time (TR)] of two conditions (faces and objects) were presented alternatively during fMRI recording. In each epoch, 18 stimuli were presented, each stimulus being presented for 500 ms followed by a fixation cross (300 ms). The patient was required to perform a one-back task (detection of immediate repetition of an item) by pressing a response key.

Imaging was performed on a 3T wide-bore scanner (Verio, Siemens, Engerlingen, Germany), using 32-channel head coil. Both a high resolution T1-weighted anatomical image (100 contiguous sagittal slices, echo time (TE)=2.2 ms; TR=1900 ms; flip angle=9°; field of view (FOV)=260 cm; pixel size=1×1 mm; slice thickness=1 mm) and a gradient echo, echo-planar sequence (TE=27 ms; TR=3600 ms; FOV=244 cm; pixel size=2×2 mm; slice thickness=2.5 mm; acquisition time (TA)=9 min 48 s) were acquired. Data processing (linear trend removal, slice scan time correction, high-pass filtering of > 3-cycles/run, and head motion correction) and statistical analysis were performed using Brain Voyager QX. The fMRI data was spatially smoothed (full width at half maximum (FWHM) 4 mm, all three directions), and coregistered with the 3D T1-weighted scans. Functional data were analyzed using a General Linear Model with two predictors (faces, objects). Predictors' time courses were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation. A conservative statistical threshold (Bonferroni-corrected, $p<0.05$) was used to define face-selective areas (faces – objects), corresponding to t-values above 5.095. The statistical map was then interpolated on a cubic grid of resolution 0.5 mm using trilinear interpolation for the coregistration with the computed tomography (CT)-scan using a custom-based application.

2.5 Face-selectivity: intracerebral ERP and gamma activity

Face-selectivity of the electrode contacts was determined by comparing the response to faces, objects, and phase-scrambled stimuli, exactly as in a scalp event-related potential (ERP) study (Rossion and Caharel, 2011). Color photographs of full-front segmented faces and cars were used, in addition to their phase-scrambled versions. All stimuli subtended approximately 6.52° x 7.44° of visual angle at a distance of 60 cm.

2.5.1. Procedure. The patient was seated in a chair in her hospital room facing a computer screen placed 60 cm from her face. In each trial, a fixation point was displayed at the center of the screen for 100 ms, followed approximately 300 ms (200-400 ms) later by the test stimulus for 300 ms. An inter-trial interval of about 1700 ms (1600–1800 ms) was used. The patient was asked to judge whether the presented stimulus was an object (face or car) or a ‘‘texture’’ (scrambled versions), by pressing one of two response keys with her right hand. The patient performed two blocks of 86 trials (172 trials in total with 43 trials per condition, randomized).

2.5.2. ERP analysis. Stereo-electroencephalographic ERPs were analyzed using *Letswave* (Mouraux and Ianetti, 2008) and MATLAB v7.9 (The Mathworks, Inc.). The analysis consisted of: (i) bandpass filtering (0.1 – 48 Hz, 24 dB/oct), (ii) epoching (-200 ms to +1000 ms relative to stimulus onset), (iii) baseline correction (-200 ms to 0 ms), and (iv) averaging of epochs per condition. Conditions were compared by pairs on each time-point and differences were considered to be significant if they reached $p < 0.05$ for 10 consecutive time-points (10 ms). To compare ERPs that were shifted in time, a paired t-test ($p < 0.05$) was done on maximum amplitudes of single trials.

2.5.3. Gamma-ERSP analysis. Event-related spectral perturbations (ERSP) were computed using *Letswave* and MATLAB v7.9. Variation in signal amplitude as a function of time and frequency was estimated by a Morlet wavelet transform on each single trial from frequencies of 2 to 200 Hz, in 120 steps (non-filtered data). The number of cycles (i.e., central frequency) of the wavelet was adapted as a function of frequency from 2 cycles at the lowest frequency to 10 cycles at the highest frequency. The wavelet transform was computed on each time-sample and the resulting amplitude envelope was downsampled by a factor of 10 (i.e., to a 102.4 Hz sampling rate). Amplitude was normalized across time and frequency to obtain the percentage of power change generated by the stimulus onset relative to the mean power in a pre-stimulus time-window (-600ms to -300ms relative to stimulus onset).

The amplitude difference between the gamma-band signal (30-100 Hz) generated by face and car stimuli was statistically assessed by running a permutation test at each time-sample of the response between -100 and 800 ms relative to stimulus onset. This frequency range for gamma was selected on the basis of the prior intracerebral studies (Engell and McCarthy, 2011). In short, the single-trial amplitudes obtained in the two conditions at a given time-point were randomly assigned in two bins, the number of trials in each bin being equal to the number of trials in each original condition. Next, the difference between the means of the two random bins was computed and stored. Because permutation shuffles the assignment of the conditions, the difference between the means of the two new bins reflects the difference between conditions under the null hypothesis. This process was performed 10000 times to generate a distribution of differences at a $p<0.001$

(two-tailed) and values that reached this threshold for at least 3 consecutive time-samples (i.e., 30ms) were considered as significant.

2.6 Repetition suppression effects for individual faces measured with fast periodic visual stimulation

The main aspects of the procedure for this experiment have been previously described in two different studies comparing the presentation of trains of different faces to identical faces at a fixed frequency rate (Rossion and Boremanse, 2011; Rossion et al., 2012b). From a methodological perspective, this fast periodic visual stimulation (FPVS) approach – which leads to so-called steady-state visual evoked potentials (SSVEPs, Regan, 1966, 1989) – has multiple advantages: objectivity of definition and quantification of the response of interest, high signal-to-noise ratio (SNR), short time duration of the experiment, and recording of the response of interest during a simple incidental task (see Rossion, 2014 for a review), making it a tool of choice for the study of patients implanted with intracerebral electrodes. Here faces were presented at a 6 Hz rate because this frequency rate provides the largest repetition suppression effect on the right occipito-temporal scalp (Alonso-Prieto et al., 2013).

2.6.1. Stimuli*.* Eighteen full-front color pictures of unfamiliar faces (7° x 10° of visual angle for the base face size) equalized in luminance online by the stimulation software were used.

2.6.2. Procedure. In each condition, a face stimulus appeared and disappeared (sinusoidal contrast modulation) on the screen, at a stimulation rate of 6 faces/sec (one face every 166.66 ms; Figure 3; see Movie 1 for an example of a 6 Hz periodic stimulation of different faces). A trigger was sent to the parallel port of the EEG recording computer at each minimal level of visual stimulation (gray background), using a photodiode placed on the left upper corner of a laptop monitor. In the *identical face* condition, a randomly selected face picture was presented repeatedly during the whole stimulation duration (70 s). In the *different face* condition, the same face identity was presented for the first 15 s, and from then on the face identity changed with every cycle until the end of the sequence (Rossion et al., 2012b). In that condition, 18 individual faces of the same sex were used and presented in random order. The same face identity never appeared twice in a row, so that the face identity change rate was always 6 Hz. To minimize repetition suppression effects due to low-level cues, the face stimulus changed substantially in size with each presentation, i.e., at a rate of 6 Hz, in all conditions (random face size between 82% and 118% of base face size).

The patient performed 8 sequences of 70 s in total: 2 (identity change: identical or different faces) x 2 (orientation: upright/inverted) x 2 repetitions (sex: male or female faces). The whole experiment lasted about 10 min, including the pauses between the runs. The order of conditions was randomized. During each 70 s run, the patient was instructed to fixate on a small black cross located centrally on the face, slightly below the bridge of the nose. The fixation cross changed color (black to red) briefly (200 ms) 6 to 8 times during each run and the patient was instructed to report the color changes by pressing a response key.

2.6.3. SEEG analysis for periodic stimulation. All analyses were performed using Letswave (http://nocions.webnode.com/letswave/, Mouraux and Ianetti, 2008) and MATLAB v7.8 (The Mathworks, Inc.), according to the procedure described in Rossion et al. (2012b). Fifty seconds of stimulation (300 cycles at 6.0 Hz) from the 18th second onset point (i.e., 18s onset to 67s offset) were considered for analysis. Discrete Fourier Transform (DFT) was applied to the individual windows, and SEEG amplitude extracted at a high spectral resolution of 1/50=0.02 Hz. Frequency spectra of the two trials of each condition were averaged. Signal-to-noise ratio (SNR) was computed at each channel for all frequency bins between 0 and 100 Hz as the ratio of the amplitude at each frequency to the average amplitude of the 20 neighboring bins (e.g., Rossion et al., 2012b). Significant responses above noise level were defined by computing a Z-score, using the mean and standard deviation of the 20 neighboring bins of the frequency of interest. Comparison between conditions was made separately for each orientation, by computing Z-scores on the subtracted SEEG spectra (*different faces* – *identical face*). A complementary analysis was performed by segmenting the SEEG windows in 13 pieces of 4 s (17 s to 69 s), which were Fourier Transformed (resolution 0.25 Hz). A paired t-test was then performed between the two conditions using 26 trials by condition.

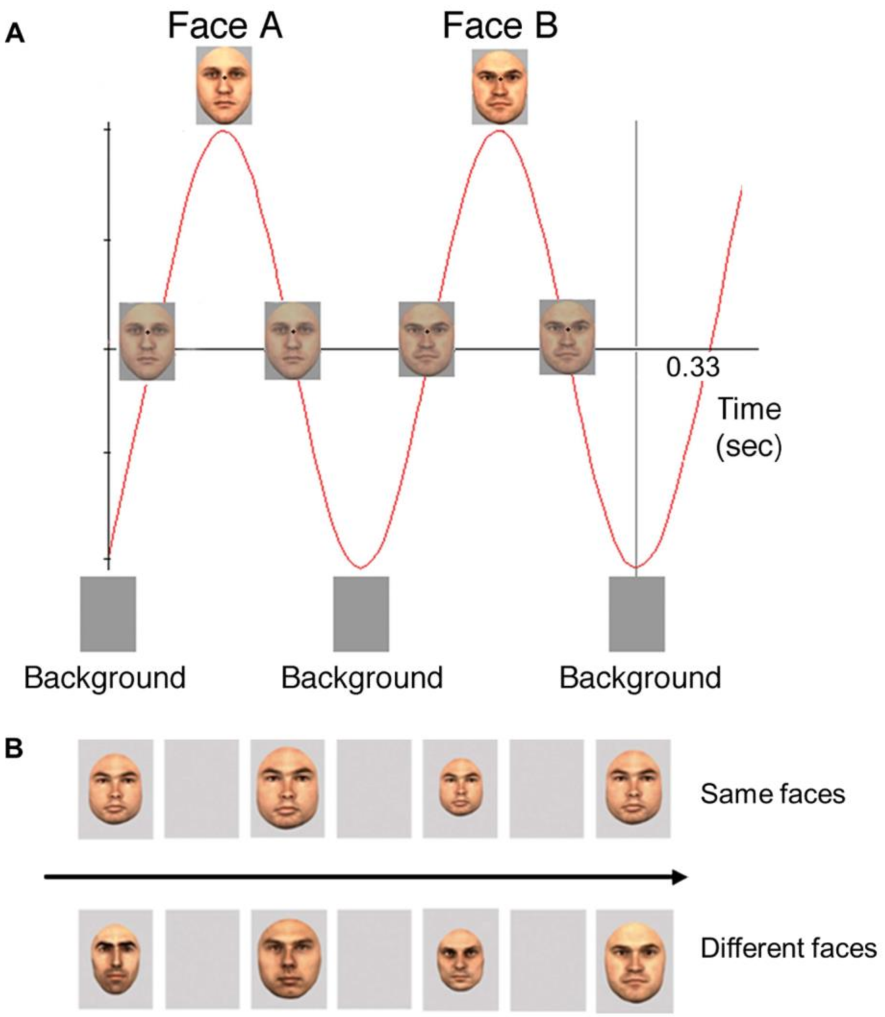

Figure 3. A. Visual stimulation to measure an electrophysiological index of individual face discrimination. Full-front pictures of faces were presented at a periodic rate of 6 cycles/s (6 Hz, one face every 166 ms, here two cycles presented), following sinusoidal contrast stimulation (Rossion and Boremanse, 2011; see movie 1). The beginning of the 70-s stimulation (420 cycles in total, here 2 cycles represented) was always the (gray) background. The lower contrast face stimulus in the midline, in between the background and the full face stimulus, represents an intermediary stage of stimulation at the onset of the face stimulus. **B**. The two main conditions of the study, in which either the same face was repeated throughout the 70-s stimulation sequence (above), or different face identities were presented successively (below). Note that there were large changes of size between each face picture to minimize low-level adaptation effects. A fixation cross was also present on the top of the nose.

3. RESULTS

3.1 Functional location of intracerebral contacts

Contacts D5, D6 and D7 were located within a functionally face-selective area in the right inferior occipital gyrus (right OFA; Figure 4). Lateral contacts of electrode L (L6 and L7) were adjacent to the right OFA. Contacts D5 and D7 were found face-selective in ERP and/or in gamma-ERSP. On contact D5, a P170 component and the gamma-ERSP were much larger for faces than for cars (normal pictures only, Figure 5). Contact D7 was only face-selective in gamma-ERSP. The adjacent D6 was not face-selective (but located in the white matter, see Figure 1).

Twenty other contacts in the right occipito-temporal cortex were also found to be face-selective in ERP and/or in gamma-ERSP. Eight contacts were found face-selective in both ERP and gamma-ERSP (D4, L3, L4, L5, F6, F7, F8, F9). The remaining 12 contacts (D3, D8, L1, L6, L7, L8, F1, F2, F3, F4, F10, F11) were only found face selective in gamma-ERSP. This is in line with a previously reported co-localization on the occipito-temporal cortical surface of electrode sites showing both ERP and gamma-ERSP face-selective responses and sites showing only gamma-ERSP face-selective responses (Engel and McCarthy, 2011). Figure 1 shows selectivity results across all intracerebral contacts in MRI axial slices. No amplitude differences were found between responses evoked by scrambled faces and scrambled cars on face-selective contacts in ERP or in gamma-ERSP.

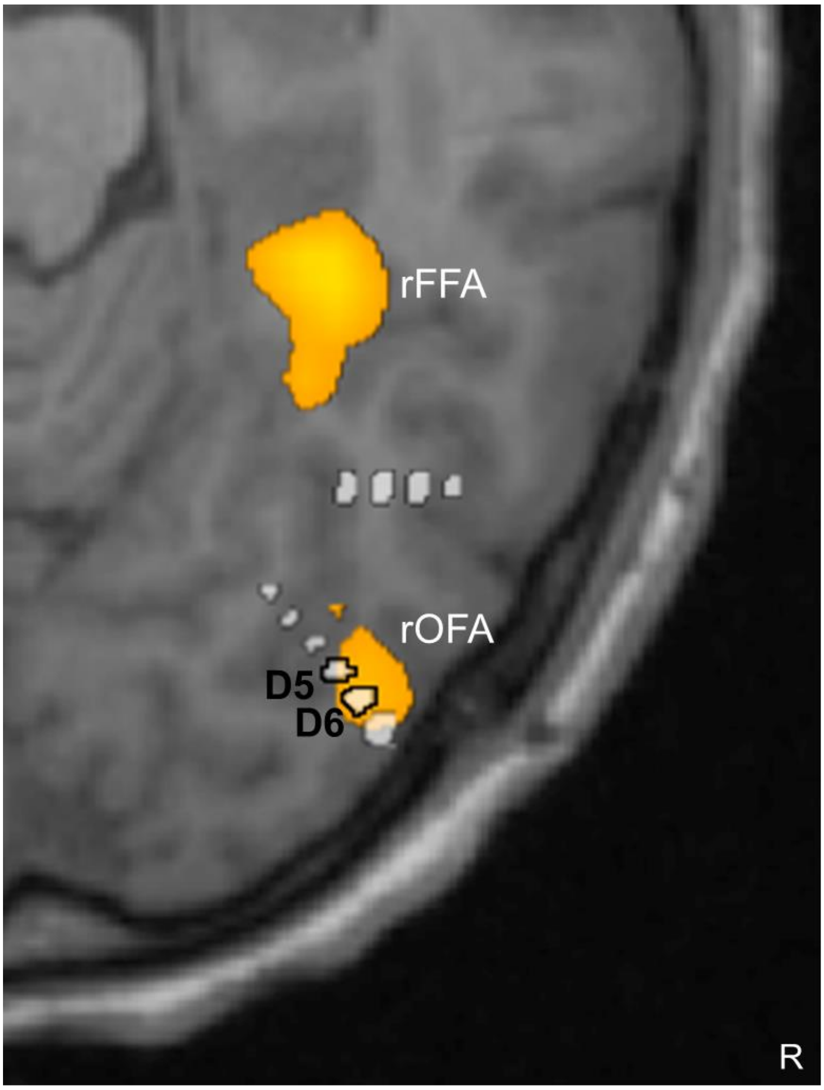

Figure 4. Functional location of the 2 stimulated contacts D5-D6 inducing reproducible impairment of individual face discrimination (6 times). Contacts D5-D6 are both located within the right OFA. D7 is located also within this region also, just laterally to D6. The figure was obtained by fusing the functional MRI and the post-operative stereotactic CT-scan.

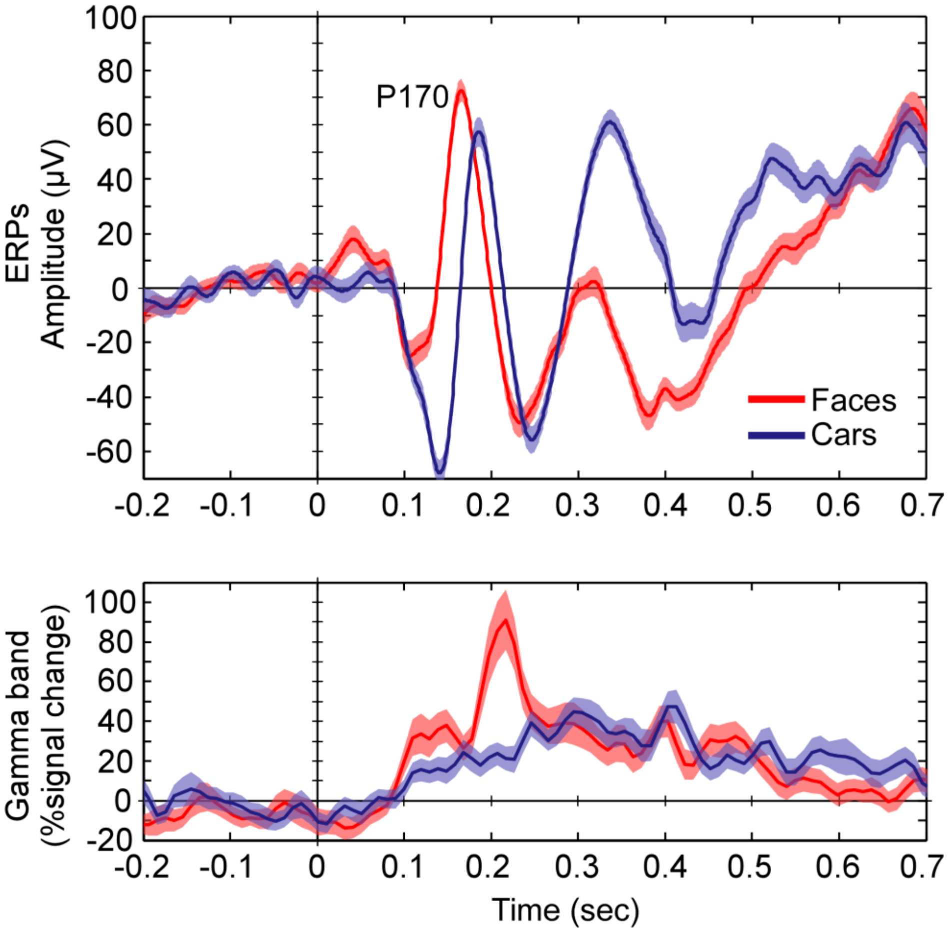

Figure 5. Face-selectivity in ERP (above) and gamma-ERSP (below) of the stimulated contact D5. On average, the potential evoked by faces (i.e., P170, see Jonas et al., 2012) peaked earlier (167ms) and had larger amplitude (75.3 µV) than the P170 evoked by cars (186 ms, 55.7 µV). At this contact, the P170 peak could be identified on single trials (after low-pass filtering at 20 Hz). The maximum amplitude was extracted automatically for each single trial between 140 and 200 ms for faces and 160 ms and 223 ms for cars. The P170 at contact D5 was significantly larger for pictures of faces than pictures of cars (t=2.021; p=0.036).

3.2 Intracerebral electrical stimulation

3.2.1. Pre-experiment recognition task. Among the 15 sites tested with the recognition task (Table 1), the patient reported difficulties in recognizing famous faces during stimulation of 3 sites, all located in the right inferior occipital gyrus. When stimulating contacts located within the right OFA, the patient reported such difficulties for 4 out of 4 stimulations (D5-D6: 2 stimulations; D6-D7: 2 stimulations).

When stimulating contacts adjacent to the right OFA, she also reported such subjective difficulties but with less reproducibility (L6-L7: 3 out of 5 stimulations). The patient reported these difficulties specifically for famous faces presented during the stimulation and never for faces presented without stimulation. These difficulties occurred only after stimulation onset and recovered immediately upon termination of the stimulation. The patient spontaneously reported: "*something disturbs the identification of an entity that is the face*", "*I did not process the face as a whole*", "*my brain had to process the different facial elements simultaneously*", "*my brain had to process several pieces of information simultaneously, the forehead, the chin, the eyes, the nose*". It is important to note that the patient was able to name all the famous faces (without and with stimulation) and she never reported distortions of faces during stimulation; she correctly recognized all the non-face images and she never reported these recognition difficulties when presented objects or visual scenes during stimulations (in total, her performance at the recognition task was at 100% for face and non-face stimuli, including the stimuli presented during stimulation).

3.2.1. Main experiment: individual face discrimination task. Without stimulation, the patient performed the individual discrimination task with an accuracy rate of 91% (49/54, 4 errors when faces were different). For comparison, a group of 11 age-, sex- and education level-matched controls performed the same task with an accuracy rate of 74%, +/- 8% (91% vs. 74%, t=1.858, p=0.093). In contrast, when stimulating the contacts D5-D6 located in the right OFA, the patient's correct response rate dropped to 0% (0/6) (for functional location of contacts D5-D6 see Figure 4; for a video of stimulation see Movie 2). Specifically, although the morphed faces were different, the patient always responded "same". The patient stated: "*I saw the faces, I had a feeling of a strong resemblance*", "*for me, there were two identical* *faces*". She clearly stated that there were no visual distortions of the presented faces and that she was always aware that she was seeing faces: "*the faces are not distorted*", "*there was no deformation*", "*I knew it was a face*", "*the outlines are distinct, there is no blurring*", "*there was no disturbed arrangement of the facial elements*". Note that her score of 0/6 should not be compared to chance level but to her performance without stimulation, on the 'different' trials (23/27, 85.2%) ($p=0.037$, Fischer's exact test). She was also incorrect for 2 out of 4 morphs presented when stimulating contacts L6-L7, adjacent to the right OFA. At contacts D6-D7, she responded correctly during the single stimulation tested (1/1). Stimulations at these sites (D5-D6, D6-D7 and L6-L7) never produced epileptic discharges. When present, afterdischarges were always limited to the immediate vicinity of the stimulated site.

3.3 Repetition suppression effects for individual faces

3.3.1. Upright faces. For upright faces, a large response confined to the 6 Hz frequency bin and its harmonics (2F=12Hz, 3F=18 Hz, etc.) was observed on many contacts of electrodes D and L. Much weaker responses were observed on electrode F. There were large repetition suppression effects on electrode contact D5, whose stimulations evoked impairment in individual face discrimination (i.e., 6 Hz response 2 µV larger for different than same faces, $Z>2.9$, $p<0.05$, corrected for multiple tests on all electrodes, Figure 6A). A t-test performed using the 26 segments of EEG data (see methods) showed the same results ($t_{25}=31.34$, $p<0.0001$ at channel D5). Figure 6C shows the time-frequency analysis for the eloquent contact D5. The response is centered on the 6 Hz stimulation band, showing an immediate rebound and then sustained activity when different face identities are presented, as compared to when the exact same face is presented until the end of the sequence. There were also statistically significant repetition suppression effects recorded on other electrode contacts located in the right inferior occipital gyrus and in the right posterior fusiform gyrus (D7, D8, L7, L8, F3, F8, see Figure 7 for quantification of repetition suppression effects in each contact and Figure 8 for anatomical locations of repetition suppression results). In Figure 8, we can see clearly see that the largest effect for upright faces was located in the right inferior occipital cortex, in contacts located within or close to the right OFA (D5, D7, D8, L7, L8).

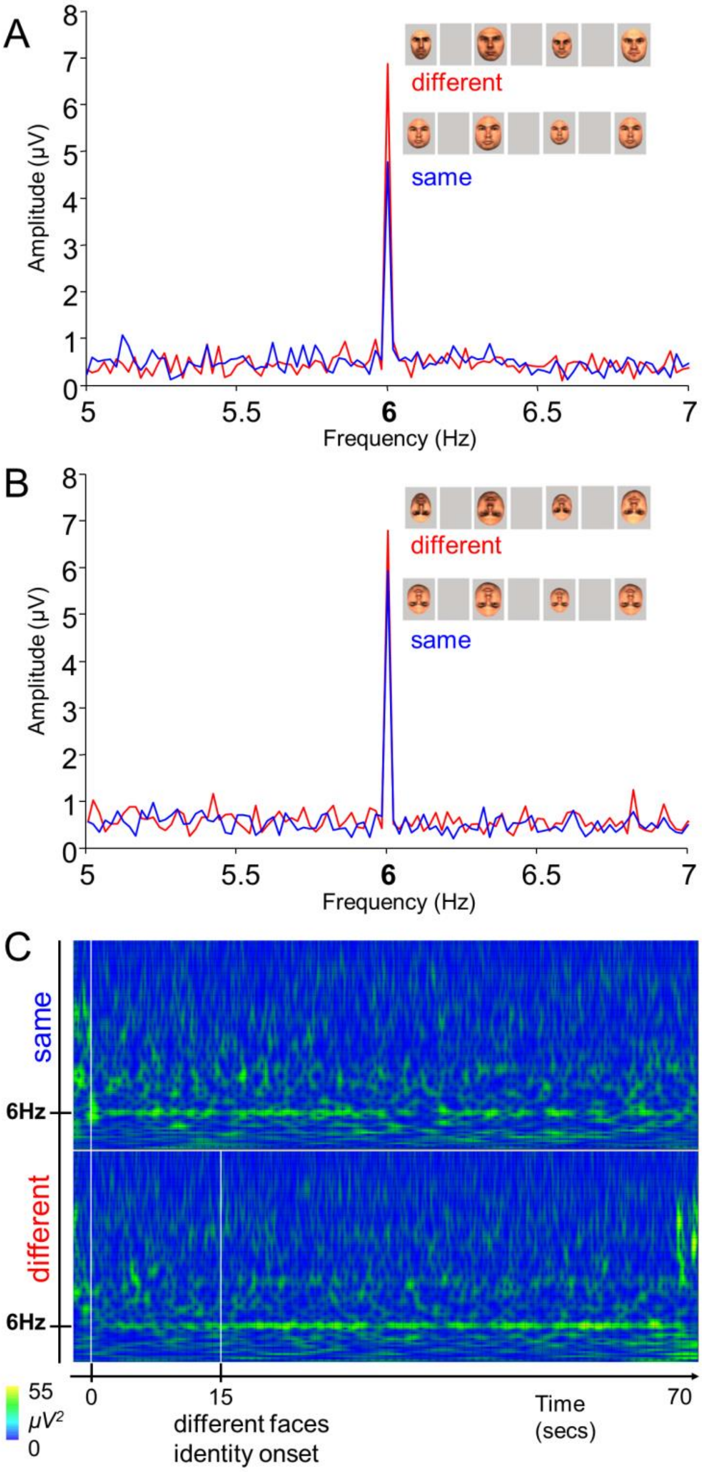

Figure 6. Repetition suppression effect for individual faces on intracerebral contact D5 with fast periodic visual stimulation. **A.** For upright faces in the frequency domain. **B.** For inverted faces in the frequency domain. **C.** For upright faces in the time domain: time-frequency analysis (Morlet wavelet) for the eloquent contact D5 between −1 and 70 s and between 0 and 30 Hz for same and different upright faces.

3.3.2. Inverted faces. Large 6 Hz-specific responses were also observed for inverted faces at the same contacts as for upright faces. Although the differences between conditions were much smaller than in the upright condition, the 6 Hz response was significantly larger for different than for same faces on contacts located in the right inferior occipital gyrus and in the right posterior fusiform gyrus (D7, D8, L7, L8, F6, F8, F9, $Z>2.9$, $p<0.05$, corrected for multiple comparisons, see Figure 7 for quantification of repetition suppression effects on each contact). For contact D5, the difference was strongly reduced as compared to the upright condition (0.99 µV vs. 2.03 µV; see Figure 6B) and was not statistically significant in the inverted condition ($p>0.05$). This reduction of repetition suppression effects for inverted faces is consistent with effects observed on the scalp with the same approach in normal participants (Rossion and Boremanse, 2011; Rossion et al., 2012b). More generally, inversion is a manipulation that preserves low-level features of the face but disrupts individual face discrimination performance (e.g., Yin, 1969; Freire et al., 2000; Rossion, 2008 for a review) and substantially reduces repetition suppression effects in face-selective areas (Yovel and Kanwisher, 2005; Mazard et al., 2006; Gilaie-Dotan et al., 2010). This effect is known to be highly specific to faces (i.e., non-face stimuli elicit either no inversion effect or an inversion effect of smaller magnitude than face stimuli, Yin, 1969; Rossion, 2008). Therefore, the lack of repetition suppression effect for inverted faces on contact D5 reinforces the fact that this contact was located in a face-selective region involved in individual face discrimination.

3.3.3. Upright vs. Inverted faces. For all contacts, the repetition suppression effect for upright faces was subtracted out from the effect for inverted faces (i.e. repetition suppression index). This index reflects the specificity of repetition suppression to upright faces on each intracerebral contact. Of all recorded contacts, the largest repetition suppression index was observed on electrode contact D5 (1.24 μV, Z=5.24, p<0.0001; Figure 7).

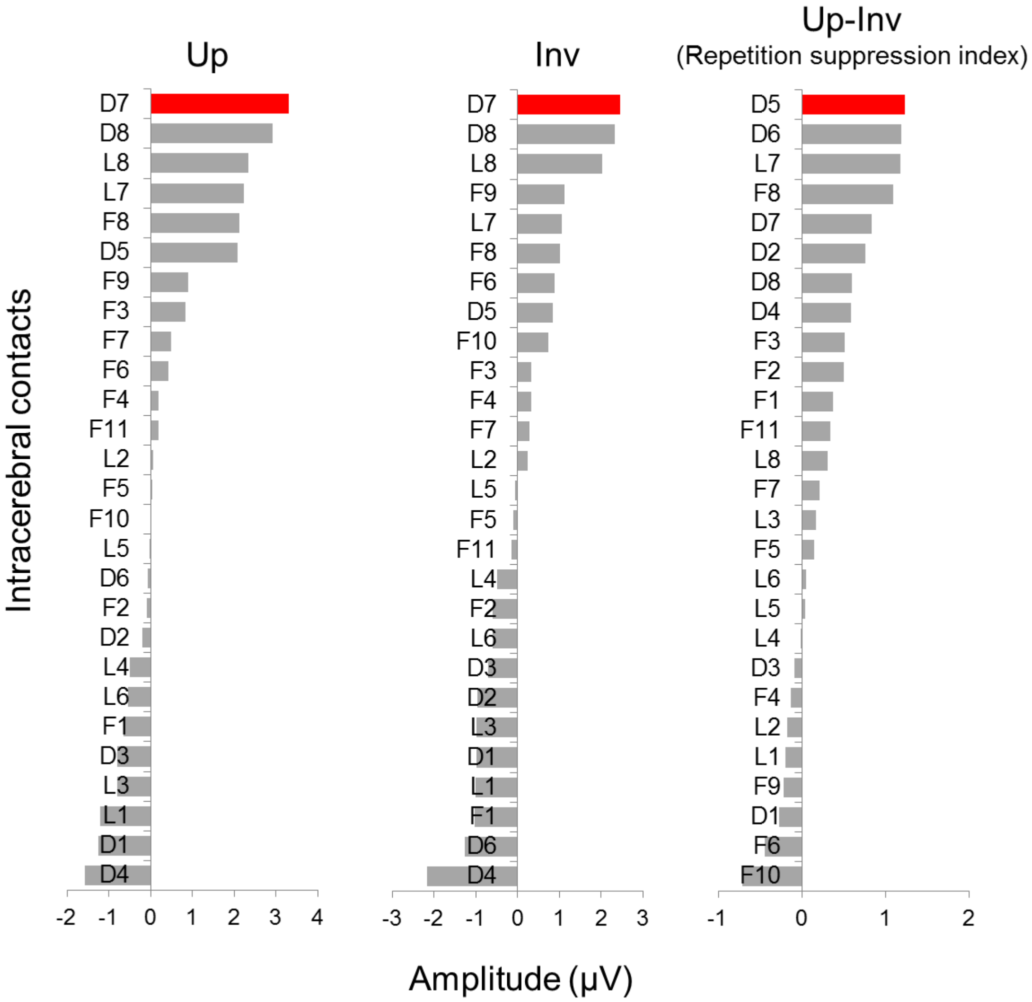

Figure 7. Graphical representation of individual face repetition suppression effects obtained on each intracerebral contact (upright condition, inverted condition and repetition suppression index that is upright condition minus inverted condition). Of all contacts, the largest difference when comparing the magnitude of the effect between upright and inverted faces was observed on contact D5. It is important to note that there was also a large repetition suppression index on contact D6, but essentially related to a larger response for identical than for different faces in the inverted condition. Therefore, the high repetition suppression index found on D6 does not reflect a high sensitivity to individual faces, which is consistent with the absence of face-selective responses and repetition suppression effect for upright faces recorded on this contact and its anatomical location in the white matter.

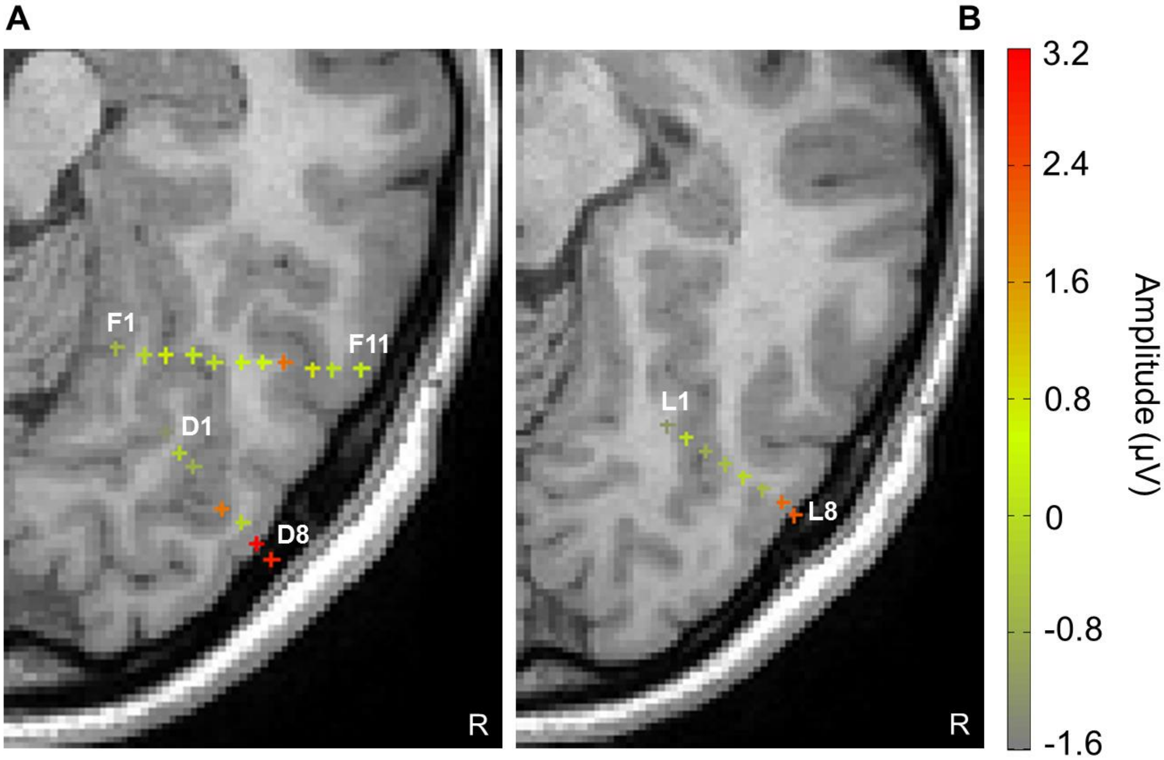

Figure 8. Anatomical location of individual face repetition suppression effects for the upright condition on MRI axial slices. **A.** Electrodes D and F. **B.** Electrode L. Each contact is represented by a cross. The color of the cross indicates the magnitude of repetition suppression in the upright condition. Only the most medial and the most lateral contacts of each electrode are named. Electrode L is located slightly above electrodes F and D. Note that the largest repetition suppression is located in the lateral section of the right inferior occipital cortex. Contact D8 is the most lateral contact of electrode D and was not located inside the brain but sitting on the surface of the lateral occipital cortex.

4. Discussion

In the present study, we had a unique opportunity to test the critical role of a face-selective region of the right inferior occipital cortex in individual face discrimination. We were able to test only a single case because the patient had a rare electrode implantation. Moreover, the patient performed extremely well at face recognition and individual face discrimination when she was not stimulated in this brain region. Electrically stimulating contacts within this region (contacts D5-D6) evoked a transient impairment at discriminating two simultaneously presented photographs of different faces. By means of fast periodic visual stimulation with unfamiliar faces, we found on the stimulated contact D5 the most specific face identity repetition suppression effects of all recorded contacts in the patient’s brain. Altogether, these data provide converging evidence for a causal role of the right face-selective inferior occipital cortex in individual face discrimination.

4.1 The right OFA is critical for individual face discrimination behavior

Intracerebral electrical stimulation of a face-selective cortical area in a unique patient impaired individual discrimination of unfamiliar faces. This observation goes beyond our previous report of impairment in recognizing famous faces during a previous implantation in the same region (Jonas et al., 2012) and other electrical stimulation studies reporting impairment in face vs. no face categorization (Chong et al., 2013, see also Afraz et al., 2006 for modulation of face categorization by electrical stimulation of the monkey infero-temporal cortex), impairment in face naming (Allison et al., 1994, Puce et al., 1999) or distortions of the physician’s face following electrical stimulation of other face-selective regions (Vignal et al., 2000, Parvizi et al., 2012)**.** More related to our observations, Mundel et al. (2003) reported an epileptic patient who stated that “all faces look the same” following electrical brain stimulation o the right fusiform gyrus, suggesting impairment in individual face discrimination. However, the patient reported the same feeling during epileptic seizures, and individual face discrimination was not tested experimentally during electrical stimulation. Most importantly, eloquent electrical stimulations were performed over a undefined brain lesion in the right fusiform gyrus.

Here, to our knowledge, we report the first in case in which individual face discrimination was experimentally tested during electrical stimulation of the human brain. Indeed, here we were able to design a psychophysical task of matching similarly looking faces that specifically tested individual face discrimination. Moreover, since the faces were unfamiliar and were presented simultaneously on the screen, there were no memory processes involved during the individual face discrimination task. Hence, these findings indicate that the area targeted by the intracerebral stimulation is critical for the *perception* of the individuality of the face, independently of long-term memory representations.

It is very unlikely that others factors were involved in the impairment in individual face discrimination reported here: (i) low-level process: the patient clearly stated that there were no distortions of the face stimuli and the eloquent electrical stimulations were done within a high-level visual area (i.e. OFA); (ii) habituation or simulation: the patient was not informed about the exact time and duration of electrical stimulation, which was performed randomly during one out of five consecutive individual face discrimination trials; (iii) neuropsychological deficit in face perception: without electrical stimulation, the patient’s performance was similar to normal controls, and her performance at an extensive battery of neuropsychological tests of face perception indicates that she has no impairment at individualizing faces (Jonas et al., 2012). Hence, her failure to discriminate the individual faces in six out of six trials during electrical stimulation (a relatively high number of stimulations at the same location in a clinical setting) cannot be attributed to chance. Rather, the effect of focal electrical stimulation appears to disrupt the processing of visual information that is necessary to discriminate individual faces.

The eloquent stimulation producing this transient inability in individual face discrimination was located in a face-selective cortical region, as determined both by electrophysiological (ERP, gamma synchronization) and hemodynamic responses (fMRI). This area corresponds to the most posterior face-selective area of the cortical face network, the so-called right OFA. Therefore, the effect of focal electrical stimulation provides original evidence for a causal link between a well-defined face-selective region (i.e., the right OFA) and behavioral individual face discrimination.

Although due to the constraints of the clinical setting we were not able to test stimuli other than faces in the individual discrimination task, the functional location of the stimulation (i.e., a cortical region identified as face-selective) and the much larger repetition suppression effects to upright faces as compared to inverted faces recorded at the stimulation site suggest that the impairment in individual face discrimination is limited to the category of faces. Moreover, the patient was also tested with a recognition task of face and non-face stimuli at 15 different anatomical sites and she reported recognition difficulties only for faces. These face recognition difficulties were observed specifically during stimulation of contacts located within or adjacent to the right OFA (D5, D6, D7, L6, L7), thus reinforcing the view that stimulation of this region impairs face-specific processes.

This observation of a critical role of the face-selective right occipito-temporal cortex in individual face discrimination is in agreement with lesion studies, the right occipital cortex being one of the most consistent sites of brain damage causing prosopagnosia (Bouvier and Engel, 2006). Interestingly, patients with prosopagnosia following lesions to the right inferior occipital cortex are impaired at individual face discrimination (e.g., Rossion et al., 2003; Busigny et al., 2010b) and may be impaired for faces only (Busigny et al., 2010a). Moreover, applying TMS on the scalp above the right OFA may specifically impair face discrimination in a delayed matching task (Pitcher et al., 2007; Pitcher et al., 2009; Solomon-Harris et al., 2013). However, an impairment of individual discrimination of faces with TMS is not always found (e.g. Pitcher et al., 2008) and this effect remains relatively small in magnitude, whether it is expressed in terms of a slowing down of the response or a small drop of accuracy rates. Here, during intracerebral stimulation of the right OFA, our patient was completely unable to discriminate individual faces. Moreover, while the localizing value of TMS is limited, the Stereo-EEG approach used here provides electrical stimulation contacts that are embedded into brain tissue, with the low voltage-electrical currents, causing local disruptive effects.

4.2 The functional value of repetition suppression effects during fast periodic visual stimulation

The effect of stimulation in the right face-selective occipito-temporal cortex is also consistent with fMRI studies showing repetition suppression effects for individual faces in this OFA region (e.g., Gauthier et al., 2000; Grill-Spector and Malach, 2001; Andrews and Ewbank, 2004; Schiltz et al., 2006; Gilaie-Dotan and Malach, 2007; Davies-Thompson et al., 2009; Ewbank et al., 2013). This stimulation result complements these observations by indicating that the right OFA is a critical node among the set of areas showing sensitivity to individual face information. More importantly, our observation shows that the right OFA carries crucial individual face information that is directly related to individual face discrimination behavior.

A recent study has reported electrophysiological face repetition suppression effects at multiple frequency rates (alpha, low and high gamma) for face-selective contacts over the ventral occipito-temporal cortex (Engell and McCarthy, 2014). Here, release from repetition suppression was evidenced intracerebrally by means of a fast periodic visual stimulation paradigm, providing a robust face identity repetition suppression effect at an experimentally defined stimulation frequency (Rossion & Boremanse, 2011; Rossion, 2014 for a review). The electrode contact D5, associated with the transient impairment in individual face discrimination, recorded the largest and most specific repetition suppression effect for individual faces (i.e., the largest difference when comparing the magnitude of the repetition suppression effect between upright and inverted faces among all contacts). This observation – which is consistent with the right occipito-temporal localization of this effect on the scalp (Rossion and Boremanse, 2011; Rossion et al., 2012b) – provides further evidence for the sensitivity of the right OFA to differences between individual faces. Moreover, the unique correlation between the repetition suppression effect and the behavioral impairment at individual face discrimination highlights the functional value of face adaptation/repetition suppression effects, at least when they are measured in electrophysiology with the fast periodic visual stimulation approach.

Given the fact that the most consistent effect of electrical stimulation and the largest repetition suppression effect were found on the same electrode site, our findings even suggest that crucial information for individual face discrimination may be encoded in brain regions showing the largest repetition suppression effect to individual faces. If this is the case, measuring the magnitude and specificity of repetition suppression effects objectively (i.e., at an experimentally-defined frequency rate) and with a high signal-to-noise ratio may be particularly important, suggesting that the fast periodic visual stimulation approach used here may be a tool of choice in the future to rapidly identify cortical nodes that are critical for individual face discrimination and other brain functions.

5. Conclusion

In summary, to our knowledge, this is the first report of transient impairment of individual discrimination of unfamiliar faces following intracerebral electrical stimulation. These findings point to the causal role of the right face-selective inferior occipital cortex in the perception of the individuality of the face, independently of long-term memory representations. These findings also support the functional relevance of repetition suppression/visual adaptation effects obtained with high-level visual stimuli by means of fast periodic visual stimulation, and provide evidence that these effects index the neural representation of the changed stimulus property.

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